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Review

Oncological Applications of Photodynamic Therapy in Dogs and Cats

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Abstract: Photodynamic therapy (PDT) in small animals' oncology has been under research focus, pointing to new treatment possibilities. Moreover, several animal studies constitute experimental human disease models due to the similarity of tumor biology between animals and man. PDT uses photosensitizing compounds without toxicity per se. When subjected to a specific wavelength, the photosensitizers are activated, triggering the production of reactive oxygen species (ROS) that lead to cell death. Additionally, antiangiogenic effects and immune stimulation may also be elicited. PDT is minimally invasive, non-toxic, and does not induce carcinogenic or mutagenic side effects. Thus, it is safe for non-neoplastic tissues compared with other neoplasms treatment modalities. This review describes the applications of PDT in the cancer treatment of small animals, particularly dogs and cats, focusing on the respective photosensitizers and treatment protocols used in trials in this therapeutic modality.

Keywords: photodynamic therapy; photosensitizers; veterinary oncology

1. Introduction

Many animals are affected by spontaneous occurring neoplasms [1–4]. Surgery, chemotherapy, and radiation are among the most used approaches in veterinary medicine [5,6]. However, responses to these therapies have variable success, and their side effects have motivated the scientific community to seek new, safer, and more effective treatments [7].

Dougherty and collaborators first recognized the potential benefits of photodynamic therapy (PDT), a type of treatment that uses light along with chemicals known as photosensitizers or photosensitizing agents in veterinary medicine, and investigated hematoporphyrin derivatives in solid tumors in dogs and cats [8]. However, chemotherapy and radiotherapy availability postponed the application of PDT in veterinary oncology. Recently, promising results and technological developments have contributed to widespread interest in PDT [9–12].

The advantages of PDT include its minimal invasiveness, low toxicity, and absence of carcinogenic or mutagenic effects [13–15]. Compared with other treatment modalities, PDT is safer for non-neoplastic tissues far and near the neoplasms, producing selective cytotoxicity in tumor cells [16,17]. A satisfactory result might be achieved in just one application, but PDT can be repeated without prejudice to normal tissues or eliciting drug resistance [18–20].

Another advantage is that PDT can alter and inhibit drug resistance pathways and resensitize cells resistant to standard therapies [21]. Besides that, the PDT, in most cases, uses non-ionizing radiation and produces limited cytotoxic DNA damage [22].

The photosensitizer, visible light, and oxygen are the three non-toxic vital components of the photodynamic reaction [11,12,19,23]. To prompt PDT, the photosensitizer is administered and, in principle, accumulates mainly in the target tissues. Irradiation with a specific wavelength and energy light source activates the molecule, leading to a photophysical and photochemical process, producing reactive oxygen species (ROS) [24,25]. When the photosensitizer is activated, it passes to an excited state. In this higher energy state, two types of photodynamic reactions occur. In the type 1 reaction, the photosensitizer interacts with biomolecules forming radicals and other ROS. In the type 2 reaction, energy is transferred to oxygen, forming singlet oxygen [10,12,26]. This process is at the origin of the photodynamic reaction that can have several outcomes and is represented in Figure 1.

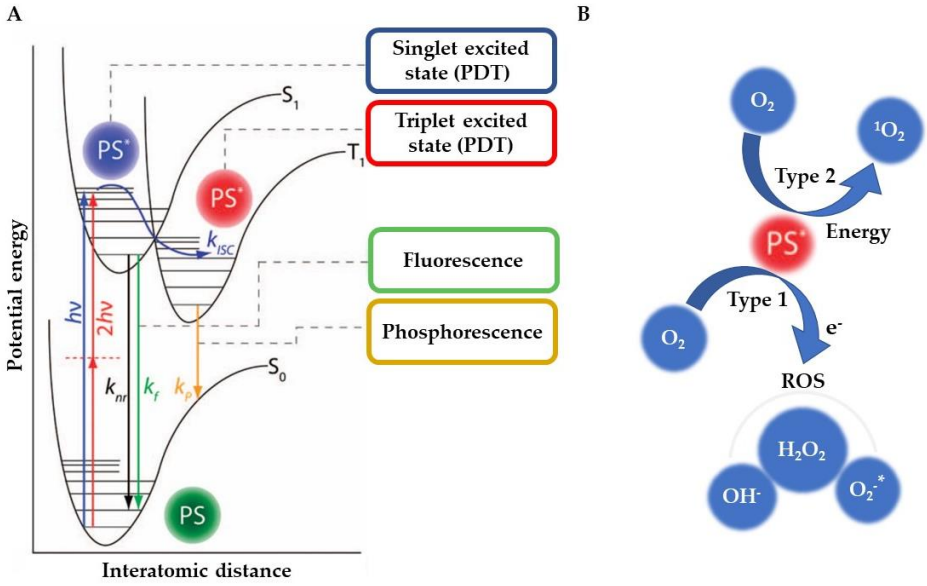

Figure 1. Perrin–Jablonski energy diagram for a photosensitizer (PS). (**A**) The absorption of a photon (hν) leads to electronic excitation to singlet (S_1) or triplet (T_1) states. In the singlet state, the photosensitizer can react with neighboring molecules, or transition to the triplet excited state, T_1, by intersystem crossing (ISC), or relax, S_0, with energy dissipation (nr). (**B**) Type 1 and 2 reactions. The triplet state is the longest-lived state; hence it mediates the biological and photochemical reactions that lead to the production of radical species through the transfer of electrons to oxygen or other electron-accepting cell substrates, type 1 reaction, or the transfer of energy for oxygen molecules with formation of singlet oxygen ($^1O_2$), type 2 reaction. The $^1O_2$-mediated photodynamic mechanism is the most important for PDT-induced cytotoxicity.

The production of high ROS amounts exerts the therapeutic effect on the neoplasm. Irreversible oxidation leads to cancer cell death that can involve apoptosis, necrosis, and autophagy [24–28]. Moreover, the tumor microenvironment can also be altered due to vascular and inflammatory responses. PDT can induce endothelial cell damage and occlusion of tumor vessels, limiting the nutrient supply and causing ischemia, an additional mechanism to favor cancer cell death [24–26]. PDT also promotes several pro-inflammatory cytokines, such as interleukins and tumor necrosis factor α (TNF-α), and adhesion molecules, such

as E-selectin and intercellular adhesion molecule 1 (ICAM-1) [25,29,30]. The involvement of immune modulators points to the possible activation of immunity. In theory, PDT mediators can destroy neoplasm tissue and contribute to eliminating cancer cells in the body by activating the immune system, potentially preventing possible recurrences or metastases [24,31].

Several factors can influence the treatment outcome, including neoplasms dimensions, location, tumor biology, tissue oxygenation, and dosimetry [32]. Indeed, the photosensitizer is considered the most important factor [11,13]. Thus, several authors revised an ideal photosensitizer's characteristics [19,24,25,33–35]. The photosensitizer should be a chemically pure compound, have absorbance spectra compatible with photoactivation within the 600–800 nm therapeutic window, be non-toxic in the absence of light, offer high singlet oxygen yield, be preferentially accumulated in the tumor, and be rapidly excreted [24,25,35,36]. Additionally, the formulation must allow a safe administration and be versatile to allow oral, topical, or parenteral administration [37].

The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved PDT to treat neoplasms and non-malignant diseases associated with several medical specialties, including dermatology, ophthalmology, urology, and pneumology [32,38–40]. In veterinary medicine, several trials were performed, frequently with encouraging outcomes. Still, no specific approval or recommendation for PDT exists. PDT is a little-known treatment modality in veterinary oncology; however, it is indicated for feline squamous cell carcinoma [41]. Nevertheless, other neoplasms could be treatable with PDT. This review aims to outline the applications of PDT in the scope of veterinary medicine, from clinical applications to the most recent developments applied to dogs and cats.

2. Photosensitizers

Most photosensitizers are based on the tetrapyrrole structure, presenting unique photodynamic and photodiagnostic abilities [10,11]. Other common photosensitizers present the chemical structure of phenothiazine dyes (like toluidine and methylene blue), cyanines, and polycyclic aromatic compounds (like hypericin) [11].

Among tetrapyrroles, porfimer sodium (Photofrin) was the first photosensitizer used in clinical practice. From the synthetic point of view, it allows modifications and structural changes in peripheral pyrrolic positions that can lead to new macrocycles [42]. However, its outcome is limited by the low absorption coefficient at 630 nm, the need for high fluence (100 to 200 J/cm^2), long exposures, low solubility in polar solvents, and intravenous administration [10,19,42,43]. High persistence in some tissues is associated with prolonged patient photosensitivity [44–46]. Porfimer sodium and other hematoporphyrins constituted the first generation of photosensitizers.

The second generation includes photosensitizers like hypericin and benzoporphyrin derivatives and other porphyrins, chlorins, bacteriochlorins, and phthalocyanines. These are more optimized molecules with higher purity, higher absorption in the therapeutic window (600–800 nm, Figure 2B), and higher ROS yields [10]. Temoporfin (meta-tetra(hydroxyphenyl)chlorine, mTHPC) was introduced in the European Union in 2001 under the name Foscan as a palliative or local treatment for patients with advanced head and neck cancer who did not respond to previous therapies and who were not indicated for chemotherapy or radiotherapy [47]. With an absorption band at a deeper penetrating wavelength (652 nm) and a high singlet oxygen yield, it was considered 100 times more effective than first-generation photosensitizers [48]. Despite the advantages from a photochemical point of view, there were weaknesses associated with its clinical application. Excessive lighting can result in fibrosis, scarring, and fistulas, and it can take up to six weeks to be eliminated [33,49].

The benzoporphyrin derivative monoacid ring A (BPD-MA, Verteporfin, Visudyne), initially developed to treat macular degeneration, presents advantages in cancer treatment. It has absorption at 690 nm and is quickly eliminated, avoiding cutaneous photosensiti-

zation [50]. The mono-L-aspartyl chlorin e6 (NPe6, Talaporfin sodium, Laserphyrin) is water-soluble, has an absorption band at 664 nm, and has a high singlet oxygen yield. Despite a low accumulation period in neoplastic tissue, patients may experience prolonged skin photosensitivity [33,51]. This photosensitizer is approved in Japan to treat superficial squamous cell carcinoma of the lung [33,51–53].

As a precursor of protoporphyrin IX, 5-ALA (5-aminolevulinic acid) is a pro-drug metabolized through the heme pathway. Protoporphyrin IX activation wavelength is at 630 nm. The rapid clearance within 12 h results in a short photosensitivity period [10]. 5-ALA was frequently administered topically to treat actinic keratosis, basaliomas, and cutaneous T-cell lymphomas [54–57]. Still, due to hydrophilic characteristics, 5-ALA's ability to penetrate the skin is limited [10]. Methyl and benzyl esters of 5-ALA overcome this limitation [58,59], being used to treat actinic keratosis and basaliomas and photodiagnosis of bladder neoplasms [10,60].

BODIPYs are highly photoactive agents that arose as potentially interesting photosensitizers and also for cancer theragnostics [61]. In addition to their high fluorescence potentially enabling image-guided PDT, they also demonstrated high ROS generation ability [62,63].

The accumulations of first- and second-generation photosensitizers can reach 5:1 in neoplastic tissues compared to normal tissues [64]. Nevertheless, the mechanisms behind this effect are still questionable [10]. Enhanced permeability and retention due to leaky tumor neovascularization are associated with an absence of lymphatic drainage, an increase in low-density lipoproteins receptors, phagocytosis by tumor-associated macrophages, and a lower pH contributes to photosensitizer ionization and retention seem to explain higher accumulation in tumors [25,65,66].

Still, the need to improve PDT by increasing the uptake by tumor cells led to a series of developments named third-generation photosensitizers. This includes biologic conjugates such as carriers, antibodies, or liposomes to improve delivery, selectivity, and pharmacokinetics [66]. Nanoparticles, including polymeric nanoparticles, micelles, and metallic nanoparticles, are another promising delivery vehicle [67].

Another exciting application of photosensitizers is photodynamic diagnosis. The photodiagnosis uses the fluorescence of photosensitizers to identify neoplasms in situ [10,68–70]. A lower wavelength promotes fluorescence when photosensitizers are used in photodiagnosis [71]. This application has particular relevance in glioma microsurgery and bladder surgery, where 5-ALA analogues are used to identify the tumor tissue [72,73]. The ambition of associating diagnosis with therapy in a single procedure led to the development of several molecules with theragnostic capabilities [61–63,74,75]. Photosensitizers with theragnostic properties constitute a dynamic area of research [76,77].

3. PDT in Veterinary Oncology

Until now, several photosensitizers have been applied in veterinary oncology, including porfimer sodium [78–82], phthalocyanines [83,84], and 5-ALA [85–87], among others. The use of third-generation approaches was also reported [18]. Besides treatment, 5-ALA was also used for the photodynamic detection of tumors [68,71]. The main chemical structures of photosensitizers used to treat veterinary neoplasms are presented in Figure 3.

Photosensitizers can be administered by various routes. Systemic [81,82] and oral [82] administrations are common in dogs and cats. Nonetheless, topical administration might have the advantage of avoiding generalized photosensitization. Other administration routes, such as intralesional, were reported less frequently [9]. It should be considered that the administration route can affect the photosensitizer biodistribution, influencing the action at the target tissue [88–90].

The chemical features and concentration of the photosensitizer, light dosimetry and target tissue may influence side effects [91]. However, severe adverse effects were rarely observed, even with systemic administration [89,92,93]. The most commonly reported side effects were itching and local discomfort when PDT was performed topically [91]. When

PDT was performed systemically, there were reports of sneezing, oedema, alopecia, emesis, thrombocytopenia, anorexia, elevated body temperature during treatment, and prolonged photosensitization [9,94–96].

Light sources are also a relevant component of PDT. Red or near-infrared light sources are preferred due to longer wavelengths, higher tissue penetration, and appropriate energy (Figure 2A). Thus, wavelengths between 600 and 1200 nm are considered the optical window for PDT [97]. The primary light sources include lasers, light-emitting diodes (LEDs), and lamps [33]. Lasers and light-emitting diodes are the most commonly used [9,10]. Nevertheless, some reports suggest that sunlight has the potential for superficial skin cancer therapy in animals [10]. The light source selection depends on the photosensitizer to be used and the location and characteristics of the tumor tissue to be treated [32,71]. Light for superficial neoplasms (superficial PDT) involves treatments with low penetration depth (e.g., skin, typically <2 mm, with the use of lasers, LEDs, and broadband lamps). Light sources for interstitial PDT can treat tumors beyond 1 cm, assisted by using needles, catheters, and optical fibers, but conventional light sources have light penetration similar to superficial PDT. For deep PDT, light sources being developed include a wide variety of technologies, including multifunctional nanoparticles (near-infrared light-excited nanomaterials, X-ray/Cherenkov excited scintillating/afterglow nanoparticles, and self-illuminated nanoconjugates) [22].

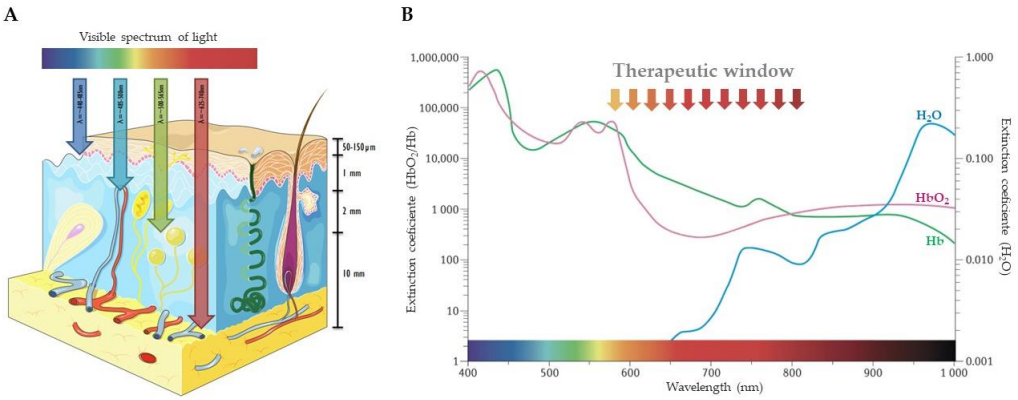

Figure 2. Light penetration into tissues. (**A**) The scheme represents a section of the epidermis-dermis. The arrows represent the depth of light penetration considering different wavelengths. Adapted from Laranjo, 2014 [98]. (**B**) Therapeutic window in the visible spectrum and extinction coefficient of water (H_2O), hemoglobin (Hb), and oxyhemoglobin (HbO_2). Adapted with permission from Kobayashi et al., 2010 [99]. Copyright 2010 American Chemical Society.

Veterinary biosafety regarding PDT comprises measures the professional, animal species, and waste disposal [9]. Animals are always subjected to sedation and/or an aesthesia; in some patients, antibiotic therapy is also provided [64,100]. Treated areas must be protected with bandages [9], and the post-treatment use of the Elizabethan collar may be essential to avoid licking and local mutilation [9].

Personal protective equipment must include appropriate clothing, gloves, masks, and glasses to protect from light sources [9]. Photosensitizers should be protected from light and handled with sterile syringes for safe practice [7]. The placement of a protective physical barrier on the areas not receiving treatment is also recommended (e.g., gauze bandage or similar). All equipment and cables associated with the light source must be cleaned and disinfected before and after treatment [9].

PDT was investigated in various neoplasms in veterinary medicine [9,10] despite not being actively used in clinical practice, as presented in Figure 4. Several of these studies point to PDT's potential to be used in veterinary oncology. Clinical studies will be detailed in the following sections per type of cancer, focusing on photosensitizers, treatment protocols, and main outcomes.

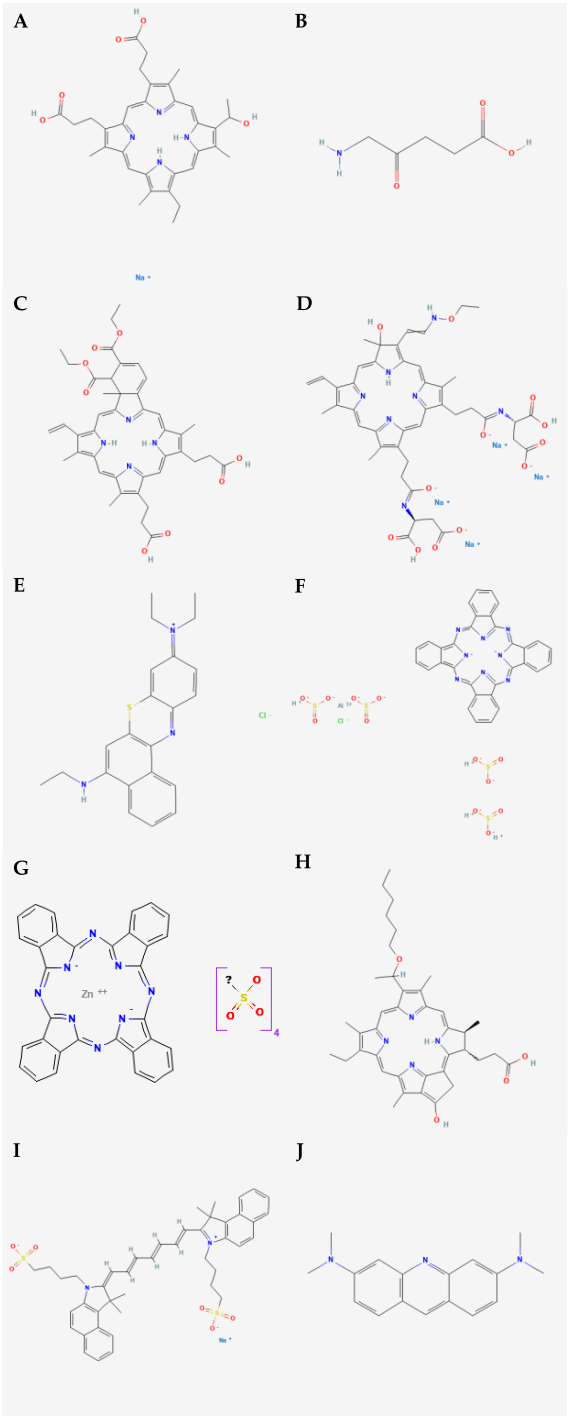

Figure 3. The main chemical structures of photosensitizers used in veterinary neoplasms. Structures retrieved from PubChem Compound. (**A**) Chemical structure of hematoporphyrin ether (CID 3086257). The molecule depicted constitutes the purified component of the hematoporphyrin derivative, a mixture of oligomeric porphyrins. (**B**) 5-aminolevulinic acid, 5-ALA (CID 137). (**C**) Benzoporphyrin derivative monoacid ring A, BDP-MA (CID 9896625). (**D**) 13,17-bis (1-carboxypropion) car-bam-oylethyl-3-ethenyl-8-ethoxyiminoethylidene-7-hydroxy-2,7,12,18-tetramethyl-porphyrin sodium, PAD-S31 (CID 136700393). (**E**) 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride, EtNBS (CID 131995). (**F**) Chloro-aluminum sulfonated phthalocyanine, CASPc (CID 156614097). (**G**) Zinc phthalocyanine tetrasulfonate, $ZnPcS_4$ (CID 135106689). (**H**) pyropheophorbide-a-hexyl ether, HPPH (CID 148160). (**I**) Indocyanine Green, ICG (CID 5282412). (**J**) Acridine Orange, AO (CID 62344).

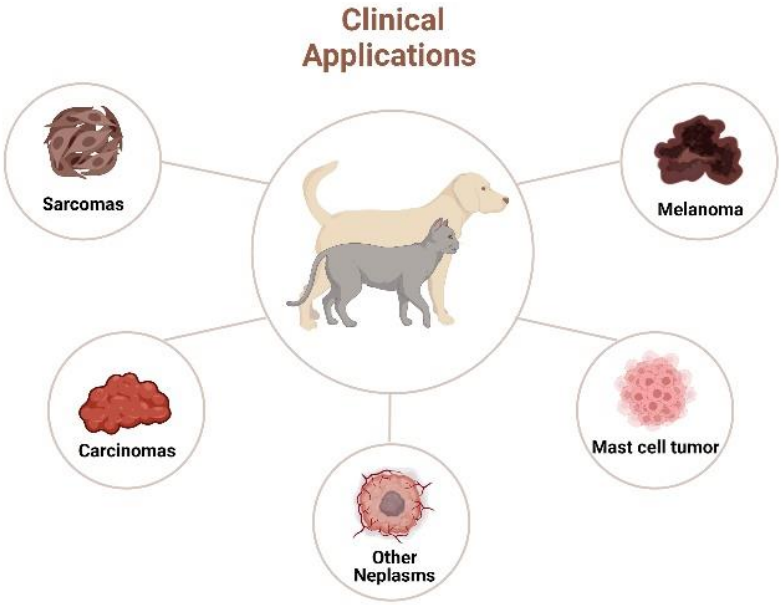

Figure 4. Clinical applications of PDT in veterinary medicine. Created with Biorender.com.

3.1. Carcinomas

Carcinomas are malignant tumors of epithelial and glandular origin arising in several organs, including the skin, breast, stomach, and prostate.

Several clinical trials in dogs and cats evaluated the outcomes of PDT in the treatment of squamous cell carcinoma [18,44,71,93]. Hematoporphyrin derivative (HPD) was administered intravenously to 12 cats diagnosed with cutaneous squamous cell carcinoma. The cats that presented small non-infiltrating lesions showed partial and complete responses. However, several side effects were seen, including local oedema, redness, itching, erythema, photosensitization, and alopecia [44]. In a trial including five dog patients with neoplasms of different origins, HPD was activated by a 631 nm argon laser. A total response of 67% was observed at two and nine months [101]. A similar approach was performed to treat a dog with nose squamous cell carcinoma, a dog with adenocarcinoma of the oral cavity, and a dog with gastric mucosa squamous cell carcinoma. The patients presented a complete response at 12 months, a complete response at six months, and a partial response (60/40% reduction), respectively [79].

A dog with esophageal carcinoma was treated with three PDT sessions. Porfimer sodium at 2.7 mg/kg was administered intravenously, 200 J/cm^3 were used in the first session, and 250 J/cm^3 were used in the following sessions. The patient presented progressive anorexia, weight loss, and other signs, being euthanized 278 days after the first treatment [102]. Porfimer sodium-based PDT was performed via electromagnetic navigational bronchoscopy to treat three dogs with lung carcinomas [82]. The treatment was successful, and the side effects were tolerable and manageable. One week after PDT, the involved lung lobes were surgically excised and evaluated histologically, showing necrosis, inflammatory cells, and arterial thrombosis in the PDT-treated tumors [82].

5-ALA at a concentration of 20% was used topically in 11 cats with superficial squamous cell carcinoma, namely ten nasal planum lesions, two pineal lesions, and one eyelid lesion [86]. In the following study, 5-ALA-based PDT treated 55 cats with superficial nasal planum squamous cell carcinomas [85]. PDT was well-tolerated and effective. A high complete response rate was obtained, with some cases showing partial response and recurrences [85,86]. In the cohort of 55 animals, 96% responded to therapy, and 85% showed a complete response [85]. Six dogs diagnosed with transitional cell carcinoma of the lower urinary tract were treated with 5-ALA, resulting in neoplasm-free intervals of 4 to 34 weeks in five dogs [95]. More recently, 5-ALA (40 mg/kg)-based PDT was performed using a diode laser or LED in four dogs diagnosed with transitional cell carcinoma or adenocarci-

noma and one cat with sebaceous gland carcinoma. One of the dogs with adenocarcinoma showed a complete local response; however, the progression of the disease was observed. The other patients showed partial response [71]. A dog diagnosed with transitional cell carcinoma of the prostate was submitted to a 5-ALA-based PDT. During the 24 weeks of follow-up after PDT, the disease proved stable with no relevant changes in the animal's health status. However, 34 weeks after treatment, the dog presented an abrupt increase in hematuria, urinary incontinence, and tenesmus. The canine evaluation showed an increase in the tumor size, despite the absence of pulmonary metastases. At week 35, the dog was euthanized for reasons unrelated to the treatment performed [103]. Six dogs diagnosed with prostate carcinoma were treated with 5-ALA-based PDT. The administration was performed into the prostate by injection into the periurethral and subcapsular prostatic tissue. The disease progressed locally, causing urethral strangulation signs and distant metastases. The survival time ranged from 10 to 68 days, negatively compared with other treatment approaches [104].

BPD-MA (Verteporfin, 0.5 mg/kg) and diode laser (690 nm) were used to treat four dogs with squamous cell carcinoma, which originated in the nasal planum (two cases), rostral mandible, and nasal cavity. A few days after treatment, necrosis was observed in the tumor site. It was suggested that a protocol with a shorter drug-light interval could be an interesting option to target tumor vasculature [105]. The same author later published the effectiveness of the antivascular PDT based on the same compound (BPD-MA, 0.5 mg/kg) and the use of a 690 nm diode laser. Despite tumor recurrence, the treatment was a promising method for treating dogs' squamous cell carcinoma and adenocarcinoma (oral and nasal) [106].

The l3,17-bis [1-carboxypropionyl] carbamoylethyl-3-ethenyl-8 ethoxyiminoethylidene-7-hydroxy-2,7,12,18-tetramethyl porphyrin sodium (PAD-S31) was used in a cat with a basal cell carcinoma. PAD-S31 was administered intravenously and irradiated with an argon laser (670 nm, 150 J/cm^2). Three sessions of the PDT were performed, and no lesion recurrence was reported [107].

After radiotherapy's tumor recurrence, three dogs affected by intranasal carcinoma were treated with talaporfin sodium. In this report, PDT induced almost complete remission and prolonged survival time, suggesting that it is a functional therapeutic approach for recurrent intranasal carcinomas [108].

The use of 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride (EtNBS) was considered safe for dogs and cats. Two feline sublingual squamous cell carcinomas showed minor response; six feline facial squamous cell carcinomas showed partial response in two cases and complete long-term responses in four cases. A cat with eyelid squamous cell carcinoma presented a partial response to therapy. Two dogs with intraoral squamous cell carcinomas showed a case of minor response and another of complete long-term responses [96].

Two dogs and a cat diagnosed with intranasal adenocarcinomas were submitted to a PDT session. Overall, all animals presented facial swelling after PDT with pyropheophorbide-a-hexyl ether (HPPH) without the need for treatment and no photosensitizer-associated adverse effects. PDT decreased the frequency and severity of some clinical signs, such as epistaxis, sneezing, and nasal content release, demonstrating the ability to control the disease for some time [109]. HPPH-based PDT was performed in 51 cats with naturally occurring facial skin squamous cell carcinomas. Outcomes of one-year follow-up pointed to local control of 62% of the neoplasms and hematological and biochemical toxicity or clinical side effects [110]. HPPH-based PDT was investigated in four dogs. Three dogs had squamous cell carcinomas in the rostral mandibula, ventral abdominal skin, and footpad. The other dog had an apocrine gland adenocarcinoma of the skin of the muzzle. After PDT, eschar formation occurred. Two months later, the squamous cell carcinomas were considered complete responses. The dog with apocrine gland adenocarcinoma remained unchanged for 56 weeks after treatment. This study included three cats with squamous cell carcinoma, which showed complete responses for 60 days [111]. Eleven dogs diagnosed

with oral squamous cell carcinomas were treated with HPPH, intravenously injected at a 0.3 mg/kg dose. Tumors were irradiated 48 h later at 665 nm with 100 J/cm^2. Eight dogs were considered cured without recurrence for 17 months. PDT outcome was comparable to surgical removal, but was superior regarding the aesthetic results [112].

Ten cats were diagnosed with carcinomas, with one of the animals presenting squamous cell carcinoma and carcinoma in situ. The patients were treated with chloro-aluminum sulfonated phthalocyanine (CASPc, 1 mg/kg) and irradiation of 50–150 J/cm^2 [113]. Tumors with more than 1.5 cm were surgically thinned before PDT. As the first three animals produced oedema, dexamethasone sodium phosphate was administered by intravenous infusion for approximately 10 min before laser irradiation of most animals. Two cats with a planum nasal lesion showed complete response, and one with a forehead lesion recurred. Therapeutic responses were variable, but no significant systemic toxicity or skin photosensitization were reported [113].

Squamous cell carcinoma lesions in 15 cats were followed up three months after CASPc-based PDT. 3/15 cats had no response, 2/15 cats had a partial response (50% reduction), 10/15 cats had a complete response, and 2/15 cats had a recurrence following a complete initial response [83]. CASPc activated by 100 and 200 J/cm^2 was used to determine whether an increase in fluency would improve the advanced squamous cell carcinoma remission period. Among ten cats, neoplasms subjected to 100 J/cm^2 had an inferior remission period, of 0 to 619 days free of neoplasms, compared to those treated with 200 J/cm^2, which had 151 to 1057 days of remission [114].

Zinc phthalocyanine tetrasulfonate ($ZnPcS_4$) was applied to six dogs with squamous cell carcinomas. Irradiation was performed with a diode laser at 100 J/cm^2. PDT was well-tolerated, with no toxicity signs and partial to complete tumor response [84].

A liposomal formulation of meta-(tetra hydroxyphenyl) chlorine (m-THPC) was investigated in 18 cats with cutaneous squamous cell carcinomas. While mild erythema was observed in 15% of patients, all patients responded completely. Nevertheless, the tumor recurrence rate was 20%, with an average recurrence time of 172.25 ($\pm$87.1) days [93]. The same formulation was administered to 38 cats affected by 63 tumors in the head and neck. Patients with invasive tumors progressed in up to six months. The overall response rate was 84% (complete remission in 61% and partial remission in 22%), with an average-free disease interval of 35 months and an average overall survival time of 40 months. Tumor location did not seem to influence response, but larger tumors were less responsive [18]. The liposomal and lipophilic formulation of mTHPC was investigated in felines with squamous cell carcinomas. The bioavailability in the tumor was 2 to 4 times higher with the liposomal formulation. All cats responded to therapy with both formulations [115]. The vascular effects of PDT in squamous cell carcinomas in cats were investigated with power Doppler ultrasonography. Liposomal and lipophilic mTHPC photosensitizers were administered intravenously and irradiated with a diode laser (652 nm). During PDT, a significant decrease in vascularity and blood volume was noted. The lowest values were found 24 h after PDT [116].

PDT with the photosensitizer acridine orange (AO) was used in a pilot study including five dogs with intranasal tumors, namely three adenocarcinomas, one transitional carcinoma, and one undifferentiated carcinoma [117]. Fourteen dogs with intranasal carcinomas were included in the continuity of the study. The photosensitizer was administered into the tumor bed through a five-minute placement of a gauze soaked in a solution (1 µg/mL). Irradiation took place with xenon light between 400 and 700 nm. The median progression-free and overall survival time after treatment were 13 and 22 months, respectively [118]. In the retrospective study, the effects of PDT associated with other therapies (surgery, chemotherapy, and radiotherapy) were evaluated in treating intranasal dog tumors. Overall results showed that 54% of dogs presented recurrence and a median interval of disease-free progression of 12 months after AO-PDT. Cases of recurrence were retreated. After re-AO-PDT, dogs presented an overall recurrence median of 27 months, while dogs submitted to hypofractionated radiotherapy presented a median of 14 months. Side effects were mild

and included subcutaneous emphysema and rhinitis [60]. PDT protocols used to treat carcinomas are presented in Table 1.

Table 1. Clinical studies on PDT in animals with carcinomas.

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[44]	SCC	12 Cats	**PS:** HPD, 1–5 mg/mg, iv **Light:** LED, 300 J/cm^2, 630 nm, 1 session	• Variable tumor responses (complete, partial and no response) • Tumors localized in the pinna and those highly invasive of the nose and nasal planum presented no response
[101]	SCC	4 Dogs	**PS:** HPD, 5 mg/kg, iv **Light:** Argon laser, 293–900 J/cm^2, 631 nm, 1–3 sessions	• 67% total response (at 2 and 9 months for different animals) • 33% recurrence
[101]	Circumanal gland carcinoma	1 Dog	**PS:** HPD, 5 mg/kg, iv **Light:** Argon laser, 144–400 J/cm^2, 631 nm, 1 session	• Cured in 5 months evaluation.
[79]	SCC	1 Dog	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 348 J/cm^2, 631 nm, 1 session	• Complete response at 12 months.
[79]	Adenocarcinoma, oral cavity	1 Dog	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 100 J/cm^2, 631 nm, 1 session	• Complete response at 6 months
[79]	SCC, gastric mucosa	1 Dog	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 240 J/cm^2, 631 nm, 1 session	• Partial response (40–60% reduction).
[102]	Esophageal SCC	1 Dog	**PS:** Porfimer sodium, 2.7 mg/kg, iv **Light:** Argon laser, 200–250 J/cm^3, 630 nm, 3 sessions	• Tumor size reduction • Patient returned to oral feeding • Nine months after treatment, marked local invasiveness and regional lymph node metastasis were seen
[82]	Lung carcinoma	3 Dogs	**PS:** Porfimer sodium, 2 mg/kg, oral **Light:** Diode laser, 200 J/cm, 630 nm, 1 session	• Tolerable and manageable side effects • 100% success rate • Tumors presented coagulative central necrosis, arterial thrombosis, and the presence of few inflammatory cells
[86]	SCC	11 Cats	**PS:** 5-ALA, cream 20%, topical **Light:** LED, 12 J/cm^2, 635 nm, 1 session	• 85% complete response rate with a single PDT treatment • Recurrence in 63.6% of cases • Recurrence occurred after 19 to 56 weeks
[85]	SCC	55 Cats	**PS:** 5-ALA, cream 20%, topical **Light:** LED, 12 J/cm^2, 635 nm, 1 session	• Temporary mild local adverse effects after treatment • 96% of animals responded to treatment (11% presented partial and 85% complete response) • Of those with complete response, recurrence occurred in 51% after a median time of 157 days • 22 cats received repeated PDT treatments, and after a median time of 1146 days, 45% were alive and disease free, and 33% had tumor recurrence

Table 1. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[95]	Transitional cell carcinoma	6 Dogs	**PS:** 5-ALA, 60 mg/kg, oral **Light:** Diode laser, 100 J/cm^{-2}, 635 nm, 1–3 sessions	• Disease-free period ranged from 4 to 34 weeks in five dogs • One dog died after treatment (pre-existing hydronephrosis)
[71]	Transitional cell carcinoma	2 Dogs	**PS:** 5-ALA, 40 mg/kg, oral **Light:** LED, 300 J/cm^2, 635 nm, 3 sessions; Diode laser, 270 J/cm^2, 630 nm, 15 sessions	• Partial response
[71]	Adenocarcinoma	2 Dogs	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 270 J/cm^2, 700 J/cm, 630 nm, 15–19 sessions	• Complete response and partial response
[71]	Sebaceous gland carcinoma	1 Cat	**PS:** 5-ALA, 40 mg/kg, oral **Light:** LED, 120 J/cm^2, 635 nm, 4 sessions	• Partial response
[103]	Transitional cell carcinoma of the prostate	1 Dog	**PS:** 5-ALA, 60 mg/kg **Light:** Diode laser, 100 J/cm^2, 75 mW/cm^2, 635 nm, 1 session	• Stable disease during 34 weeks after PDT
[104]	Prostate Carcinoma	6 Dogs	**PS:** 5-ALA, intratumoral **Light:** Halogen lamp, 75 J/cm^2, 570-670 nm, 1 session	• Median survival time of 41 days • Disease progression occurred both locally and in metastatic sites
[105]	SCC	4 Dogs	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 40–90 J/cm^2, 690 nm, 1 session	• PDT used as anti-angiogenic • Tumoral necrosis occurred after a few days • Granulation tissue formed in the surrounding tissues before healing
[106]	SCC	3 Dogs	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 80–600 J/cm^2, 690 nm, 1–2 sessions	• Oedema and fistula were observed as side effects • Tumor recurred, and metastasis were observed
[106]	Adenocarcinoma	3 Dogs	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 50–350 J/cm^2, 200–300 J/cm, 690 nm, 1–2 sessions	• Oedema and fistula were observed as side effects • Tumor remained and recurred
[107]	Basal cell carcinoma	1 Cat	**PS:** PAD-S31, 15 mg/kg, iv **Light:** Argon laser, 150 J/cm^2, 670 nm, 3 sessions	• A scab had formed over the irradiated tumor • The size of the mass decreased gradually until it completely disappeared
[108]	Intranasal carcinoma	3 Dogs	**PS:** Talaporfin sodium, 5.0 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 665 nm, 1–3 sessions	• Prolonged survival time in the three dogs • Almost complete remission
[96]	SCC	8 Cats	**PS:** EtNBS, 5 mg/kg, iv **Light:** Diode laser, 400–800 J/cm^2, 652 nm, 1–2 sessions	• Minimal systemic toxicity • Minor response in two sublingual SCCs • Four complete responses at long-term evaluation and two partial responses in six facial SCCs
[96]	SCC	2 Dogs	**PS:** EtNBS, 2.0–2.5 mg/kg, iv **Light:** Diode laser, 303–400 J/cm^2, 652 nm, 1–2 sessions	• One complete long-term response • One minor response (recurrence after two weeks)

Table 1. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[109]	Intranasal carcinoma	2 Dogs	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Potassium titanyl phosphate–pumped dye laser, 100 J/cm^2, 665 nm, 1 session	• No relevant side effects were observed • PDT showed a limited capacity to control intranasal malignancies
[109]	Intranasal carcinoma	1 Cat	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Potassium titanyl phosphate–pumped dye laser, 100 J/cm^2, 665 nm, 1 session	• No relevant side effects were observed • PDT showed a limited capacity to control intranasal malignancies
[110]	SCC (facial lesions)	51 Cats	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Argon laser, 100 J/cm^2, 665 nm, 1–3 sessions	• No systemic toxicity • Complete response in T1a tumors • Partial response in T1b (56%) and T2b (18%) tumors • 100% one-year local control rate for T1a and 53% for T1b tumors
[111]	SCC	3 Dogs	**PS:** HPPH, 0.15 mg/mg, iv **Light:** LED, 100 J/cm^2, 665 nm, 1 session	• Complete response in all tumors two months after treatment
[111]	Adenocarcinoma apocrine gland	1 Dog	**PS:** HPPH, 0.15 mg/mg, iv **Light:** LED, 100 J/cm^2, 665 nm, 1 session	• Remained unchanged after the eschar sloughed and was considered stable disease
[111]	SCC	3 Cats	**PS:** HPPH, 0.15 mg/mg, iv **Light:** LED, 100 J/cm^2, 665 nm, 1 session	• Complete response in all tumors two months after treatment. • Recurrence was seen in one cat (new lesion adjacent to the treated site)
[112]	Oral SCC	11 Dogs	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Argon laser, 100 J/cm^2, 665 nm, 1 session	• No recurrence was observed in eighth dogs at 17 months after treatment
[113]	SCC	8 Cats	**PS:** CASPc, 1 mg/kg, iv **Light:** Argon laser, 100–150 J/cm^2, 675 nm, 1–2 sessions	• No systemic toxicity • No skin photosensitization • Overall treatment response similar to surgery, hyperthermia, and cryotherapy
[113]	Carcinoma in situ	3 Cats	**PS:** CASPc, 1.0 mg/kg, iv **Light:** Argon laser, 100 J/cm^2, 675 nm, 1–2 sessions	• Complete response after the second PDT • Surgical debulk was made prior to PDT in deeper tumors
[83]	SCC	15 Cats	**PS:** CASPc, 1 mg/kg, iv **Light:** Argon laser, 50–150 J/cm^2, 675 nm, 1 session	• At three months post-treatment, 20% of cats presented no response, 7.5% partial response, and 67% complete therapeutic response • 7.5% presented tumor recurrence
[114]	Cutaneous SCC	10 Cats	**PS:** CASPc, 1.0 mg/kg, iv **Light:** Argon laser, 100–200 J/cm^2, 675 nm, 1 session	• A fluence of 100 J cm^{-2} induced a significantly shorter median remission period (69 days) than 200 J cm^{-2} (522 days)
[84]	SCC	6 Dogs	**PS:** $ZnPcS_4$, 1–4 mg/mg, iv **Light:** Diode laser, 100 J/cm^2, 675 $\pm$ 0.2 nm, 1 session	• 50% complete response • 33% partial response • 16% no response (disease progression)

Table 1. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[93]	SCC	18 Cats	**PS:** Liposomal mTHPC, 0.15 mg/mg, iv **Light:** Diode laser, 10 J/cm^2, 652 nm, 1 session	• 100% complete response rate • 75% overall control rate at 1-year • 20% tumor recurrence (median time to recurrence of 173 days)
[18]	SCC	38 Cats	**PS:** Liposomal mTHPC, 0.15 mg/mg, iv **Light:** Diode laser, 10–20 J/cm^2, 652 nm, 1 session	• 84% response rate (61% complete response and 22% partial response) • Mean disease-free period of 35 months • Median survival period of 40 months
[115]	SCC	10 Cats	**PS:** Liposomal and lipophilic mTHPC, 0.15 mg/mg, iv **Light:** Diode laser, 10 J/cm^2, 652 nm, 1 session	• No side effects, with all cats responding to PDT with both the liposomal and the lipophilic formulation
[116]	SCC	6 Cats	**PS:** Liposomal and lipophilic mTHPC, 0.15 mg/mg, iv **Light:** Diode laser, 10 J/cm^2, 652 nm, 1 session	• All animals well-tolerated the treatment • Complete or partial responses were observed
[117]	Adenocarcinoma	3 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Rhinitis was observed as a side effect • Tumors intact and destroyed were observed
[117]	Carcinoma transitional	1 Dogs	**PS:** AO, 1 µg/mL, tumor bed and 0.1 mg/kg, iv **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Subcutaneous emphysema and rhinitis were observed as a side effect • Tumor destruction was observed
[117]	Carcinoma undifferentiated	1 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Rhinitis was observed as a side effect • Tumor destruction was observed
[118]	Intranasal carcinoma	14 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Recurrence was detected in the median of 6 months • Adverse events were mild
[60]	Adenocarcinomas	14 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Destroyed tumors were observed in 13 dogs, and only one dog had the tumor intact
[60]	Transitional cell carcinomas	10 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Destroyed tumors were observed in nine dogs, and only one dog had the tumor intact
[60]	SCC	2 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Tumor destruction was observed
[60]	Adenosquamous carcinomas	2 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Tumor destruction was observed
[60]	Carcinoma	3 Dogs	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Tumors intact and destroyed were observed

Table 1. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[60]	Undifferentiated adenocarcinomas	1 Dog	**PS:** AO, 1 μg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Tumor destruction was observed
[60]	Undifferentiated carcinomas	1 Dog	**PS:** AO, 1 μg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 1 session	• Tumor destruction was observed

Legend: 5-ALA, 5-aminolevulinic acid; AO, acridine orange; BPD-MA, benzoporphyrin derivative monoacid ring A; CASPc, chloro-aluminum sulfonated phthalocyanine; EtNBS, 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride; HPD, hematoporphyrin derivative; HPPH, pyropheophorbide-a-hexyl ether; iv; intravenous; mTHPC, meta-(tetra hydroxyphenyl) chlorine; PAD-S31, l3,17-bis [1-carboxypropionyl] carbamoylethyl-3-ethenyl-8 ethoxyiminoethylidene-7-hydroxy-2,7,12,18-tetramethyl porphyrin sodium; PS, photosensitizer; SCC, squamous cell carcinoma. $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

3.2. Mastocytomas

The proliferation of neoplastic mast cells characterizes mast cell tumors, frequently affecting the skin and, more rarely, systemic organs.

A cat with lip mastocytoma was submitted to HPD-based PDT. After the first treatment, complete tumor response was seen in ten days, plus total re-epithelialization within 15–25 days. There was a recurrence in 5 months. A second treatment was performed, and relapse occurred two months later [101]. The same study submitted a dog with a lip mastocytoma to PDT after surgical excision. The animal was considered disease-free for a period of six months [101].

A dog with a cutaneous mast cell tumor was orally given 5-ALA (40 mg/kg). Irradiation was performed with LED light (60 J/cm^2). The complete response was reported, and the disease was considered stable [71].

The PAD-S31 was used in two dogs with cutaneous mast cell tumors. The site of irradiation showed slight depigmentation immediately after laser irradiation. Two days after treatment, a scar progressively formed over its surface but decreased in size to 50% by the seventh to the tenth day. Local recurrence of tumors receiving PDT was not observed during the sixth and seventh months of follow-up [107].

The photosensitizer EtNBS was administered intravenously (2.0 mg/kg) in two dogs with eye neoplasms: a subconjunctival mast cell tumor and an eyelid mast cell tumor. PDT was completed with 100 and 400 J/cm^2, respectively. The dog with a subconjunctival mast cell tumor briefly responded to therapy. The dog with eyelid mast cell tumor showed a complete response but initiated chemotherapy for two cutaneous mast cell tumors at other sites for four months; thus, PDT efficacy was difficult to ascertain [96].

A dog affected on the skin's right flank, subcutaneous cervical, and submandibular region was submitted to CASPc-based PDT. The right flank tumor was surgically reduced before PDT, remaining a lesion with less than 1 cm. Complete response was reported in all injuries [113].

A phase I clinical trial with a mast cell tumor in the gingiva showed a partial response after $ZnPcS_4$ (4 mg/kg)-based PDT [84]. PDT protocols used to treat mastocytomas are presented in Table 2.

3.3. Sarcomas

Sarcomas can affect muscle, bones, cartilage, and other tissues of mesodermal origin. Two dogs with sarcomas (a lip reticulum cell sarcoma and a gingival fibrosarcoma) were submitted to HPD-based PDT. The patient with reticulum cell sarcoma underwent two treatments with PDT; recurrence occurred two months after the first treatment and five months after the second treatment. The dog with fibrosarcoma was free of disease during the nine-month follow-up [101].

Table 2. Clinical studies on PDT in animals with mastocytomas.

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[101]	Mastocytoma (Lips)	1 Cat	**PS:** HPD, 5.0 mg/kg, iv **Light:** Argon laser, 324 J/cm^2, 631 nm, 2 sessions	• Recurrence at five months after the first treatment • Recurrence at two months after the second treatment
[101]	Mastocytoma (Lips)	1 Dog	**PS:** HPD, 5.0 mg/kg, iv **Light:** Argon laser, 103 J/cm^2, 631 nm, 1 session	• Cured at the six months follow-up
[71]	Mast cell tumor	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** LED, 60 J/cm^2, 635 nm, 1 session	• Complete response and stable disease
[107]	Mast cell tumor	2 Dogs	**PS:** PAD-S31, 15 mg/kg, iv **Light:** Argon laser, 150 J/cm^2, 670 nm, 1 session	• Slight depigmentation immediately after irradiation • No recurrence was observed during the sixth and seventh months of follow-up
[96]	Mast cell tumor	2 Dogs	**PS:** EtNBS, 2.0 mg/kg, iv **Light:** Diode laser, 100–400 J/cm^2, 652 nm, 1–2 sessions	• Brief and complete response
[113]	Mast cell tumor	1 Dog	**PS:** CASPc, 1.0 mg/kg, iv **Light:** Argon laser, 50–100 J/cm^2, 675 nm, 1 session	• Complete response
[84]	Mast cell tumor	1 Dog	**PS:** $ZnPcS_4$, 4.0 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 ± 0.2 nm, 1 session	• Partial response

Legend: 5-ALA, 5-aminolevulinic acid; CASPc, chloro-aluminum sulfonated phthalocyanine; EtNBS, 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride; iv; intravenous; HPD, hematoporphyrin derivative; PAD-S31, l3,17-bis [1-carboxypropionyl] carbamoylethyl-3-ethenyl-8 ethoxyiminoethylidene-7-hydroxy-2,7,12,18-tetramethyl porphyrin sodium; PS, photosensitizer; $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

Three dogs diagnosed with histiocytoma, chondrosarcoma, hemangiopericytoma, and a cat with fibrosarcoma were submitted to 5-ALA-based PDT. The photosensitizer was administered at a 40 mg/kg dose 4 h before diode laser or LED irradiation. The light fluences varied, being 240 J/cm^2 for histiocytoma, 800 J/cm^2 for chondrosarcoma, 200 J/cm^2 for hemangiopericytoma, and 270 J/cm^2 for fibrosarcoma. The cat further underwent surgical treatment and had stable disease. The dog with hemangiopericytoma showed a partial response and underwent surgical extraction. The dog with histiocytoma had a complete response, and the dog with chondrosarcoma died of progressed disease [71].

The efficacy of a single treatment of BPD-MA-based PDT was evaluated as a therapeutic option for primary osteosarcoma in dogs. Thus, seven dogs were intravenously injected with BPD-MA, being later irradiated with laser light at a fluence of 500 J and a 200 mW/cm rate. Forty-eight hours after PDT, magnetic resonance imaging (MRI) showed that PDT induced hemorrhagic necrosis in all tumors without evidence of adverse effects [119]. Seven dogs affected with osteosarcoma underwent a pilot study with BPD-MA-based PDT to investigate PDT's ability to induce necrosis in large osseous tumors. The photosensitizer was administered intravenously and activated with a total light dose of 500 J/cm. The animals were submitted to amputation 48 h after therapy. PDT induced necrosis in all osteosarcomas treated [120]. Three dogs with fibrosarcoma and one with osteosarcoma underwent PDT with BPD-MA. Tumor color changes and tumor necrosis were observed [105]. Aiming for antivascular PDT, oral (four fibrosarcomas, one osteosarcoma, one sarcoma) and nasal (one fibrosarcoma) sarcomas were treated with BPD-MA-based PDT. The 1-year overall survival was 71% and 57% for dogs with oral and nasal tumors, respectively [106].

HPPH-based PDT was used as adjuvant therapy in 16 dogs with hemangiopericytoma. Most of the 16 animals treated have recurred (56%) [121]. PDT with HPPH was performed in a dog with intranasal chondrosarcoma. The right and left nasal passages were treated with PDT. A second PDT treatment was performed; however, the dog was euthanized two weeks later because of progressive disease [109].

CASPc-based PDT was administered to three dogs with fibrosarcoma and four with hemangiopericytoma. Of the three animals with fibrosarcoma, one had no response, one had recurrence after nine months, and the other had regional metastasis in 15 months and a relapse after 18 months of treatment [83]. In the case of the hemangiopericytoma patients, the masses were surgically excised, and PDT was performed seven days later. An average remission period of 9 to 21 months (mean of 15.25) was observed [83]. The same approach was performed on a dog with undifferentiated sarcoma in the abdominal wall after surgical and adjuvant treatment failure. However, the patient was lost due to metastatic disease [113].

PDT using $ZnPcS_4$ was performed on a dog with malignant fibrous histiocytoma in the elbow, a dog with spindle cell sarcoma in the carpus and a dog with intranasal undifferentiated sarcoma. The two animals with lesions in the elbow and carpus partially responded to therapy. However, the patient with intranasal sarcoma showed a complete response [84].

Using an aluminum-chloride-phthalocyanine nanoemulsion (AlClPc-nano) administered intra and peritumorally, PDT was performed in eight dogs with cutaneous hemangiosarcomas. Two to four PDT sessions were repeated every seven days. Seven of the eight cases showed complete remission of neoplasia. Microscopic analysis of the excisional biopsies showed necrosis and hemorrhage, with no cancer cells, except in one case. Inflammation and necrosis were macroscopically observed in the treated areas [37].

Ten dogs and six cats with malignant soft tissue sarcoma were submitted to a combined therapeutic approach. The treatment consisted of surgical resection followed by hyperthermia and PDT based on indocyanine green (ICG), irradiation with broadband light, and chemotherapy. No severe side effects were reported. Seven dogs and three cats did not show recurrence [122].

A combination of photodynamic surgery (PDS) and PDT using AO was explored as a new approach to avoid feline injection-site sarcoma (FISS) recurrence. In this study, thirty-seven cats with FISS were included. PDT was performed on seven cats, with AO administration to the surgical field, then irradiated with visible light for 10 min. Findings revealed that, at the last follow-up, five of seven PDS-PDT-treated cats did not present relapse and/or metastatic disease. This combined therapy was associated with a higher disease-free survival rate than PDS-treated cats. Two PDS-PDT-treated cats were euthanized during the follow-up due to other treatment-non-related health problems. Nevertheless, none of these animals showed recurrence at the time of death. These results suggested that PDT can be an effective adjuvant therapeutic modality to prevent FISS recurrence [123].

To determine the photodynamic threshold, soft tissue optical properties were estimated. The threshold dose for three photosensitizers (porfimer sodium, AlClPc, and SnET2) was evaluated in dogs with spontaneous tumors. AlClPc presented the highest threshold, thus needing more photon absorption than porfimer sodium and SnET2 [124]. PDT protocols used to treat sarcomas are presented in Table 3.

3.4. Melanomas

Melanomas originate from melanocytes or other neoplastic cells that develop from melanocytes or melanoblasts [15]. In dogs and cats, primary melanomas can occur in the oral cavity, nailbed, footpad, nasal cavity, anal sac, mucocutaneous junction, or in the eyes [41].

HPD was given to a dog with melanoma of the hard palate by intravenous injection (2.5 mg/kg). A significant reduction of over 60% was achieved after the second session. Irradiation was performed with an argon laser at 528–960 J/cm^2 (631 nm) [79].

Table 3. Clinical studies on PDT in animals with sarcomas.

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[101]	Reticulum cell sarcoma	1 Dog	**PS:** HPD, 5 mg/kg, iv **Light:** Argon laser, 120/585 J/cm^2, 631 nm, 1 session	• Recurrence at two months after the first treatment • Recurrence at five months after the second treatment
[101]	Fibrosarcoma	1 Dog	**PS:** HPD, 0.5 mg/kg, iv **Light:** Argon laser, 300 J/cm^2, 631 nm, 1 session	• Cured at the nine months evaluation
[71]	Histiocytoma	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** LED, 240 J/cm^2, 635 nm, 5 sessions	• Complete response
[71]	Chondrosarcoma	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 800 J/cm, 630 nm, 16 sessions	• Died (disease progression)
[71]	Hemangiopericytoma	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 200 J/cm, 630 nm, 11 sessions	• Partial response, underwent surgical extraction
[71]	Fibrosarcoma	1 Cat	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 270 J/cm^2, 630 nm, 5 sessions	• Stable disease, underwent surgical extraction
[119]	Osteosarcoma	7 Dogs	**PS:** BPD-MA, 0.4 mg/kg, iv **Light:** 690 $\pm$ 5 nm, 500 J, 1 session	• A single PDT treatment promoted tumor cell death, namely hemorrhagic necrosis, without collateral effects in animals
[120]	Osteosarcoma	7 Dogs	**PS:** BPD-MA, 0.4 mg/kg, iv **Light:** Diode laser, 500 J/cm, 690 nm, 1 session	• Tumor necrosis was observed in histological examination
[105]	Fibrosarcoma	3 Dog	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 525 J/cm, 600–1275 J/cm^2, 690 nm, 1 session	• PDT used as anti-angiogenic • Tumoral necrosis occurred after a few days • Granulation tissue formed in the surrounding tissues before healing
[105]	Osteosarcoma	1 Dog	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 800 J/cm^2, 690 nm, 1 session	• PDT used as anti-angiogenic • Tumoral necrosis occurred after a few days • Granulation tissue formed in the surrounding tissues before healing
[106]	Fibrosarcoma	5 Dogs	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 300–600 J/cm^2, 450–525 J/cm, 690 nm, 1–2 sessions	• Different responses have been reported, including tumor-free, recurrence, and metastases. • Oedema and alopecia have been reported as a side effect
[106]	Osteosarcoma	1 Dog	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 150–950 J/cm^2, 690 nm, 5 sessions	• Tumor remained
[106]	Sarcoma	1 Dog	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 800 J/cm^2, 690 nm, 1 session	• The patient was alive in the last follow-up

Table 3. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[121]	Hemangiopericytoma	16 Dogs	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Argon laser dye, 100 J/cm^2, 665 nm, 1 session	• Recurrence occurred in 56% of dogs (2 to 29 months after treatment) • Results are comparable or inferior to other forms of treatment
[109]	Chondrosarcoma	1 Dog	**PS:** HPPH, 0.3 mg/kg, iv **Light:** Potassium titanyl phosphate–pumped dye laser, 100 J/cm^2, 665 nm, 2 sessions	• No relevant side effects were observed • PDT showed a limited capacity to control intranasal malignancies
[83]	Fibrosarcoma	3 Dogs	**PS:** CASPc, 1 mg/kg, iv **Light:** Argon laser, 50–150 J/cm^2, 675 nm, 1 session	• 33% no response • 33% recurrence after nine months • 33% entered remission, but regional metastasis occurred after 15 months and in the original site after 18 months
[83]	Hemangiopericytoma	4 Dogs	**PS:** CASPc, 1 mg/kg, iv **Light:** Argon laser, 50–150 J/cm^2, 675 nm, 1 session	• Remission in all dog evaluation times from 9 to 21 months)
[113]	Sarcoma	1 Dog	**PS:** CASPc, 1 mg/kg, iv **Light:** Argon laser, 100 J/cm^2, 675 nm, 1 session	• Died or killed because of metastatic disease • No evidence of tumor at necropsy
[84]	Histiocytoma	1 Dog	**PS:** $ZnPcS_4$, 0.5 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 $\pm$ 0.2 nm, 1 session	• Partial response
[84]	Spindle cell Sarcoma	1 Dog	**PS:** $ZnPcS_4$, 2 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 $\pm$ 0.2 nm, 1 session	• Partial response
[84]	Undifferentiated Sarcoma	1 Dog	**PS:** $ZnPcS_4$, 4.0 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 $\pm$ 0.2 nm, 1 session	• Complete response
[37]	Hemangiosarcoma	8 Dogs	**PS:** AlClPc-nano, 13.3 µM, intra/peritumoral **Light:** LED, 120 J/cm^2, 658–662 nm, 1–4 sessions	• 88% complete remission • Necrosis and hemorrhage were observed in the histological evaluation, but without cancer cells (except for one case) • Inflammation and necrosis were observed during the treatment
[122]	Malignant soft tissue sarcoma	10 Dog	**PS:** ICG, 5 mg/9 mL, tumor bed **Light:** Broadband light, 48 J/cm^2, 600–800 nm, 3–21 sessions	• The overall canine survival time ranged from 225 to 1.901 days (median survival time: 767 days)
[122]	Malignant soft tissue sarcoma	6 Cats	**PS:** ICG, 5 mg/9 mL, tumor bed **Light:** Broadband light, 48 J/cm^2, 600–800 nm, 3–21 sessions	• The overall feline survival time ranged from 383 to 1.521 days (median survival time: 1.344 days)
[123]	Injection-site sarcoma	37 Cats	**PS:** AO, 1 µg/mL **Light:** Surgical light, 24 V/250 Watt, 80,000 Lux, 1 session	• No recurrence cases were observed in PDS-PDT-treated cats • Animals submitted to the PDS-PDT modality presented a higher disease-free survival rate

Table 3. *Cont.*

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[124]	Sarcomas	12 Dogs	**PS:** Porfimer sodium, 3.0 mg/kg, iv; AlClPc, 0.175–0.589 mg/kg, iv; SnET2, 0.83 mg/kg, iv **Light:** Argon laser, 150–280 J/cm^2, 1 session	• Independent of photosensitizers uptake and light dose, more photon absorption is needed to induce tumor necrosis

Legend: 5-ALA, 5-aminolevulinic acid; AlClPc-nano, aluminum-chloride-phthalocyanine nanoemulsion; AO, acridine orange; BPD-MA, benzoporphyrin derivative monoacid ring A; CASPc, chloro-aluminums sulfonated phthalocyanine; HPD, hematoporphyrin derivative; HPPH, pyropheophorbide-a-hexyl ether; ICG, indocyanine green; iv; intravenous; PS, photosensitizer; $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

The photosensitizer EtNBS was administered intravenously (2.0 mg/kg) to a dog with scleral melanoma in the eye. PDT was completed with 100 to 200 J/cm^2. Unfortunately, the tumor did not respond to therapy [96].

A dog with melanoma in the soft palate showed a complete response after $ZnPcS_4$-based PDT. PDT protocol consisted of the administration of 0.25 mg/kg of the photosensitizer and irradiation with 100 J/cm^2 (675 $\pm$ 0.2 nm) [84].

A cat (9 years) with melanoma in the eyelid, with a history of recurrence after four surgeries, underwent a new surgical resection associated with intraoperative PDT. AO was used to fill the tumor bed for 5 min. Irradiation with a 400–700 nm lamp and a fluence of 20.7 mW/cm^2 lasted 10 min. There were no adverse effects of PDT at the surgery site during the follow-up. Tumor recurrence was not detected until 16 months [125]. PDT protocols used to treat melanomas are presented in Table 4.

Table 4. Clinical studies on PDT in animals with melanomas.

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[79]	Melanoma, hard palate	1 Dog	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 528–960 J/cm^2, 631 nm, 3 sessions	• The patient showed a complete response at 6 months; considered cured at the last follow-up (8 months)
[96]	Melanoma, sclera	1 Dog	**PS:** EtNBS, 2.0 mg/kg, iv **Light:** Diode laser, 200 J/cm^2, 652 nm, 1 session	• No response to therapy • Reported hyperthermia and vomiting during infusion
[84]	Melanoma, soft palate	1 Dog	**PS:** $ZnPcS_4$, 0.25 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 $\pm$ 0.2 nm, 1 session	• Free of disease 1 year after PDT without any subsequent treatment
[125]	Melanoma, eyelid	1 Cat	**PS:** AO, 1 µg/mL, tumor bed **Light:** Xenon light, 20.7 mW/cm^2, 400–700 nm, 2 sessions	• At 14 months postoperatively, metastases were distributed • At 16 months, the cat died, but on necropsy, recurrence was not detected at the original tumor site • There were no adverse effects associated with the AO-PDT

Legend: AO, acridine orange; EtNBS, 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride; HPD, hematoporphyrin derivative; iv; intravenous; PS, photosensitizer; $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

3.5. Other Tumors

Other types of tumors and some reports that are unclear regarding the histological type of tumors addressed are included in this section.

HPD (2.5 mg/kg) was used to treat a cat's lip eosinophilic granuloma. A complete therapeutic response was seen, with the animal showing a complete response up to 6 months of follow-up and being considered cured eight months later. In the same study, a dog with

sebaceous glands adenoma of the ear was given treatment. In this case, a complete response was achieved. Irradiation was performed with an Argon laser at 288 J/cm^2 (631 nm) [79].

Mammary gland tumors in cats and dogs were submitted to 5-ALA-based PDT. The two cats showed partial response and stable disease [71]. The disease progressed in a dog treated in combination with Lapatinib [71]. Progressive disease was also observed in a dog with myeloma, undergoing simultaneous therapy with melphalan [71].

Two dogs with ameloblastoma were treated with BPD-MA, and a change in the color of the tumor and tumor necrosis was observed after a few days in the PDT-treated animals. Moreover, a tumor-free interval of up to 7 months was observed, and a potential anti-angiogenic effect was demonstrated [105].

$ZnPcS_4$ was used in a dog with viral papilloma in the mouth and vulva, which showed a partial response to PDT and neutropenia of unknown cause [84].

One dog with spontaneous advanced primary prostate cancer was prepared for surgery and PDT with palladium-bacteriopheophorbide (Tookad, WST09, 2 mg/kg, iv). Light (diode laser, 763 nm) was applied to a total light dose of 100–150 J/cm. The dog survived one week of postsurgical and PDT procedures. Changes included necrosis and a 25% volume reduction in cancerous nodules of the partially treated area [126]. PDT protocols used to treat other veterinary neoplasms are presented in Table 5.

Table 5. Clinical studies on PDT in animals with other tumors.

Ref.	Neoplasm	Patients	PDT Protocol	Main Results
[79]	Eosinophilic granuloma	1 Cat	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 480 J/cm^2, 631 nm, 1 session	• The patient showed a complete response at the last follow-up (6 months)
[79]	Sebaceous glands adenoma	1 Dog	**PS:** HPD, 2.5 mg/kg, iv **Light:** Argon laser, 288 J/cm^2, 631 nm, 1 session	• The patient showed a complete response at the last follow-up (9 months)
[71]	Mammary gland tumor	2 Cats	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 20 J/cm^2, 200 J/cm, 630 nm, 3 sessions	• Stable disease and partial response
[71]	Inflammatory mammary gland tumor	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 1.000 J/cm, 630 nm, 5 sessions	• Partial response
[71]	Myeloma	1 Dog	**PS:** 5-ALA, 40 mg/kg, oral **Light:** Diode laser, 270 J/cm^2, 630 nm, 16 sessions	• Progressive disease
[105]	Ameloblastoma	2 Dogs	**PS:** BPD-MA, 0.5 mg/mg, iv **Light:** Diode laser, 1.275 J/cm^2, 75 J/cm, 690 nm, 1 session	• PDT used as anti-angiogenic • Tumor-free interval (0–7 months) • Tumor necrosis at the treatment site was observed
[84]	Viral papilloma	1 Dog	**PS:** $ZnPcS_4$, 4 mg/kg, iv **Light:** Diode laser, 100 J/cm^2, 675 ± 0.2 nm, 1 session	• Progressive disease
[126]	Spontaneous advanced primary prostate cancer	1 Dog	**PS:** WST09, 2.0 mg/kg, iv **Light:** Diode laser, 100–150 J/cm, 763 nm, 1 session	• PDT-induced severe necrosis in cancerous glandular tissue was observed • 1/3 of the prostate underwent a palliative treatment • The untreated tumor spread outside the capsule and invaded the tissues surrounding the prostate

Legend: 5-ALA, 5-aminolevulinic acid; BPD-MA, benzoporphyrin derivative monoacid ring A; HPD, hematoporphyrin derivative; iv; intravenous; PS, photosensitizer; WST09, palladium-bacteriopheophorbide; $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

4. Preclinical Studies

This section summarizes the use of PDT in in vivo and in vitro studies, as schematized in Figure 5.

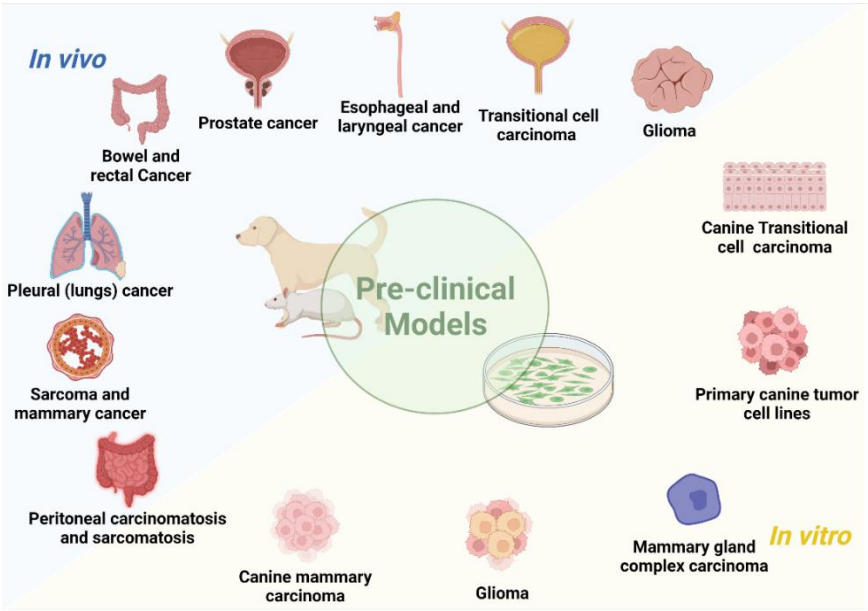

Figure 5. Preclinical applications of PDT in in vivo and in vitro models. Created with Biorender.com.

4.1. In Vivo Studies

Despite clinical trials, dogs and cats have also been used in research as animal models. The clinical and histopathological similarity of small animals' tissues and neoplasms to humans makes them relevant models for studying treatments in veterinary and medicine. Researchers are dedicated to developing photosensitizers that can be extended to clinical use in human medicine [24,34,35,74,127,128] and with possible applications in veterinary oncology. This section describes the studies where PDT was applied to health animals used as preclinical models.

Porfimer sodium was studied in a canine animal model of glioma obtained by surgical implantation of glioma cells in the brain. The animals received the photosensitizer intravenously and were irradiated with a laser at 630 nm. Despite tumor cell uptake being four times higher than normal brain tissue, severe unwanted effects were associated with higher doses. Still, a lower dose (0.75 mg/kg) of photosensitizer could eliminate the tumor without permanent brain toxicity [129].

The development of a centering balloon for PDT of esophageal cancer has been studied in a canine model. PDT was based on porfimer sodium. The centering balloon led to minimal damage to the normal esophagus in a dose and energy dependent-manner, as increasing photosensitizer concentration and light energy led to increasing damage [130]. Notwithstanding, exposure to 600 J/cm with a 180° windowed esophageal balloon severely damaged irradiated areas [131]. The size effect of a 360° windowed balloon was also assessed in a canine esophageal model. PDT-induced lesions were decreased by increasing the balloon size [132]. The normal canine esophagus has also been exploited to compare continuous wave and pulsed laser light. Both pulsed and continuous wave lasers were used in proximal and distal sites. Regardless of the laser type, mucosal ulceration, acute inflammation, serosal oedema, oedema, hemorrhage, and vascular degeneration with inflammation were observed. Based on the gross and histological examination of the lesions, the continuous and pulsed laser-induced injuries could not be distinguished [81].

Sequential porfimer sodium-based PDT sessions were shown to be safe in 13 dogs. Bladder capacity fully recovered in most cases. However, persistent bladder capacity loss

was observed after the second session. The histopathologic analysis revealed a superficial focal muscle injury in a dog that received three treatments [133].

Fifteen dogs were submitted to an intrathoracic HPD-based PDT to explore thoracic tissue tolerance. Following the photosensitizer administration, the animals underwent a thoracotomy and red-light irradiation (5 to 40 J/cm^2). One week after PDT, the extension of the lung's hemorrhagic lesions increased with an increasing light fluence rate. The higher light doses induced superficial hemorrhagic lesions in the heart and diaphragm. Six months later, complete healing was achieved in the lungs, and fibrotic plaques in the heart and diaphragm were observed. The most unaffected tissue was the chest wall [134].

A canine model of transmissible sarcoma was used to investigate the effects of PDT on malignant tumors and normal tissues. Tumors were developed through canine transmissible sarcoma cells subcutaneous implantation. After tumor development (35 mm in diameter), the animals received HPD (5 mg/kg) intravenously. Irradiation took place with an excimer dye laser at 630 nm. The mean diameter of tumor necrosis rapidly increased in parallel with the increase in total irradiation energy, and, as a side effect, cutaneous tissue showed a deep open ulcer [135].

In an animal model for laryngeal cancer, 11 dogs were given 3 mg/kg of HPD three hours before surgery. Then, varying irradiation amounts were delivered through argon laser (10 to 150 J/cm^2 of 630 nm), with simultaneous and serial temperature readings. As expected, the final temperature was proportional to the total energy given [136].

Seven dogs were given 2 mg/kg HPD intravenously. After 24 h, 450 J/cm of 630 nm wavelength laser light was delivered interstitially to the prostate. Interstitial PDT in the canine prostate using HPD produced modest volumes of tissue necrosis [137].

5-ALA was used in nine healthy dogs to model the transitional cell carcinoma of the lower urinary tract [95]. Vomiting was reported in 70% of dogs after administration of the compound, and submucosal bladder wall oedema was detected by ultrasound. However, no hematological or biochemical alterations were observed [95].

5-ALA and disulfonated aluminum phthalocyanine (AlS_2Pc) were studied in the normal canine prostate. PDT was performed by applying red light interstitially at 100 mW (100 J) through fibers placed under transrectal ultrasound guidance. Peak levels of AlS_2Pc appeared at 5–24 h and 3 h for ALA. Macroscopic PDT lesions were up to 12 mm in diameter using AlS_2Pc, but only 1–2 mm with ALA. Light at 300 mW (1080 J) caused thermal damage. At 28 days, the damaged glands remained atrophic, but the interlobular supporting stroma was well-preserved. The urethral lesions healed in 28 days without functional impairment [138].

The biological responses of the dog's prostate submitted to mTHPC and AlS_2Pc-based PDT were investigated as a preparatory step for clinical trials. PDT with mTHPC and AlS_2Pc is safe and promising for necrosing a substantial amount of prostate tissue. Note that prostate PDT was well-tolerated by the experimental animals [139].

mTHPC was administered to dogs to investigate light dosimetry. A light energy dose–response relationship was estimated, and the threshold that induced prostate gland necrosis was 20 to 30 J/cm^2 [140].

BPD-MA was administered to 24 healthy dogs to uncover the amount of light needed to ablate the canine esophageal mucosa effectively. Desirable results were obtained at a light dose of 60, 80, 145, and 200 J/cm when delivered 15, 30, 60, and 120 min after drug injection, respectively [141].

The safety of combining PDT with cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, was evaluated in a canine model. The dogs were subjected to different dose levels of intraperitoneal PDT based on BPD-MA, small bowel resection, and cetuximab. The results showed that dogs had acute or severe adverse events, demonstrating acceptable safety and toxicity associated with the light dose experienced, with or without bowel resection and cetuximab. The highest photosensitizer concentration was found in the small bowel, which may explain the anastomotic failure observed [142].

The esophageal region was the target of talaporfin sodium in a study aiming to evaluate the damage to dogs' normal tissue. Areas of 5 cm were irradiated at doses of 25, 50, and 100 J/cm^2. Tissue injury was seen at the muscle layer or even deeper and became more severe as the radiation increased. Histological examination revealed necrosis and inflammation extra-adventitious at a dose of 100 J/cm^2. Nevertheless, irradiation at a dose of 25 J/cm^2 seemed safe with minor tissue lesions [143].

Motexafin lutetium was studied in six dogs preoperatively. The dogs underwent irradiation of the rectum at 730 nm with 0.5 to 10 J/cm^2. All dogs recovered uneventfully. Significant light penetration into the rectum and sidewall of the pelvis was revealed without generating significant toxicity or histological sequelae [144]. This photosensitizer was also used as an experimental treatment in 11 dogs for intraperitoneal motexafin lutetium-based PDT, assessing the toxicity of normal tissues and targeting applications for treating peritoneal carcinomatosis and sarcomatosis. Mild transient abnormalities were observed on liver function tests, and no renal function abnormalities were found. No severe PDT-related abnormalities were observed on laparoscopy or necropsy; however, thickening of the glomerular capillary wall and mesangium was observed microscopically in the kidneys of seven dogs [145].

To determine the viability of canine prostate treatment and toxicity of the motexafin lutetium, 25 dogs were administered intravenously (2 or 6 mg/kg) and irradiated with a 732 nm laser light (75–150 J/cm). The light was delivered interstitially transurethrally to the prostate via cylindrical diffusing fibers. Interstitial PDT results in minor toxicity, with initial inflammation and necrosis, followed by fibrosis and glandular epithelial atrophy [146]. In another study, isotropic interstitial detectors used in normal canine prostate observed no significant changes before, during, and after motexafin lutetium-based PDT within a single treatment site, suggesting real-time dosimetric measurement and system feedback to monitor light fluences during treatment [147]. Motexafin lutetium-based PDT was explored in another group of canine prostate models. The feasibility of the interstitial photodynamic treatment for prostate cancer was explored in dogs. The dogs were treated with 6 mg/kg of motexafin lutetium and irradiated with different light doses (75–150 J/cm). The study demonstrates a safe and comprehensive treatment of the prostate. However, there is significant variability in the dose distribution and the subsequent tissue necrosis throughout the prostate [148].

To determine the conversion of 5-ALA into protoporphyrin IX (PpIX), four healthy cats were administered intravenously at 100, 200, or 400 mg/kg. Blood and skin biopsies were performed 24 h after administration. PpIX was detected in the tissues analyzed, with the greatest intensity in the epithelia. Due to hepatotoxicity, doses greater than 100 mg/kg were not considered safe [149].

The normal canine prostate was used as a model to study the compound WST09 (Tookad). All animals recovered well, without urethral complications. Histopathological exams showed necrosis, hemorrhage, and glandular tissue atrophy [150]. PDT based on WST09 has been shown to destroy normal prostate tissue, even with a lower photosensitizer concentration and low light energies [126]. However, treatment with WST09 and 100 J/cm^2 resulted in localized nerve injury and decreases in nerve conduction velocities. Treatment with 200 J/cm^2 severely damaged the saphenous nerve [151]. The safety and efficacy of soluble (WST11) vs. unsoluble (WST09) Tookad to target prostate vascular tissue were compared. Vascular PDT with WST11 was advantageous. Mild urinary clinical signs that resolved within 24 to 48 h were observed. All dogs evolved well, except one animal that developed intestinal intussusception [152].

$ZnPcP_2S_2$ (Di-sulfo-di-phthalimidomethyl phthalocyanine zinc)-based PDT was developed as a new anticancer method to eliminate residual leukemic cells in normal mononuclear cells. The toxicity of $ZnPcP_2S_2$ was evaluated in 24 dogs in doses of 0.5, 1.5, and 4.5 mg/kg. The injection sites of all animals were irradiated with a laser at 670 nm. Irradiations were performed in 48 and 72 h, once every four days, successively for ten times. The observations reported were dysphoria and mild oedema. No adverse effects were

observed in the ophthalmoscopy, electrocardiography, hematology, blood biochemistry, or urinalysis [153].

The technical feasibility of destroying prostate tissue using SnET2 was also evaluated in 15 dogs. Absorption and biodistribution were evaluated in the prostate and adjacent tissues. SnET2 was administered intravenously at a concentration of 0.5 or 1.0 mg/kg, the tissue was irradiated with 100–200 J/cm, and destruction of prostatic tissue was achieved [154]. Canine prostate was also subjected to experiments to determine the effects of transperineal interstitial PDT with SnET2. The treated areas showed extensive hemorrhagic necrosis and replacement by fibrous connective tissue [155]. The concentration of the SnET2 within the dog prostate was found to be heterogeneous. Thus, computerized modelling must consider the uneven sequestration of photosensitizer and the consequential asymmetrical necrosis of the prostate. In fact, animals treated with PDT showed differences in the necrotic front around the diffuser site [156].

The photosensitizer cyclohexane-1,2-diamino-hypocrellin B (SL052) was investigated in canine prostate models. SL052 was formulated in liposomes or dissolved in dimethyl-sulphoxide and administered intravenously or via the prostate arteries. Irradiation was performed with a laser diode at 635 nm. The intra-arterial route resulted in a more complete photoablation. Associated side effects included acute urinary retention, which resolved over time [157].

Sinoporphyrin sodium toxicity was evaluated in dogs. The animals were irradiated in the skin with a 630 nm wavelength laser for 10 min, once every seven days for five weeks. No deaths were reported; however, the animals that underwent PDT showed oedema and skin ulcerations. Changes in blood clotting time, splenomegalia, and organ pigmentation were also observed [158].

Canine mammary carcinoma cells (SNP) were used to obtain a murine model. For this, the cells were inoculated subcutaneously in female mice. PDT using a glucose-conjugated chlorin e6 (G-Ce6, 10 mg/kg) was achieved by irradiation with a 677 nm diode laser. A significant tumor regrowth delay was observed both with a 5 min and 3 h drug light interval. Nevertheless, the shorter drug light interval was the most effective [159].

The studies where PDT was applied to health animals used as preclinical models are systematized in Table 6.

Table 6. Studies on healthy dogs and cats as preclinical models.

Ref.	Disease, Model	Animals	PDT Protocol	Main Results
[129]	Glioma, cell inoculation in the brain	8 Dogs	**PS:** Porfimer sodium, 0.75–4.0 mg/kg, iv **Light:** Laser light, 1800 J, 630 nm, 1 session	• Animals receiving 2.0–4.0 mg/kg: necrosis and hemorrhage of the brainstem, with consequently severe neurological deficits • Animals receiving 0.75 mg/kg: Tumor ablation without severe brain-stem toxicity
[130]	Esophageal cancer, normal tissue	11 Dogs	**PS:** Porfimer sodium, 2–4 mg/kg, iv **Light:** Argon laser, 75–600 J/cm, 630 nm, 1 session	• Minimal or no endoscopic or histological damage for low dose PDT with centering balloon • Small and separate tissue damage sites for cylindrical diffuser and PDT energies of 300 J/cm and 600 J/cm • Progressive damage with increasing energy doses with high dose PDT
[131]	Esophageal cancer, normal tissue	8 Dogs	**PS:** Porfimer sodium, 4 mg/kg, iv **Light:** Argon laser, 300–600 J/cm, 630 nm, 1 session	• PDT with 4.0 mg/kg led to progressive severe damage to exposed areas both with 180° and 360° windowed balloon, with increasing energy

Table 6. *Cont.*

Ref.	Disease, Model	Animals	PDT Protocol	Main Results
[132]	Esophageal cancer, normal tissue	10 Dogs	**PS:** Porfimer sodium, 4 mg/kg, iv **Light:** Argon laser, 300 J/cm, 630 nm, 1 session	• Less tissue damage with increasing balloon sizes
[81]	Esophageal cancer, normal tissue	7 Dogs	**PS:** Porfimer sodium, 4 mg/kg, iv **Light:** Argon laser, 300 J/cm, 630 nm; KTP/532 laser, 300 J/cm, 532 nm, 1 session	• More extensive lesions in proximal treatment regardless of continuous or pulsed light • Presence of several lesions regardless laser type with signs of mucosal ulceration, acute inflammation, serosal oedema, oedema, hemorrhage, vascular degeneration with inflammation
[133]	Bladder cancer, normal tissue	13 Dogs	**PS:** Porfimer sodium, 1.5 mg/kg, iv **Light:** Red light, 15 J/cm^2, 630 nm, 1–3 sessions	• A single PDT induced average bladder capacity losses of 11% and 0% at post-PDT weeks 1 and 12, respectively • A second sequential PDT, caused average bladder capacity losses of 36% and 17% at weeks 1 and 12, respectively • Three sequential PDT, induced average bladder capacity losses of 22% and 0% at weeks 1 and 12, respectively
[134]	Pleural cancers, normal tissue	15 Dogs	**PS:** HPD, 6 mg/kg, iv **Light:** Argon laser, 5–40 J/cm^2, 630 nm, 1 session	• The extension of the lesions was dependent of the light dose • Lungs were the most sensitive organ, while the chest wall was revealed to be the most resistant tissue
[135]	Sarcoma, cell inoculation in the inguinal region	5 dogs	**PS:** HPD, 5 mg/kg; iv **Light:** Excimer dye laser; 0–1200 J/cm, 630 nm, 1 session	• The mean diameter of tumor necrosis increased rapidly in parallel with the increase in total irradiation energy below 240 J/cm; the mean diameter of tumor necrosis was 20.7 mm at an energy of 120 J/cm and 24.5 mm at 240 J/cm. Beyond 240 J/cm, the diameter gradually increased to 26 mm at 960 J/cm • As a side effect, the skin tissue showed a deep open ulcer at 240 J/cm, a shallow open ulcer at 180 J/cm, and a healed scar at 120 J/cm
[136]	Laryngeal cancer, normal tissue	11 Dogs	**PS:** HPD, 3.0 mg/kg, iv **Light:** Argon laser, 10–150 J/cm^2, 630 nm, 1 session	• The maximum change in temperature ranged from 0.5 °C when 10 J/cm^2 was delivered to 2.1 °C for 150 J/cm^2 • The final temperature achieved was proportional to the total energy given
[137]	Prostate cancer, normal tissue	7 Dogs	**PS:** HPD, 2.0 mg/kg, iv **Light:** Argon laser, 450 J/cm, 630 nm, 1 session	• Interstitial PDT in the canine prostate using Photofrin produced modest volumes of tissue necrosis

Table 6. *Cont.*

Ref.	Disease, Model	Animals	PDT Protocol	Main Results
[95]	Bladder cancer, normal tissue	9 Dogs	**PS:** 5-ALA, 30–90 mg/kg, oral **Light:** Tunable dye laser with titanyl potassium phosphate, 100 J cm^{-2}, 635 nm, 1 session	• No hematological or biochemical alterations • Side effects: submucosal oedema of the bladder wall, vomiting
[138]	Prostate cancer, normal tissue	11 dogs	**PS:** 5-ALA, 100–200 mg/kg, iv; AlS_2Pc, 1 mg/kg, iv **Light:** Diode laser, 100–1080 J, 630 nm, 1 session	• PDT with ALA does not look promising in the management of prostate cancer, but, using AlS_2Pc, it is possible to necrotize zones up to 12 mm in diameter around from each treatment site with safe healing
[139]	Prostate cancer, normal tissue	15 Dogs	**PS:** mTHPC, 0.3 mg/kg, iv; AlS_2Pc, 1.0 mg/kg, iv **Light:** KTP/532 and Argon laser, 100–200 J/cm, 650 nm, 1 session	• mTHPC was more powerful than AlS_2Pc in terms of prostate lesions induced.
[140]	Prostate cancer, normal tissue	9 Dogs	**PS:** mTHPC, 0.15 mg/kg, iv **Light:** Diode laser, 10–20 J/cm^2, 652 nm, 1 session	• Prostate gland necrosis
[141]	Esophageal cancer, normal tissue	24 Dog	**PS:** BPD-MA, 0.75 mg/kg, iv **Light:** Laser, 40–200 J/cm, 630 nm, 1 session	• Total mucosal ablation
[142]	Peritoneal carcinomatosis, normal tissue	15 Dogs	**PS:** BPD-MA, 0.125–0.25 mg/kg, iv **Light:** Diode laser, 690 nm, 2–10 J/cm^2, 1 session	• Acceptable safety and toxicity of BPD-MA-PDT and cetuximab • BPD-MA mostly accumulates in the small bowel • BPD-MA-PDT evoked anastomotic failure
[143]	Esophageal cancer, normal tissue	9 Dogs	**PS:** Talaporfin sodium, 20 mg/kg, iv **Light:** Diode laser, 25–100 J/cm^2, 664 nm, 1 session	• Deep tissue injuries (muscle and/or adventicious) • Hematological or biochemical alterations. Loss of appetite, weight, and vomiting
[144]	Rectal cancer, normal tissue	6 Dogs	**PS:** MoLut, 2.0 mg/kg, iv **Light:** Quartz tungsten halogen lamp, 0.5–10 J/cm^2, 730 nm, 1 session	• Acute moderate clinical effects
[145]	Peritoneal carcinomatosis and sarcomatosis, normal tissue	11 Dogs	**PS:** MoLut, 0.2–2.0 mg/kg, iv **Light:** Diode laser, 0.5–2.0 J/cm^2, 730 nm, 1 session	• Mild transient effects • Glomerular capillary wall thickening in some cases
[146]	Prostate cancer, normal tissue	25 Dogs	**PS:** MoLut, 2.0–6.0 mg/kg, iv **Light:** KTP/532 and Diode laser, 75–150 J/cm, 732 nm, 1 session	• Inflammation and necrosis of prostatic tissue, followed by fibrosis and gland atrophy
[147]	Prostate cancer, normal tissue	12 Dogs	**PS:** MoLut, 2.0–6.0 mg/kg, iv **Light:** Diode laser, 100–150 J/cm, 732 nm, 1 session	• Real-time dosimetry favored prostate targeting
[148]	Prostate cancer, normal tissue	16 Dogs	**PS:** MoLut, 2–6 mg/kg, iv **Light:** 75–150 J/cm, 732 nm, 1 session	• Lower doses of interstitial PDT demonstrated its feasibility as an approach for prostate

Table 6. *Cont.*

Ref.	Disease, Model	Animals	PDT Protocol	Main Results
[150]	Prostate cancer, normal tissue	16 Dogs	**PS:** WST09, 2.0 mg/kg, iv **Light:** Diode laser, 100–200 J/cm^2, 50–200 J/cm, 763 nm, 1 session	• Gland atrophy and necrosis • No severe side-effects
[126]	Prostate cancer, normal tissue	19 Dogs	**PS:** WST09, 0.25–2.0 mg/kg, iv **Light:** Diode laser, 50–300 J/cm, 763 nm, 1–2 sessions	• The zone of necrosis increased with the increasing light and drug doses • Urinalysis showed trace blood during the first hours post-treatment, but none of the animals required medical attention or treatment • Necrotic lesions could be induced at a very low drug dose (0.25 mg/kg) at a light dose of 200 J/cm
[151]	Prostate cancer, normal tissue	9 Dogs	**PS:** WST09, 1.0–2.0 mg/kg, iv **Light:** Diode laser, 50–200 J/cm^2, 763 nm, 1 session	• Nerve damage and alterations on nerve conduction for high-energy PDT
[152]	Prostate cancer, normal tissue	37 Dogs	**PS:** WST09, 2.0 mg/kg, iv; WST11, 2.0–30 mg/kg, iv **Light:** Diode laser, 100–400 J/cm, 753–763 nm, 1 session	• Ability to target prostate tissue • Mild clinical signs
[153]	Leukemia, normal tissue	24 Dogs	**PS:** $ZnPcS_2P_2$, 0.5–4.5 mg/kg, iv; **Light:** Red light laser, 7 J/cm^2, 670 nm, 10 sessions	• There were no abnormal changes in clinical observations • Histopathological examination showed hepatic spotty and lytic necrosis of in the group that received 4.5 mg/kg
[154]	Prostate cancer, normal tissue	15 Dogs	**PS:** SnET2, 0.5–1.0 mg/kg, iv **Light:** Diode laser, 100–200 J/cm, 664 $\pm$ 7 nm, 1 session	• The treatment resulted in the extensive destruction of glandular epithelium with minimal damage to surrounding structures
[155]	Prostate cancer, normal tissue	9 Dogs	**PS:** SnET2, 1.0 mg/kg, iv **Light:** KTP/YAG laser, 200 J/cm, 660 nm, 1 session	• Acutely, the treated areas showed extensive hemorrhagic necrosis. At 3 and 6 weeks, the treated lobes were largely replaced by fibrous connective tissue
[156]	Prostate cancer, normal tissue	5 Dogs	**PS:** SnET2, 1.0 mg/kg, iv **Light:** Diode laser, 200 J/cm, 665 nm, 1 session	• Differences in radii of the necrotic front around the diffuser site were observed
[157]	Prostate cancer, normal tissue	20 Dogs	**PS:** SL052, 0.75–18 mg/kg, iv, ia **Light:** Diode laser, 200–600 J/cm^3, 635 nm, 1 session	• The treatment attained either complete ablation of prostatic • Associated side effect included acute urinary retention which resolved overtime
[158]	Sarcoma, normal tissue	48 Dogs	**PS:** Sinoporphyrin sodium, 1–9 mg/kg, iv **Light:** Red light, 76 J/cm^2, 630 nm, 5 sessions	• The toxicokinetic study showed that the systematic exposure of sinoporphyrin sodium in dogs occurred in a dose-dependent manner • Showed no obvious treatment-related pathological changes

Table 6. *Cont.*

Ref.	Disease, Model	Animals	PDT Protocol	Main Results
[159]	Canine mammary carcinoma, cells were inoculated subcutaneously	6 Mice	**PS:** G-Ce6, 10 mg/kg, iv **Light:** Diode laser, 100 J/cm^3, 677 nm, 1 session	• PDT-induced significant tumor regrowth delay • Widespread tumor cells appeared necrotic, and fibrin thrombus formation within the vessels was observed

Legend: 5-ALA, Aminolevulinic acid; AlS_2Pc, disulfonated aluminum phthalocyanine; BPD-MA, benzoporphyrin derivative monoacid ring A; G-Ce6 glucose-conjugated chlorin e6; HPD, hematoporphyrin derivative; ia, intra-arterial; iv, intravenous; m-THPC, meta-(tetra hydroxyphenyl) chlorine; MoLut, Motexafin lutetium; PS, Photosensitizer; SL052 cyclohexane-1,2-diamino hypocrellin B derivative; SnET2 Tin (II) ethyl ethiopurpurin dichloride; WST09, palladium-bacteriopheophorbide; WST11, soluble palladium-bacteriopheophorbide; $ZnPcS_2P_2$ Di-sulfo-di-phthalimidomethyl phthalolcyanine zinc.

4.2. In Vitro Studies

Although animal models are appropriate for human and veterinary oncology studies, in vitro tests were used to replace animals to evaluate the photosensitizer outcomes initially. These studies mainly used cell cultures, photosensitizing molecules, and light sources. In this section, in vitro studies using cells of canine and feline origin are described.

Canine glioma cells were cloned and subjected to photosensitizer BPD-MA. After three hours of incubation in the dark, the cells were exposed to a LED light (100 J/cm^2). Approximately 24 h after PDT, cell viability was evaluated through 3H-thymidine incorporation into the DNA. A 50% growth inhibition was achieved with 10 and 4 ng/mL [160].

The hematoporphyrin monomethyl ether was administered to canine mammary carcinoma cell lines [161–163]. Apoptosis plays an important role in the reduction induced by PDT (20 mg/mL; He–Ne laser, 2.8 J/cm^2, 632.8 nm) in the viability of canine mammary carcinoma cells [161]. Treatment lead to loss of mitochondrial membrane potential [162]. Additionally, significant changes in cell morphology were observed, such as the formation of cytoplasmic vacuoles and the gradual rounding of cells, together with decreased size and detachment [163].

Aluminum-chloride-phthalocyanine encapsulated in liposomes induced cytotoxicity in a primary culture of female dog mammary gland carcinoma cells. Nevertheless, photosensitizer or laser irradiation per se did not induce cytotoxicity or morphological changes, indicating the safety and efficacy of PDT (2.5 M; LED, 10 J/cm^2, 660 $\pm$ 40 nm) [164].

Canine mammary carcinoma cells were treated with different concentrations (0.16, 0.80, 4.0, and 20 μM) of maltotriose−chlorin e6 conjugate (Mal_3-TEG-Ce6). The cells exposed to 5 J/cm^2 of 671 nm red light suggested the antitumor activity of this photosensitizer is extremely high. Cell viability was reduced to 50% when 0.16 μM was used [165].

The viability of the canine mammary carcinoma SNP cells was evaluated after PDT with NPe6 and a glucose conjugate of this photosensitizer. The half-maximal inhibitory concentration (IC50) of NPe6 against SNP cells exposed to light doses of 1, 5, and 15 J/cm^2 (650 nm) were 75.2, 30.4, and 30.6 μg/mL, respectively. The glucose conjugate was even more effective with IC50 values of 33.4, 10.4, and 1.7 μg/mL, respectively [159].

To assess the efficacy of 5-ALA-PDT in several subtypes of canine mammary gland tumors, mammary gland cancer cells were obtained from three dogs diagnosed with carcinoma, sarcoma, and carcinosarcoma, respectively. Cancer cells were then plated and treated with 0.5 and 1 mM of 5-ALA. From 6 to 24 J/cm^2, several light doses were used to activate 5-ALA through a continuous wave or pulse radiation. The intracellular PpIX peak of fluorescence was achieved after 4 h of 1 mM 5-ALA administration. The cytotoxic effect of 5-ALA was dose-dependent. Indeed, carcinoma and carcinosarcoma cells treated with a continuous wave at 12 J/cm^2 presented a substantial reduction in the cell viability and DNA damage. Nevertheless, 1 mM 5-ALA promoted apoptosis in all canine mammary gland tumor cells independently of the light dose [166].

Canine transitional cell carcinoma cells, K9TCC, were exposed to serial concentrations of 5-ALA to determine if PpIX production could cause lethal phototoxic effects when exposed to 635 nm light. Photocytotoxicity was dependent on 5-ALA concentration and exposure time. Moreover, increased laser power density and energy density decreased cell survival [87].

Fifteen primary canine tumor cell lines, nine established from carcinomas and six from sarcomas, were submitted to 5-ALA (0.03, 0.1, 0.3 and 1 mM). The results suggested that 5-ALA fluorescence may be predictive of the therapeutic effects of PDT [64]. Two canine primary lung adenocarcinoma cell lines (HDC and LuBi) were submitted to 5-ALA-mediated PDT. Although intracellular PpIX levels before irradiation were similar between HDC and LuBi cells, the first showed a higher percentage of ROS-positive and apoptotic cells [167].

5. Conclusions

In the last decades, veterinary medicine has reached many milestones in therapeutics; however, cancer remains a therapeutic challenge, compromising patients' quality of life and requiring efforts from owners. Nevertheless, domestic animals are part of the family. Their owners are extremely concerned and demanding about their animals' health and quality of life, always searching for less invasive treatments.

The applications of PDT in veterinary oncology cover a variety of neoplasms [10]. However, due to sparse investigations, therapeutic protocols are still under debate, and the use of PDT in veterinary medicine is not yet part of the clinical routine [10,90]. This contrasts with worldwide regulatory approval for treating various benign and malignant diseases in human medicine [38,168]. This review presents applications of PDT in the oncological treatment in dogs and cats, highlighting the photodynamic treatment protocols and the main photosensitizers (Table 7) used in different types of tumors.

Table 7. Main photosensitizer used in PDT in veterinary oncology.

Photosensitizer	Carcinomas		Mastocytomas		Sarcomas		Melanomas	
	Dogs	Cats	Dogs	Cats	Dogs	Cats	Dogs	Cats
HPD	8	12	1	1	2	-	1	-
Porfimer sodium	4	-	-	-	12	-	-	-
5-ALA	17	67	1	-	3	1	-	-
BPD-MA	10	-	-	-	25	-	-	-
PAD-S31	-	1	2	-	-	-	-	-
Talaporfin sodium	3	-	-	-	-	-	-	-
EtNBS	2	8	2	-	-	-	1	-
HPPH	17	55	-	-	17	-	-	-
CASPc	-	36	1	-	8	-	-	-
mTHPC	-	72	-	-	-	-	-	-
AO	52	-	-	-	-	37	-	1
$ZnPcS_4$	6	-	1	-	3	-	1	-
AlClPc-nano	-	-	-	-	8	-	-	-
ICG	-	-	-	-	10	6	-	-
Total	119	251	8	1	88	44	3	1

Legend: 5-ALA, 5-aminolevulinic acid; AlClPc-nano, aluminum-chloride-phthalocyanine nanoemulsion; AO, acridine orange; BPD-MA, benzoporphyrin derivative monoacid ring A; CASPc, chloro-aluminum sulfonated phthalocyanine; EtNBS, 5-ethylamino-9-diethylaminobenzo(a)phenothiazinium chloride; HPPH, pyropheophorbide-a-hexyl ether; HPD, hematoporphyrin derivative; ICG, indocyanine green; mTHPC, meta-(tetra hydroxyphenyl) chlorine; PAD-S31, l3,17-bis [1-carboxypropionyl] carbamoylethyl-3-ethenyl-8 ethoxy-iminoethylidene-7-hydroxy-2,7,12,18-tetramethyl porphyrin sodium; $ZnPcS_4$, zinc phthalocyanine tetrasulfonate.

Unfortunately, the current evidence arises from highly diverse protocols and studies with small numbers of animals. Carcinomas were included in several small trials performed with up to 12 patients [88], where heterogeneity of PDT protocols regarding PS, light, and DLI led to variable responses from nil to complete, associated with mild to

moderate side effects. Frequently, the disease was stabilized for some weeks [85,86,95]. We highlighted a trial of 55 cats [85] where 5-ALA was well-tolerated and provided 85% complete response, and a trial with 51 cats [110] with 62% local control. Studies also pointed to higher energies being associated with better outcomes [114] and larger tumors generally being less responsive [18]. Regarding mastocytomas and melanomas, studies with up to 2 patients using multiple PDT protocols do not allow us to draw any conclusions [79,84,96]. Regarding sarcomas, a variety of trials with small numbers of animals were reported; the larger study including only 16 dogs, showing 56% recurrence after HPPH-based PDT [121]. Additionally, a trial showed that AO can be interesting as surgical adjuvant [123].

PDT is effective in different neoplasms of dogs and cats. However, complete remission was sometimes not achieved. The heterogeneity between the studies was observed regarding the histological origin, site of the neoplasm, type of photosensitizer, concentration of photosensitizer, light source, exposure time, energies and doses used, forms of evaluation, evaluation times, and follow-up times. Thus, we limited the conclusions of an ideal PDT protocol in veterinary medicine can be achieved, as well as showing a clear comparison between treatments.

Nevertheless, PDT opens a new perspective in veterinary oncology. The resolution of the neoplasm can be achieved with a single application of PDT. Even so, repeated applications can be performed, as well as association with other therapeutic approaches. In addition, the outcome of PDT in veterinary oncology can be applied in a translational way, because animals constitute experimental models of human diseases due to the similarity of tumor biology between animals and man. Considering the potential applications of new photosensitizers on tumors of companion animals, research on novel photosensitizers and treatment protocols is highly encouraged.

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