

Pathological features of Squamous Cell Carcinoma (SCC) in domestic animals: Retrospective study of 19 cases

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Abstract:

Squamous cell carcinoma (SCC) is one of the most frequently diagnosed cutaneous malignancies in veterinary medicine, with ultraviolet (UV) radiation recognized as the principal etiological factor. Although SCC generally has a favorable prognosis, an accurate diagnosis is essential for selecting the most appropriate therapeutic strategy. This retrospective study evaluated 19 cases of SCC diagnosed between 2013 and 2025. Sex information was available for 16 animals, including 10 female dogs, 4 male dogs, and 2 female cats. The affected animals represented various breeds, including Terrier, German Shepherd, Spitz, Spitz–Terrier crossbreeds, and mixed-breed dogs. The tumors were located in the trunk, tail, inguinal region, mammary glands, nostrils, nasal planum, vagina, submandibular region, oral cavity, neck, perineum, elbow, and frontal region. Histopathological grading identified seven Grade I, five Grade II, and four Grade III SCCs. In addition, three cases were diagnosed as adenosquamous carcinoma, a histological variant of SCC. Histopathological examination revealed a broad spectrum of microscopic changes, including hyperkeratosis, parakeratosis, acanthosis, epithelial dysplasia, keratin pearl formation, lymphoplasmacytic infiltration, cellular pleomorphism, and lymphatic invasion.

1.Introduction:

Squamous cell carcinoma (SCC) is one of the most common malignant neoplasms encountered in veterinary medicine, affecting a wide range of domestic animal species. The disease is of particular significance in both large and small animals. In horses, SCC represents the most frequently diagnosed cutaneous malignancy, accounting for approximately 7–37% of all equine skin tumors [1]. Similarly, it is the most common skin cancer in cats, comprising up to 50% of feline cutaneous neoplasms, and the second most prevalent cutaneous malignancy in dogs, representing up to 20% of canine skin tumors [2]. In cattle, horn cancer (a distinct form of SCC affecting the horn-bearing tissues) is among the most frequently reported neoplasms in certain regions, particularly in India,

where it affects approximately 1% of the bullock population [3,4]. SCC has also been documented in numerous avian species, highlighting its broad distribution across diverse animal taxa [5].

SCC is an epithelial malignancy that can arise from a wide variety of anatomical sites, giving rise to diverse clinical presentations. In dogs, SCC most commonly occurs in the oral cavity and skin, each accounting for approximately 44.9% of reported cases, while less frequently affecting the mammary gland, nasal cavity, lungs, and urinary bladder [6]. In horses and cattle, SCC is particularly prevalent at mucocutaneous junctions, including the conjunctiva, vulva, and perineal region, as well as other areas of non-pigmented skin and mucosa such as the nasal mucosa, pinna, lips, eyelids, conjunctiva, and horn tissues [2]. Although SCC is typically associated with non-pigmented tissues, it may also develop in pigmented skin. Interestingly, certain variants, such as subungual SCC, have been reported more frequently in dogs with dark skin pigmentation and dark-haired coats [7]. Subungual SCC exhibits a predilection for the forelimbs, which are affected more commonly than the hindlimbs [2]. In avian species, the most frequently reported sites of SCC development include the skin, uropygial gland, and upper gastrointestinal tract, particularly the oral cavity [5].

Squamous cell carcinoma (SCC) comprises several clinicopathological variants that differ in their anatomical location, biological behavior, and histopathological characteristics. These include feline oral squamous cell carcinoma (FOSCC), the most common oral malignancy in cats, which is characterized by aggressive local invasion, a high mortality rate, and a largely unknown etiology. Other recognized variants include Bowenoid SCC (multicentric SCC in situ in cats), conventional SCC in situ, invasive SCC (ISCC), horn cancer, ocular SCC (OSCC), spindle cell SCC, acantholytic SCC, and verrucous squamous cell carcinoma. In addition, actinic keratosis is considered a premalignant lesion that may progress to SCC following prolonged ultraviolet (UV) exposure[7,8].

Despite the broad occurrence of squamous cell carcinoma (SCC) across domestic animal species, the tumor is relatively rare in goats and pigs. However, both species are susceptible to SCC, with ocular SCC being among the most commonly reported forms, particularly in Angora goats [2,7].

A variety of etiological factors have been implicated in the development of squamous cell carcinoma (SCC). Prolonged exposure to ultraviolet (UV) radiation is considered one of the most important risk factors, particularly in animals with lightly pigmented or non-pigmented skin, reduced epidermal melanin content, and sparse hair coverage at susceptible anatomical sites. Consequently, SCC occurs more frequently in subtropical regions, where UV exposure is more intense, and in animals maintained predominantly outdoors [7]. In feline oral squamous cell carcinoma (FOSCC), environmental and management-related factors have also been shown to play significant roles in disease development. Exposure to environmental tobacco smoke and the use of flea collars have been associated with an increased risk of FOSCC, potentially due to chronic oral exposure to carcinogenic compounds during grooming behavior. Dietary factors have likewise been implicated; in particular, the consumption of canned foods, especially tuna-based diets, has been linked to SCC development. This association may be attributable to dietary composition and increased dental calculus accumulation, which can contribute to poor oral hygiene, bacterial toxin production, and chronic oral inflammation-conditions that may

ultimately facilitate neoplastic transformation of the oral epithelium [9]. In addition, accumulating evidence has highlighted the role of papillomaviruses in SCC pathogenesis. Recent studies have demonstrated an association between papillomavirus infection and the development of SCC in both domestic animals and humans, suggesting a potential role for viral oncogenesis in at least a subset of cases [10].

Although breed is generally not considered a major risk factor for the development of SCC in dogs, certain breeds appear to exhibit increased susceptibility to specific forms of the disease. Higher incidences have been reported in Labrador Retrievers and black Poodles, particularly for digital SCC, as well as in Dalmatians, Beagles, Whippets, and white English Bull Terriers, which are predisposed to lesions affecting the flanks and abdominal region. Increased occurrence has also been documented in Golden Retrievers and German Shepherd Dogs. The peak age of SCC occurrence varies among species, with the highest incidence reported between 9 and 14 years of age in cats, 6 and 13 years in dogs, and 13 and 21 years in horses. In contrast, sex does not appear to be a significant risk factor for disease development. For example, one study reported SCC prevalence rates of 54.6% (41/75) in males and 45.3% (34/75) in females, indicating no meaningful sex-related predisposition [2,6,7].

SCCs usually have slow growth rate. Although SCC is invasive, it has usually a low distant metastatic potential and just regional lymph node metastasis is found in poorly differentiated neoplasms or neoplasms that have been present for a considerable time before they are diagnosed or excised by surgery. UV-light induced tumors have slower growth rates, while Oral SCC and Rhinial SCC grow faster and have worse prognoses with shorter median survival times (MSTs), compared to other types of well-differentiated tumors (MST > 1 year) [2,7].

Cats, dogs, and rodents are also valuable animal models for some types of SCC, like head and neck squamous cell carcinoma (HNSCC), which is the sixth most common cancer in Europe and the United States, additionally it's the most common oral cancer worldwide [11].

Given the considerable diversity of squamous cell carcinoma (SCC) across animal species, as well as the variability in its biological behavior, prognosis, and therapeutic management, a thorough histopathological evaluation is essential for accurate diagnosis and classification. Histopathologic examination provides critical information regarding tumor type, grade, and stage, thereby facilitating prognostic assessment and informed clinical decision-making. Although several ancillary diagnostic modalities (including dermoscopy, reflectance confocal microscopy, and positron emission tomography (PET) imaging) may aid in the detection and evaluation of SCC, histopathological examination of biopsy specimens remains the gold standard for definitive diagnosis [7].

2. case presentation:

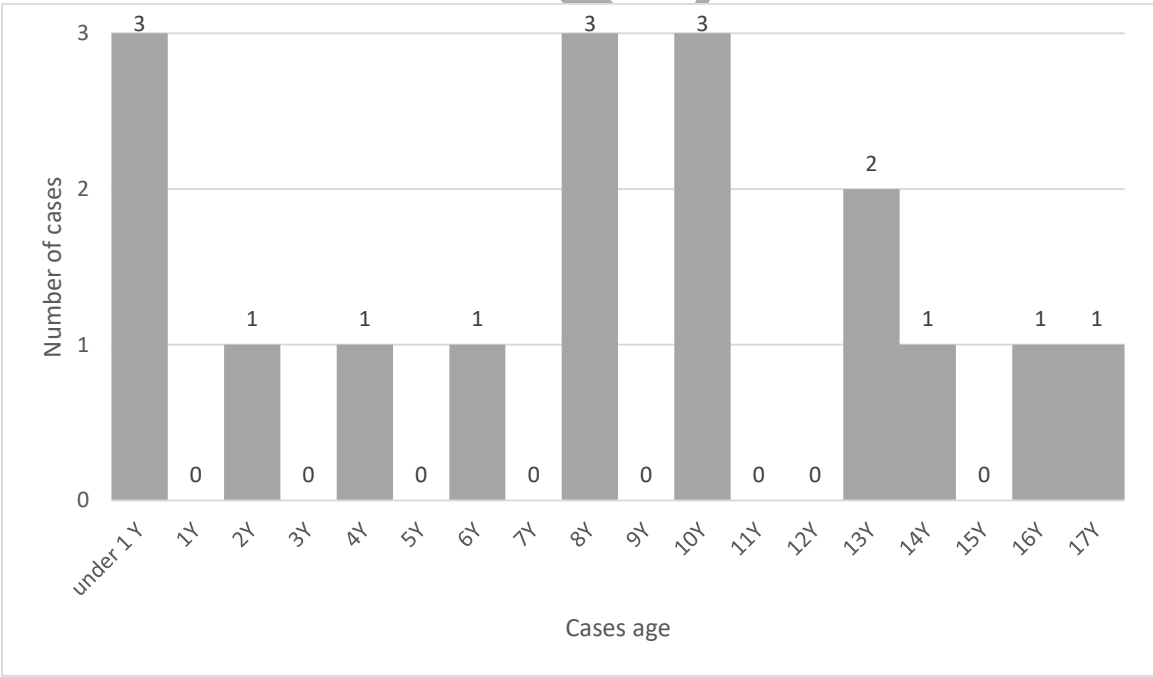
This retrospective study was conducted at the Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran, and included cases submitted to the Department of Pathology between 2013 and 2025. The study population comprised dogs and cats with tumor lesions that had been histopathologically diagnosed as squamous cell carcinoma (SCC). All canine and feline cases with a definitive diagnosis of SCC or pulmonary adenosquamous carcinoma during the study

period were included, resulting in a total of 19 cases. Following surgical excision, tissue specimens were fixed in 10% neutral buffered formalin and submitted to the Department of Pathology for histopathological evaluation. Samples underwent routine tissue processing, paraffin embedding, sectioning, and hematoxylin and eosin (H&E) staining. Prepared slides were subsequently examined microscopically. immunohistochemical analysis was performed in two selected Grade III cases, using a pan-cytokeratin marker to confirm the epithelial origin of the neoplastic cells. Clinical and demographic data were retrieved from the corresponding medical records and analyzed descriptively. These data included species, breed, age, sex, tumor location, and relevant clinical findings when available.

Nineteen cases were included in the study, comprising 16 dogs and 3 cats. The most common presenting complaint was a firm, exophytic mass involving various anatomical locations, including the trunk, tail, inguinal region, mammary glands, nostrils, nasal planum, vagina, submandibular region, oral cavity, neck, perineum, and elbow. Cutaneous ulceration and fissuring were among the additional clinical findings observed. Notably, multiple concurrent masses were present in some animals at the time of presentation.

The affected animals belonged to a variety of breeds, including Terrier, German Shepherd, Spitz, Spitz–Terrier crossbreeds, and mixed-breed dogs. Of the 19 cases evaluated, gender information was available for 16 animals, comprising 10 female dogs, 4 male dogs, and 2 female cats. Data regarding sex were unavailable for the remaining three cases, including one cat and two dogs. The age distribution of the affected animals is presented in (Diagram.1).

(Diagram 1. Age distribution of the cases)



The volume of the masses varied from 2 cm³ to 6 cm³ (Fig.1). Histopathological findings will be expressed based on the diagnosed grade and subtype of the disease. The complete information of

cases is described in the (Table.1). histopathologic grading was done based on the Broders grading system, which is described in Meuten et al. (2017).

Table.1: the number of cases, grade, and subtype of SCCs

Case number	Species	Age	Sex	Breed	Lesion site	Definitive diagnosis
1	Canine	17Y	N/A	German shepherd	Trunk skin	Well differentiated SCC Grade I
2	Canine	4Y	M	Terrier	Tail skin	SCC Grade I
3	Canine	14Y	I/M	Terrier	Mandibular gingiva	SCC Grade I+ dysplasia
4	Canine	7mo	F	N/A	Inguinal skin	In situ SCC Grade I
5	Canine	6Y	F	N/A	vagina	In situ SCC Grade I
6	Canine	10Y	I/M	Terrier	Perineal skin	Bowenoid in situ SCC Grade I
7	Canine	8Y	F	Mixed	Mammary gland region skin	Bowenoid in situ SCC Grade I
8	Feline	8Y	N/A	N/A	Submandibular region skin	SCC Grade II
9	Feline		F	N/A	Nasal skin	SCC Grade II
10	Canine	16Y	I/F	Shih tzu	Neck & thoracic & lumbar skin	SCC Grade II
11	Canine	13Y	F	Shih tzu-terrier	Elbow skin	SCC Grade II
12	Canine	6mo	I/F	spitz	Gingival mass of canine tooth of right maxilla	Conventional SCC Grade II
13	Feline	2Y	N/F	N/A	Nasal skin	SCC Grade III
14	Canine	8Y	F	N/A	Mammary gland region skin	SCC Grade III
15	Canine	13Y	N/F	Terrier	Frontal region skin near to eye	SCC Grade III
16	Canine		I/M	N/A	Maxillary mass	SCC Grade III
17	Canine	10Y	N/A	N/A	Mammary gland tumor	Adenosquamous carcinoma Grade I
18	Canine	10Y	N/F	Spitz-terrier	Mammary gland tumor	Adenosquamous carcinoma
19	Canine	8mo	F	N/A	Left lung lobe	Pulmonary adenosquamous carcinoma

F=Female, M=Male, I/F=Intact female, I/M=Intact male, N/F=neutered female, N/A=unknown, Y=years old, mo=months old



Fig.1: Gross appearance of a subcutaneous mass diagnosed as grade I SCC

Histopathological Findings in Grade I, Dysplastic, *In Situ*, and Well-Differentiated SCC:

Histopathological features of Grade I (well-differentiated) SCCs and dysplastic lesions included epidermal hyperplasia and invasion of neoplastic squamous epithelial cells into the dermis and subcutis. Multifocal keratin pearl formation, characterized by concentric accumulations of keratinized neoplastic cells, was a prominent finding. Intercellular bridges (desmosomes) between neoplastic keratinocytes were frequently observed (Fig. 2A), reflecting the retained squamous differentiation of the tumor cells. Additional findings included low mitotic activity, multifocal lymphohistiocytic inflammatory infiltrates, desmoplastic stromal reaction, multifocal hemorrhage, cholesterol cleft formation, and cytoplasmic vacuolation of neoplastic cells. Variable degrees of cellular and nuclear pleomorphism were also present (Fig. 2A). Other histopathological alterations included hyperkeratosis, mild hydropic degeneration of the epidermis, pustule formation, epidermal necrosis, papillomatosis, acanthosis, and parakeratosis. In some cases, ulceration was accompanied by secondary bacterial colonization and associated inflammatory changes.

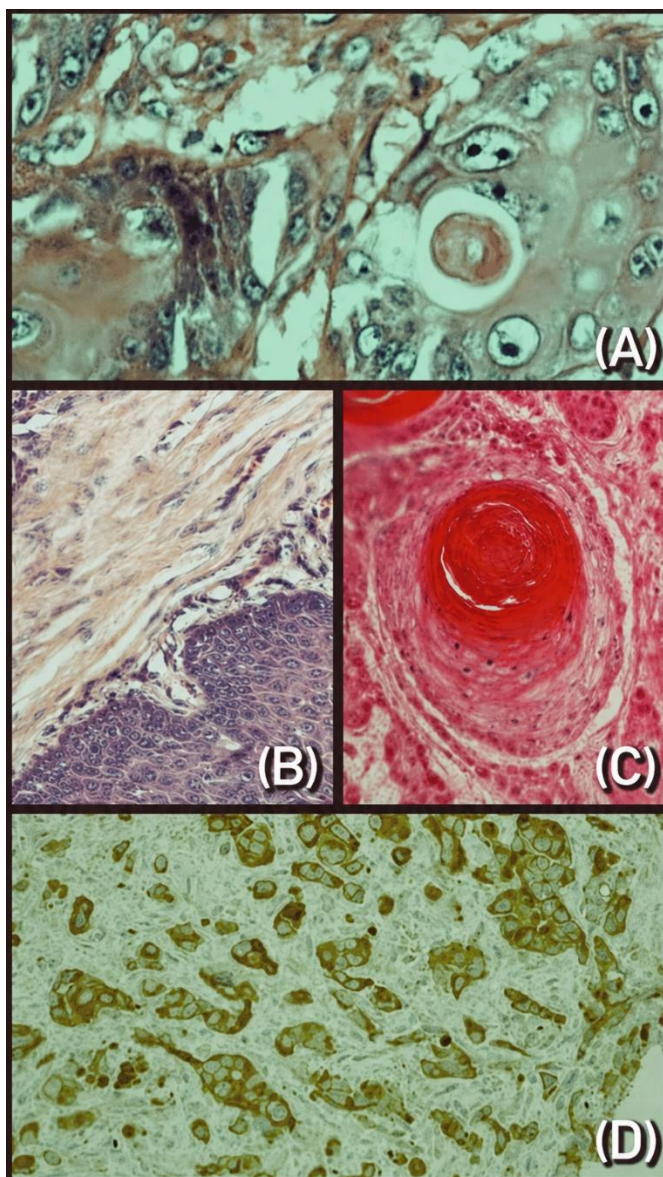


Fig.2: Photomicrographs of cellular and immunohistochemical features. (a) Malignant pleomorphic epithelial cells possessing multiple nucleoli and desmosomes (H&E). (b) SCC in situ lacking dermal invasion (H&E). (c) Keratin pearls as concentric lamellar aggregates of keratin (H&E). (d) Strong cytoplasmic immunoreactivity of the malignant keratinocytes with AE1/AE3 (IHC).

Squamous cell carcinoma in situ (SCCIS) (Fig. 2B), a non-invasive form of Grade I SCC, was characterized by mild cellular atypia and a low degree of pleomorphism. Histopathological features included hyperkeratosis, parakeratosis, hyperchromasia, mild mitotic activity, epidermal hyperplasia, elongation and accentuation of the rete ridges, and varying degrees of multifocal lymphoplasmacytic infiltration, ranging from mild to severe. Epithelial dysplasia was consistently observed. Despite the presence of marked neoplastic alterations, all atypical changes remained confined to the epidermis without invasion of the underlying dermis. Nevertheless, secondary dermal changes, including thrombosis, hyperemia, and hemorrhage, were observed in some cases. Similar histopathological features were identified in multicentric SCC in situ

(Bowenoid SCC); however, these lesions were distinguished by the presence of multiple neoplastic foci occurring simultaneously at different anatomical sites.

Histopathological Findings in Grade II SCC:

Grade II (moderately differentiated) squamous cell carcinomas exhibited a combination of proliferative, dysplastic, and invasive histopathological features. Common findings included hyperkeratosis, parakeratosis, acanthosis, epithelial dysplasia, and variable degrees of squamous differentiation. Neoplastic cells displayed moderate to marked cellular and nuclear pleomorphism, karyomegaly, prominent multiple nucleoli, and nuclear hyperchromasia. Dermal invasion was consistently observed, often in the form of infiltrative nests, islands, and trabeculae of neoplastic epithelial cells extending into the underlying connective tissue. Keratin pearl formation remained evident in many cases (Fig. 2C), accompanied by the presence of intercellular bridges (desmosomes), indicative of retained squamous differentiation. Neoplastic keratinocytes demonstrated moderate mitotic activity (mitotic count = 6 per 10 high-power fields [HPF]) and frequently contained keratin tonofilaments, observed microscopically as intracytoplasmic eosinophilic fibrillar material. Additional histopathological findings included mononuclear dermatitis, mild suppurative inflammation, ulcerative dermatitis, vacuolar degeneration, mild desmoplastic stromal response, and multifocal hemorrhage. No evidence of lymphatic or vascular invasion was identified in the examined specimens.

Histopathological Findings in Grade III (Poorly Differentiated) SCC:

Grade III (poorly differentiated) squamous cell carcinomas were characterized by marked cellular atypia and aggressive invasive behavior. Histopathological examination revealed extensive dermal invasion by neoplastic cells accompanied by severe cellular and nuclear pleomorphism. The neoplastic cells exhibited round to oval nuclei, prominent nucleoli, indistinct cellular borders, marked nuclear hyperchromasia, and frequent mitotic figures, reflecting a high proliferative index. Multinucleation was also observed in a proportion of neoplastic cells. Although squamous differentiation was markedly reduced, occasional keratin pearl formation and intercellular bridges were still identifiable in some cases. Malignant transformation of both epidermal and hair follicular epithelium was evident, further supporting the epithelial origin of the neoplasm. Additional findings included multifocal lymphocytic infiltration within the tumor microenvironment and linear subepidermal hyperpigmentation. Evidence of vascular and lymphovascular invasion was observed, indicating an increased potential for local spread and metastasis. Concurrent inflammatory and infectious changes were also present in some specimens, including deep pyoderma associated with lymphoplasmacytic infiltration and emperipolesis. These findings collectively reflected the highly aggressive and poorly differentiated nature of Grade III SCC.

Histopathological Findings in Adenosquamous Carcinoma:

In three cases, Adenosquamous Carcinoma were diagnosed. Clinically, the affected animals presented with weight loss, lethargy, and coughing, with respiratory abnormalities representing the predominant clinical manifestations. Histopathological examination revealed infiltrative pulmonary neoplasms composed of numerous tubules and papillary structures lined by malignant

epithelial cells. The neoplastic cells exhibited marked pleomorphism, moderate to abundant eosinophilic cytoplasm, and variable degrees of squamous differentiation. Tumor cells were arranged both individually and in small nests and displayed invasive growth into the surrounding pulmonary stroma. Nuclear features included round to oval and occasionally bizarre nuclei, prominent anisokaryosis, multinucleation, and frequent mitotic activity, with mitotic counts ranging from moderate to high (mean mitotic count: 5 per 10 high-power fields [HPF]). Numerous large and atypical neoplastic cells were present, and intercellular bridges (desmosomes) were observed in areas demonstrating squamous differentiation. Additional histopathological findings included mild multifocal neutrophilic infiltration, mixed inflammatory infiltrates composed of neutrophils, lymphocytes, and plasma cells, multifocal hemorrhage, necrosis, fibrosis, ceroid-lipofuscin accumulation, chronic diffuse interstitial fibrosis with a prominent desmoplastic response, myofibroblast proliferation, hemosiderosis, and subscapular fibrotic lesions associated with mononuclear inflammatory infiltrates. Evidence of lymphatic dissemination was identified, including neoplastic emboli and direct invasion of lymphatic vessels by malignant cells. Based on the presence of both glandular and squamous differentiation, together with the aforementioned histopathological features, all three pulmonary tumors were definitively diagnosed as pulmonary adenosquamous carcinoma.

General Clinicopathological Findings:

In the present study, both intact and neutered animals were represented, including females with and without a history of parturition. Based on histopathological evaluation, five cases were classified as Grade I cutaneous SCC and two as Grade I mucosal SCC. Grade II SCC comprised four cutaneous and one mucosal case. Grade III SCC included three cutaneous and one mucosal lesion. Additionally, three cases were diagnosed as pulmonary adenosquamous carcinoma. Although, mitotic figures were observed in all grades, mitotic activity was generally low and was not considered a prominent feature, even in poorly differentiated (Grade III) tumors. Keratin pearl formation was a diagnostically important finding, serving as a hallmark feature of squamous differentiation. In addition, hyperkeratosis, acanthosis, parakeratosis, and orthokeratosis were observed across all histological grades of SCC. Based on the available clinical histories, most neoplastic masses had been present for approximately one year prior to surgical excision, the most frequently affected site in this case series was mammary gland region (4/19). Several animals had a documented history of other neoplastic conditions; however, SCC cases generally showed no evidence of local recurrence following surgical excision during the available follow-up period. To further support the histopathological diagnosis, immunohistochemical staining using the AE1/AE3 (pan-cytokeratin) antibody was performed in two cases of Grade III SCC. In both cases, malignant keratinocytes exhibited strong cytoplasmic immunoreactivity, confirming their epithelial origin (Fig. 2D). Among the three feline cases included in the study, two tumors were located in the nasal region.

4. Discussion:

Squamous cell carcinoma (SCC) is a malignant tumor that commonly affects the skin and oral cavity[12,13]. Similarly, in the present study, all SCCs, except for one case identified in the vaginal mucosa, were located in the skin or oral cavity. In addition, all three cases diagnosed

with adenosquamous carcinoma exhibited pulmonary involvement. SCC should be considered as a differential diagnosis of scabbing ulcers specially on the eyelids, nasal planum or ears of light-coloured cats[12]. In the present study, apart from tumors of the oral cavity, four cases showed involvement of the facial region and one case involved the neck. However, the most frequently affected site was the mammary gland region. As with most cancers, this disease predominantly affects older cats, with a median age at diagnosis of 10 to 12 years[12]. However, in the present study, among the three affected cats, one was 2 years old and another was 8 years old, while the exact age of the third cat was not available.

Feline oral SCC is the most common oral neoplasia in cats and it may have different etiologies including, exposure to smoking, canned food consuming, feline papillomavirus and flea collars[8,14]. In this study, 3 of the 19 cases had oral SCCs; however, all of them were canine oral tumors, with one case representing each histological grade (I, II, and III), and there is no information available about the etiologic factors of them. Additionally, although all three cats included in the study exhibited lesions in the facial region, none of them had tumors within the oral cavity.

Alves D. et al. (2022) reported that SCC is particularly prevalent in tropical countries[13]. However, the present study was conducted in Iran, a country characterized by a warm and dry climate. They also reported that this tumor is more common in non-pigmented regions, particularly in ventral areas of the body. This observation is consistent with the findings of the present study, in which the majority of tumors were located in the mammary gland region.

Adenosquamous carcinomas can arise in various anatomical locations throughout the body. Although involvement of the skull bones has been reported, it is considered an uncommon presentation[14]. In the present study, three cases of adenosquamous carcinoma were identified, all of which were located in the lungs. Squamous cell carcinoma (SCC) accounts for approximately 5% of all cutaneous tumors in dogs[14]. Similarly, in the present study, 9 of the 16 dogs exhibited cutaneous involvement.

Protein kinase CK2 emerged as a promising therapeutic target for feline SCCs. A potential treatment strategy for feline SCCs may involve RNA interference directed against CK2[15]. Although such therapeutic approaches may hold promise, their application is currently not feasible in Iran. Furthermore, in the present study, Follow-up information was available only for a limited number of cases, regarding the subsequent treatment or clinical follow-up of the patients.

Immunostaining with epidermal growth factor receptor (EGFR) has been reported to possess prognostic value in feline cutaneous SCCs [16]. However, in the present study, only pan-cytokeratin immunostaining was performed, and it was used solely to confirm the epithelial origin of the neoplastic cells in grade III tumors.

Squamous cell carcinoma (SCC) generally has a low metastatic rate[17]. Consistent with this observation, lymphatic vascular invasion was identified only in grade III tumors in the present study.

Ethical Considerations:

The study involved client-owned animals undergoing routine clinical care, and no additional experimental procedures were performed. Therefore, formal institutional ethical approval was not required.

Data availability:

All the data associated with this project is presented in this manuscript.

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Authors' contributions:

Removal of masses during surgery: Mir Sepehr Pedram and Mohammad Mehdi Dehghan, Pathological diagnosis of samples and Supervision: Farhang Sasani, Data acquisition and writing the original draft: Mobina Farrokhnia Hamedani, Review and editing: Diba Golchin

Conflicts of Interest:

The authors declare no conflicts of interest.

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Using artificial intelligence: ChatGPT version 5.5 was used to improve the quality of the second photo without altering its details.

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