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Pathological and Economic Effects of Bovine Skin Tumors on Cattle Production in Ethiopia: A Review

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REVIEW
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ABSTRACT

A tumor is an abnormal mass of tissue that exceeds normal boundaries, resulting from uncoordinated and uncontrolled cell proliferation. Tumors can affect various parts of cattle animals, including the skin, bones, glands, and visceral organs. The present study aimed to explore the pathology of bovine skin tumors and their health and economic impacts on cattle. Skin tumors are the most frequently diagnosed neoplastic disorders in bovine species. The most common skin tumors in bovine include bovine papilloma, squamous cell carcinoma, and bovine lymphosarcoma. These tumors pose significant health challenges and have a negative economic impact on cattle production and its byproducts. Clinical features of skin tumors often include hyperkeratosis, acanthosis, elongated rete pegs, large nodular structures, exophytic and cauliflower-like lesions, and friable lesions. Melanomas, another type of proliferative skin tumor, are characterized by spindle to round cell shapes containing abundant black pigment. More than 90% of skin tumors are linked to prolonged exposure to ultraviolet radiation. Diagnosing a skin tumor in cattle typically involves skin biopsy and fine needle aspiration cytology. Histologically, skin tumor cells exhibit an increased nuclear-to-cytoplasmic ratio, cellular and nuclear pleomorphism, and a discohesive arrangement of cells. In addition to their health implications, skin tumors in cattle result in significant economic losses due to reduced productivity, decreased reproduction rates, carcass condemnation, and the downgrading of skins and hides. Common treatment options for skin tumors include chemotherapy, radiation, and surgical removal. Given that skin tumors are an economically significant disease in Ethiopia, they require increased attention from researchers and the centers for control and prevention. Early diagnosis and effective management of these tumors are crucial issues that must be addressed.

Keywords: Bovine, Cattle, Diagnosis, Skin tumor, Tumor

INTRODUCTION

A tumor is an abnormal growth of tissue resulting from the uncontrolled proliferation of cells (Vasconcelos et al., 2023). Based on its behavior, a tumor may be classified as benign or malignant (Constable et al., 2017). A benign tumor refers to a cluster of cells that do not spread throughout the body; instead, it invades only the surrounding tissue of its origin (Mithila Bisht et al., 2020). In contrast, a malignant tumor is more serious, with the ability to spread to other healthy tissues or organs (Khalid et al., 2020). Notably, both forms of tumors increasingly pose a significant threat to the health and well-being of cattle (Flores-Balcázar et al., 2020).

Tumors can affect various parts of the animal body, including both hard and soft tissues (Khalid et al., 2020). Commonly affected areas in cattle include the skin, bones, glands, and various visceral organs (Flores-Balcázar et al., 2020). Skin, as the largest organ of the body, is composed of three distinct anatomical layers, including the epidermis, dermis, and hypodermis (Khalid et al., 2020). It plays crucial roles in physiological regulation, protection from the external environment, and serving as a boundary for internal structures (Achalkar, 2019; Mathewos et al., 2021). Given that the skin is the outermost layer, it is frequently exposed to various pathogens and physical injuries (Khalid et al., 2020).

Tumors represent a significant challenge for the skin at multiple levels, reducing its function for cattle and its value for human consumption (Mathewos et al., 2020). Research indicates that skin tumors are among the most frequently observed tumors in cattle (Dabbagh Moghaddam et al., 2021), primarily due to the skin's continuous exposure to the external environment (Vasconcelos et al., 2023). Prolonged exposure to sunlight can lead to DNA damage in skin cells, preventing the body from recovering and resulting in uncontrolled cell proliferation (Mathewos et al., 2021). The development of tumors often occurs when DNA is damaged and the body cannot repair it (Flores-Balcázar et al., 2020). Currently, the incidence of bovine skin cancer is increasing, negatively impacting animal productivity and leading to mortality (Mathewos et al., 2020).

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Constable et al. (2017) noted that the incidence of skin tumors is rising over time in cattle, causing significant damage to the skin and hide industry. This trend contributes to economic losses, particularly in Ethiopia, where the skin and hide industry faces challenges related to quality. The objective of this review was to summarize the issue of bovine skin tumors and their economic impact.

Common skin tumors occur in cattle

Currently, many researchers report that cattle rank second after dogs for the incidence of all types of tumors occurring in domestic animals (Mathewos et al., 2020). The most common type of tumor affecting bovine species is skin tumor (Khalid et al., 2020). Many cattle are more likely to develop skin tumors, although the rate of occurrence may vary among different breeds, coat colors, agro-climates, and management practices (Moharram et al., 2019).

As indicated in Table 1, the different types of cutaneous tumors affecting cattle include bovine papilloma, squamous cell carcinoma (SCC), bovine lymphosarcoma, and melanoma. Bovine cutaneous papilloma and SCC are particularly prevalent forms of tumors in cattle (Flores-Balcázar et al., 2020). Skin tumors have been identified as serious diseases that significantly impact the health and welfare of cattle (Khan et al., 2022).

Different types of skin tumors exhibit varying prevalence across the skin of cattle. Not all parts of the skin are equally susceptible to different types of tumor diseases (Jamieson and Mohamed, 2020) as illustrated in Table 2.

Table 1. Spontaneous skin tumors prevalence in farm animals

Organ	Tumor type	Animal	Number/Percent	Sex (M/F)	Age
Skin	Fibropapilloma	Cattle	110 (54.4%)	40M/70F	M 2m-3y F 4m-6y
Skin	Equine Sarcoid	Equine	65 (32.1%)	39M/26F	M 2m-6y F 2m-7y
cutis	Fibroma	Cattle Equine	14 3(8.4%)	4M/10F 1M/2F	M 2-4y F 2-5y M 5y and F 3y
Skin and subcutis	SCC	Cattle Sheep	31(1.9%)	1M/2F 1M	M 3y F 2-3y F 3m
sub-cutis	Lymphosarcoma	Cattle Buffalo	11(0.9%)	1F 1F	2y 8m
Liver	Haemagiosarcoma	Cattle	2 (0.9%)	2M	3y
subcutis	Liposarcoma	Goat	1 (0.4%)	1F	3y
Ovary	Malignant Teratoma	Cattle	1 (0.4%)	1F	8m

M: Male, F: Female, m: Months, y: Year, Source: Moharram et al. (2019).

Table 2. Tumor description on the skin of cattle and buffaloes

Tumors	Animals	Number of tumors	Location	Sex		Age
				F	M	
Cutaneous Papillomatosis	Cattle	15	Head, around the eyes, neck, back, shoulder, axilla, and all over the body	13	2	5m to 3y
Cutaneous Fibropapilloma	Cattle	5	The skin of the head, around the eyes, neck, back, shoulder, axilla and all over the body	4	1	8m to 1y
Scc	Cattle Cattle Cattle	25 1 8	Eye Skin of muzzle Perineum	10 1 8	15 - -	2-10y 9y 7-9y
Scc	Buffalo	1	Skin of face Buccal cavity	1 1	- -	3y 8y
Epulis	Cattle	2	Gum	1	1	8m and 2y
Leiomyoma	Cattle	2	Vagina	2	-	4y
Fibroma	Cattle	1	Submandibular space	1	-	6y
Liposarcoma	Cattle	1	Neck	1	-	1y
Total		61		43	19	

SCC: Squamous cell carcinoma, m: Month, y: Year, Source: Moharram et al. (2019)

Bovine papilloma

Bovine papilloma is the most commonly identified type of skin tumor in cattle. It is an exophytic growth of squamous cell epidermis caused by bovine papillomavirus (BPV, Constable et al., 2017). This tumor rarely regresses without causing serious clinical problems for the infected animal (Vasconcelos et al., 2023). However, it can occasionally persist for an extended period, serving as a focus for malignant transformation into squamous cell carcinoma (SCC, Moharram et al., 2019). Bovine papilloma (BP) can affect cattle of all ages, but it is most commonly observed in young animals (Feyisa, 2018). The virus spreads between animals through direct or indirect contact, such as grooming materials and other fomites (Ugochukwu et al., 2019).

Gross lesion

Bovine papilloma can be found in various locations throughout the body, including the head, neck, udder, around the eyes, shoulders, limbs, and ears (Vasconcelos et al., 2023). It is characterized by elevated and diffuse multi-nodular proliferations (Constable et al., 2017), as well as a lichenified appearance, thickened epidermis, and pedunculated, firm, dense masses with rough, scaly, and dry surfaces (Feyisa, 2018). Cauliflower-like lesions are also common (Mathewos et al., 2020). The color of the affected areas can range from grayish-white to black (Moharram et al., 2019). The gross appearance of Bovine papilloma on the neck, shoulder, and face of the cattle is shown in Figure 1, and also on the teats and thoracic region of cattle is shown in Figure 2.

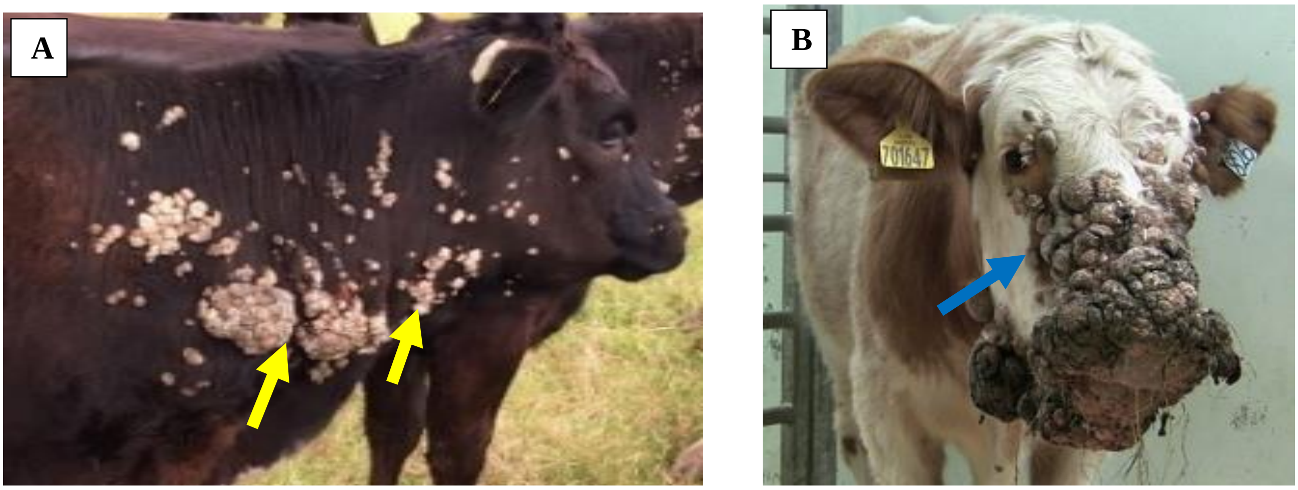

Figure 1. Gross appearance of Bovine papilloma. **A**: Bovine papilloma located on the neck and shoulder of cattle (Yellow arrows, Kumar et al., 2015). **B**: Bovine papilloma presented on the face of the cattle (blue arrow). Source: (Flores-Balcázar et al., 2020).

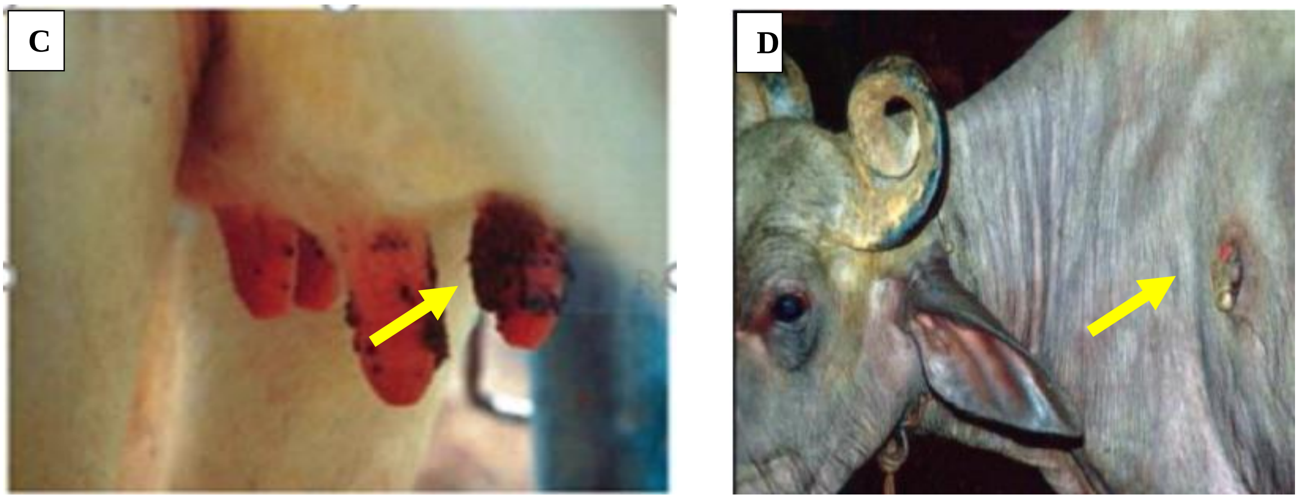

Figure 2. Gross appearance of Bovine papilloma. **C**: Bovine papilloma affected the teats of cattle (Yellow arrow, Kumar et al., 2015). **D**: Papilloma wart in a buffalo on the thoracic region (yellow arrow). Source: Flores-Balcázar et al. (2020).

Histopathological features

Bovine papilloma exhibits prominent hyperkeratosis, acanthosis, and elongated rete pegs surrounded by fibrovascular stroma when observed under a light microscope (Xiao et al., 2020). Additionally, hydropic degeneration of epidermal cells (Meuten, 2020) and hypergranulosis of the stratum granulosum are also evident, as shown in Figure 3. Fibropapillomas, a subtype, are characterized by fibromas that arise from the stroma, exhibiting hypercellularity of fibroblasts forming whorls around blood vessels (Hunt, 2017). As indicated in Figure 4, cutaneous bovine papilloma has the features of proliferation of epithelial cells at the stratum spinosum with varying degrees of ballooning degeneration, several epithelial cells have enlarged, condensed nuclei, and some are apoptotic (Crespo et al., 2019).

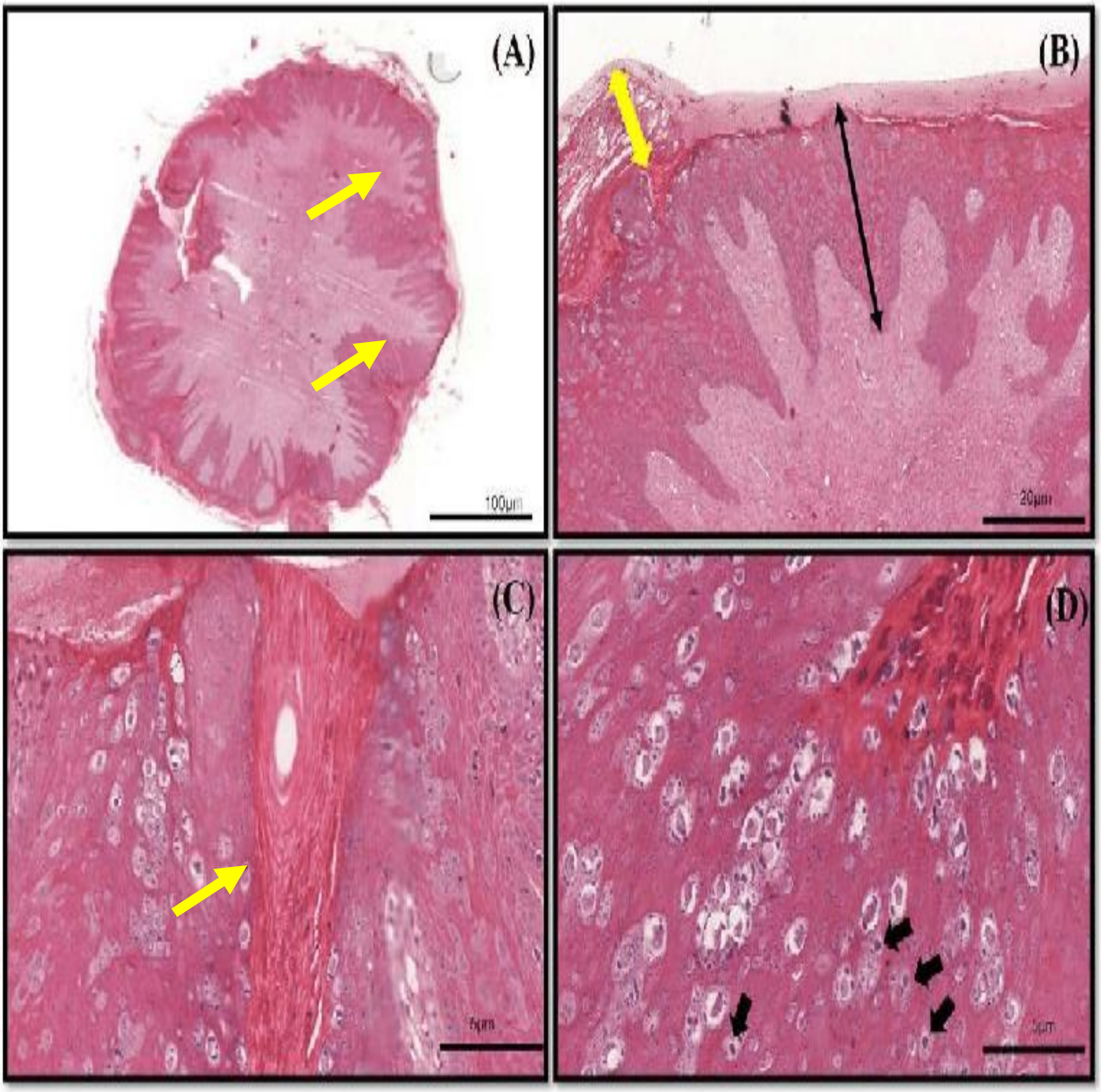

Figure 3. The histopathology findings of bovine papilloma tissues. **A**: Low magnification showing a well-developed finger-like projecting papillae rising from the surface of the epidermis to the subcutaneous layer (yellow arrows). **B**: Hyperkeratosis of the epithelial layer (double yellow arrow) with acanthosis formation (double black arrow). **C**: Epidermal proliferation with elongated rete pegs and neoplastic fibroblast (yellow arrow). **D**: Multiple koilocytosis formation on the dermis layer (black arrows). H&E staining 10X and 40X. Source: Khalid et al. (2020).

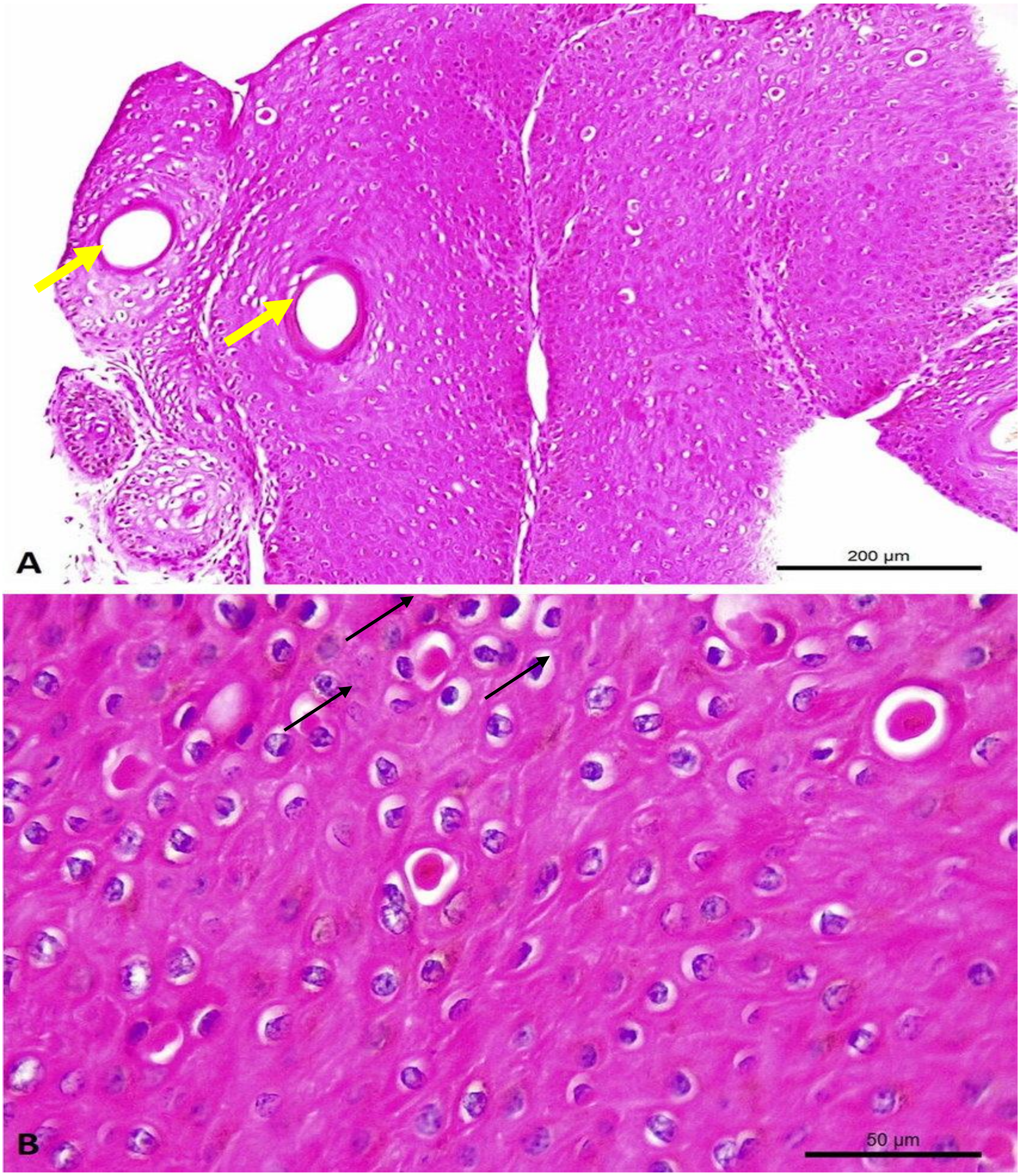

Figure 4. Histopathologic features of cutaneous bovine papilloma. **A**: There is the proliferation of epithelial cells at the stratum spinosum with varying degrees of ballooning degeneration (yellow arrows). **B**: Several epithelial cells have enlarged, condensed nuclei, and some are apoptotic (black arrows). Hematoxylin and eosin stain; Bar, A. 200 µm, B. 50 µm. Source: Crespo et al. (2019).

Squamous cell carcinoma

Bovine squamous cell carcinoma (SCC) is a cancer that develops in the squamous cells of the skin, specifically keratinocytes (Moharram et al., 2019). It is the second most common type of tumor in cattle, following bovine papilloma (Mithila et al., 2020). Bovine SCC tends to grow rapidly on various body parts, with a particular prevalence on the eyelids, especially following prolonged exposure to sunlight (da Cruz Campos and Pimentel, 2023). Additionally, mechanical irritations, injuries, and burns can also contribute to the development of SCC (Moharram et al., 2019).

This type of cancer generally occurs in cattle over the age of seven and is rare in those younger than three years old (da Cruz Campos and Pimentel, 2023). Bovine SCC is more common in cattle with white hair and light-colored skin, particularly in breeds such as Holsteins and Ayrshires (Moharram et al., 2019). Besides ultraviolet (UV) light, bovine ocular SCC may also be caused by viral agents, although the specific causative agent remains unknown (Vasconcelos et al., 2023).

Macroscopic appearance

Squamous cell carcinoma (SCC) appears as large nodular and cauliflower-like lesions, characterized by exophytic, ulcerated, and friable features (da Cruz Campos and Pimentel, 2023). As indicated in Figure 5, bovine SCC can present as nodular and hemorrhagic, accompanied by purulent discharge, and may metastasize to the retro-pharyngeal lymph nodes (Mathewos et al., 2020). Figure 6 shows Gross pictures of cattle affected with ocular squamous cell carcinoma (Timurkan and Alcigir, 2017). Similarly, Figure 7, indicates gross pictures of cattle affected with ocular Squamous cell carcinoma (Timurkan and Alcigir, 2017).

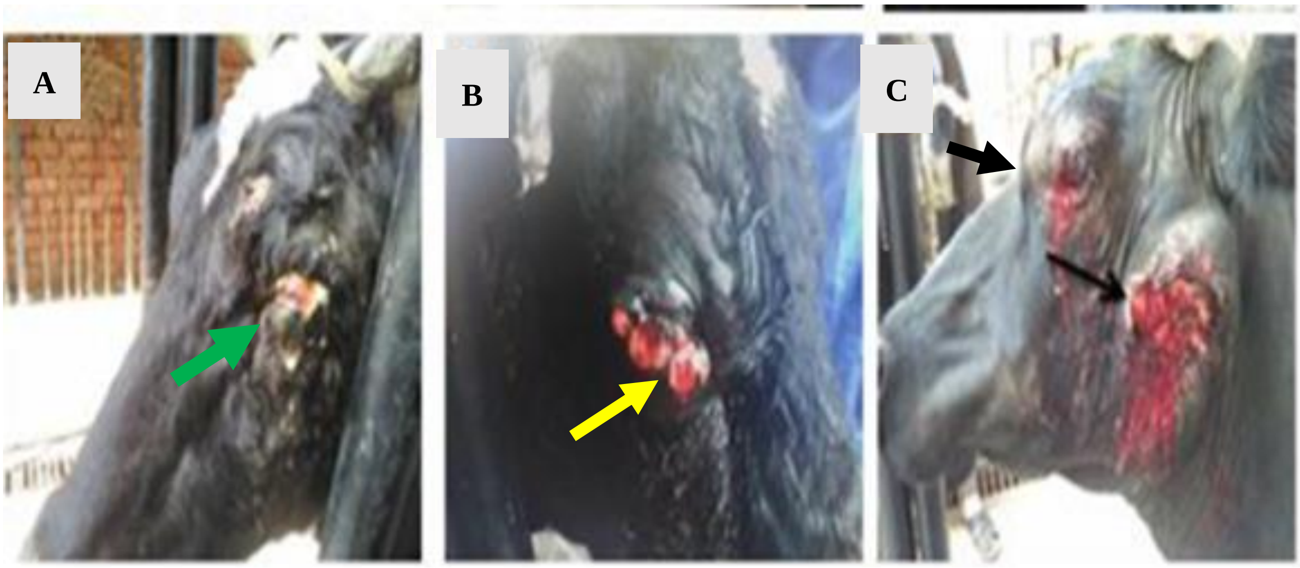

Figure 5. Gross pictures of cattle affected with squamous cell carcinoma. **A:** Bovine SCC on the eyelid (green arrow), **B:** SCC developed with hemorrhagic on the eyelid (yellow arrow), and **C:** The eyelid and the proximal part of the mandible region are affected and an ulcer is obvious (black arrows). Source: Moharram et al. (2019).

Figure 6. Gross pictures of cattle affected with ocular squamous cell carcinoma (yellow arrow). Source: Timurkan and Alcigir (2017).

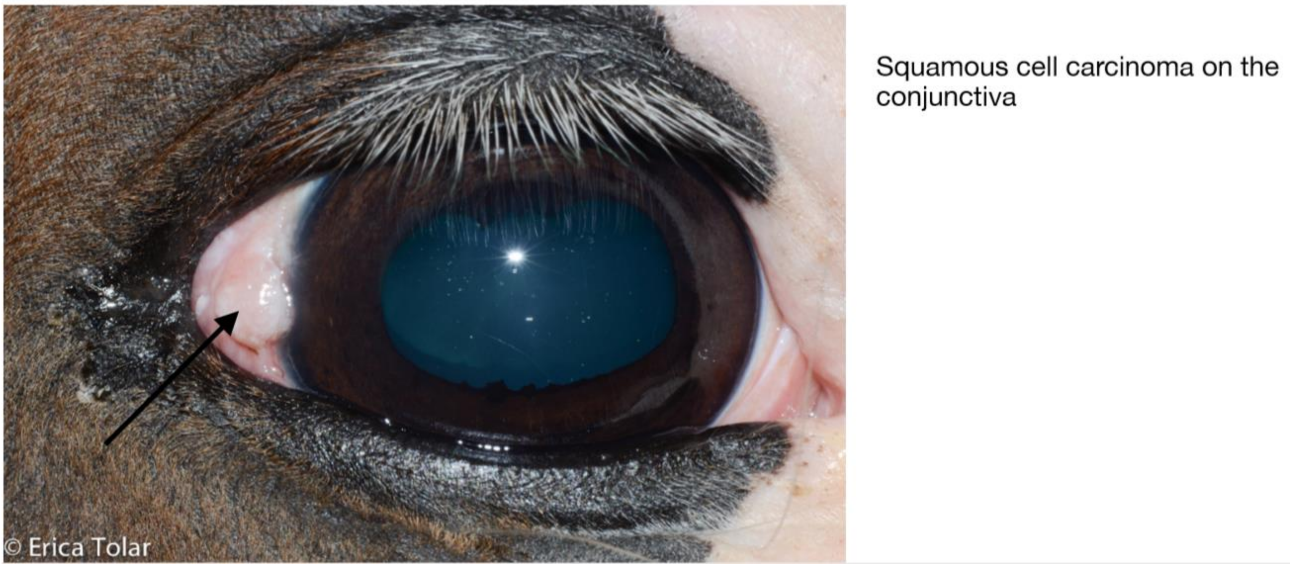

Figure 7. Gross pictures of cattle affected with ocular Squamous cell carcinoma (black arrow); Source: Timurkan and Alcigir (2017).

Microscopic appearance

The tumor reveals the proliferation of anastomosing nests, sheets, and strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis (Hunt, 2017). The neoplastic cells differentiate to form distinct keratin pearls, which are characteristic of squamous cell carcinoma (Flores-Balcázar et al., 2020). At higher magnification, keratin tonofilaments are visible as intracytoplasmic eosinophilic fibrillar material (Moharram et al., 2019). Additionally, mitotic figures, pleomorphism, hyperchromatism of the neoplastic cells, enlarged and prominent nucleoli, and vacuolation of neoplastic cells are evident (Timurkan and Alcigir, 2017). As indicated in Figure 8, Microscopic appearance of SCC in cattle, tumor masses show round masses of keratin pearls in SCC (Habte, 2022). Similarly, Figure 9, indicates the Microscopic appearance of SCC in cattle, Tumor masses show round masses of keratin pearls in SCC (Habte, 2022).

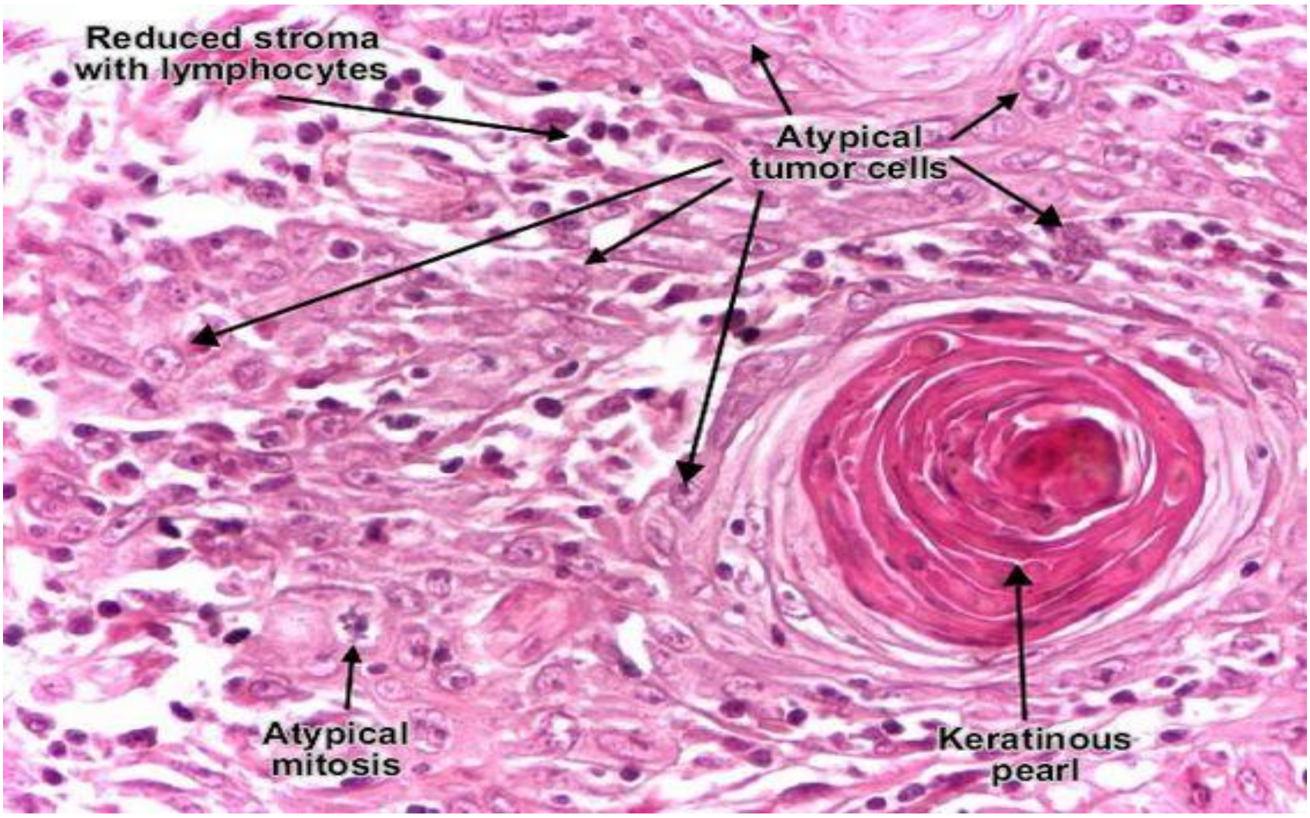

Figure 8. Microscopic appearance of Squamous cell carcinoma in cattle. Tumor masses show round masses of keratin pearls in Squamous cell carcinoma (black arrow). Haematoxylin & Eosin, 40x, Source: Habte (2022).

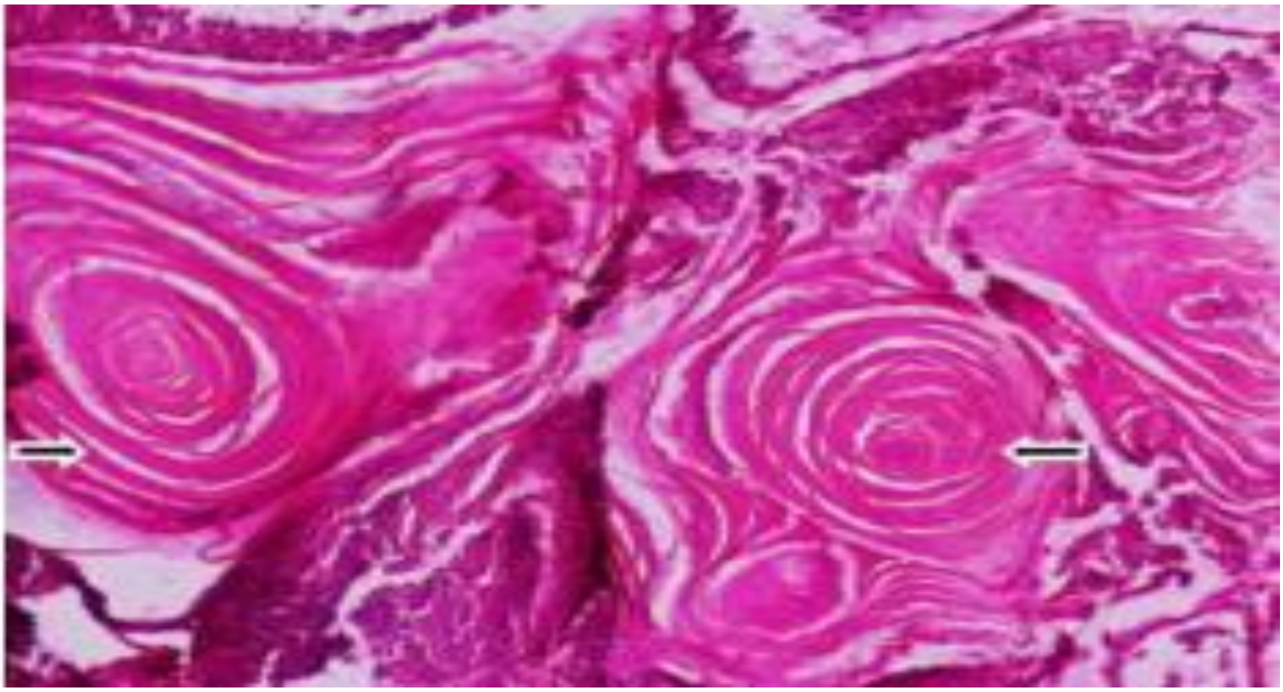

Figure 9. Microscopic appearance of Squamous cell carcinoma in cattle. Tumor masses show round masses of keratin pearls in SCC (arrows), Haematoxylin & Eosin, 40x, Source: Habte (2022).

Bovine lymphosarcoma

Cutaneous lymphosarcoma is another common type of tumor in cattle (Mathewos et al., 2020). Lymphoma is a cancer of the lymphatic system that develops from lymphocytes (Vasconcelos et al., 2023). It is classified as a diffuse malignant lymphoma that can arise in the skin, lymph nodes, or other lymphoid tissues (da Cruz Campos and Pimentel, 2023). Lymphoma is considered primarily cutaneous when the lymphatic proliferation is confined to the skin, with no involvement of the bone marrow, lymph nodes, or viscera at the time of diagnosis (Xiao et al., 2020).

Lymphosarcoma in cattle may be sporadic, occurring in calves and young herds without a known cause, or it may result from infection with the bovine leukemia virus (BLV), commonly referred to as enzootic bovine leucosis, which primarily affects adults (Vasconcelos et al., 2023). Bovine lymphosarcoma is transmitted through contaminated blood containing infected lymphocytes (Habte, 2022). Cutaneous lymphosarcoma is most common in cattle aged 1–3 years (Xiao et al., 2020) and is extremely rare in sheep, goats, and swine (Xiao et al., 2020). While lymphosarcoma can occur in all breeds, it is most frequently observed in Holsteins (Moharram et al., 2019).

Gross lesion appearance

Cutaneous lymphosarcoma presents as cutaneous plaques measuring 1–5 cm in diameter, appearing as yellow-tan discrete nodular masses or diffuse tissue infiltrates on the neck, back, rump, and thighs (Mathewos et al., 2020). This form of lymphosarcoma may undergo spontaneous remission; however, relapses can occur (Xiao et al., 2020). Additionally, local lymph nodes may become enlarged, exhibiting colors that range from white to tan (Neerja et al., 2018). Lymphosarcoma tumors are often multifocal and commonly involve the neck and trunk surfaces, presenting as variable-sized firm nodules and lesions that resemble an urticarial reaction (Constable et al., 2017). The overlying skin may appear normal, or it may show variable alopecia, hyperkeratosis, or ulceration, as indicated in Figure 10 (Sokołowska-Wojdyło et al., 2015).

Microscopic appearance

Histological and cytological preparations reveal sheets of a relatively homogeneous population of neoplastic lymphocytes (Moharram et al., 2019). The tumor masses are composed of closely packed, monomorphic lymphocytic cells (Mathewos et al., 2020), along with extensive dermal invasion by lymphoblasts (Crespo et al., 2019). As indicated in Figure 11, Microscopic appearances of lymphosarcoma have shown tumor mass showing pleomorphic small to medium and round to oval neoplastic lymphocytes separated by a delicate collagenous fibrous tissue in lymphoma (Habte, 2022). The tumor mass shows pleomorphic small to medium and round to oval neoplastic lymphocytes separated by a delicate collagenous fibrous tissue in lymphoma (Habte, 2022), as indicated in Figure 12.

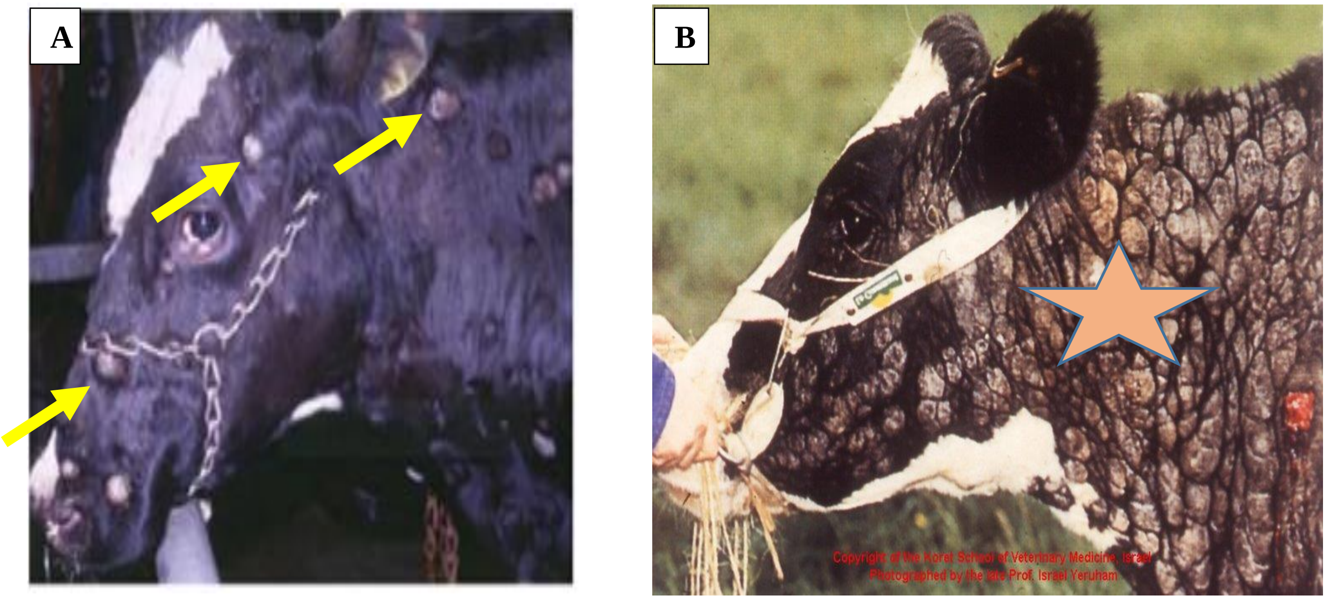

Figure 10. Gross appearance of cutaneous lymphosarcoma. **A:** Scattered lymphosarcoma on the skin (yellow arrows) and **B:** Over congested lymphosarcoma on the skin (star). Source: Mathewos et al. (2020).

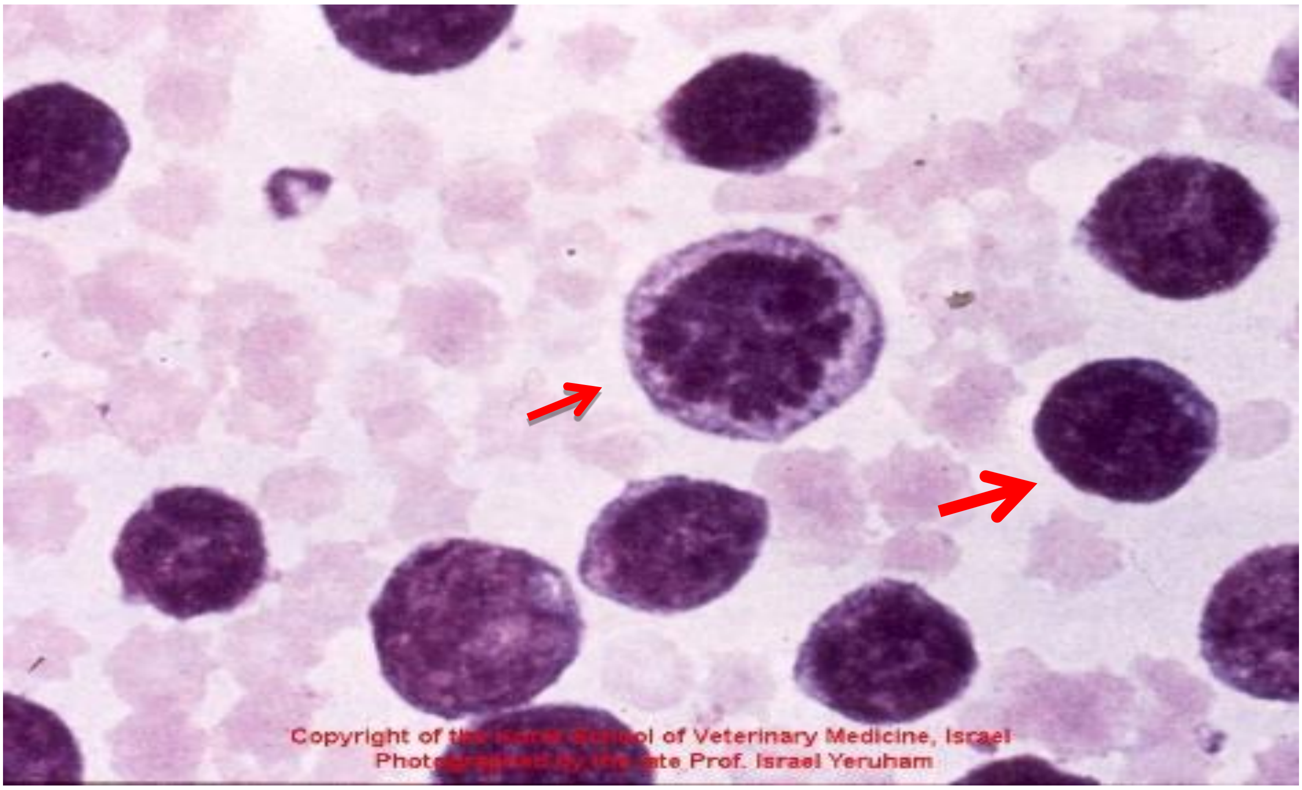

Figure 11. Microscopic appearances of lymphosarcoma. Cytological features of Lymphosarcoma (bovine leukemia) from Fine Needle Aspiration Cytology; and tumor mass showing pleomorphic small to medium and round to oval neoplastic lymphocytes separated by a delicate collagenous fibrous tissue in lymphoma (red arrows), Haematoxylin & Eosin, 40x, Source: Habte (2022).

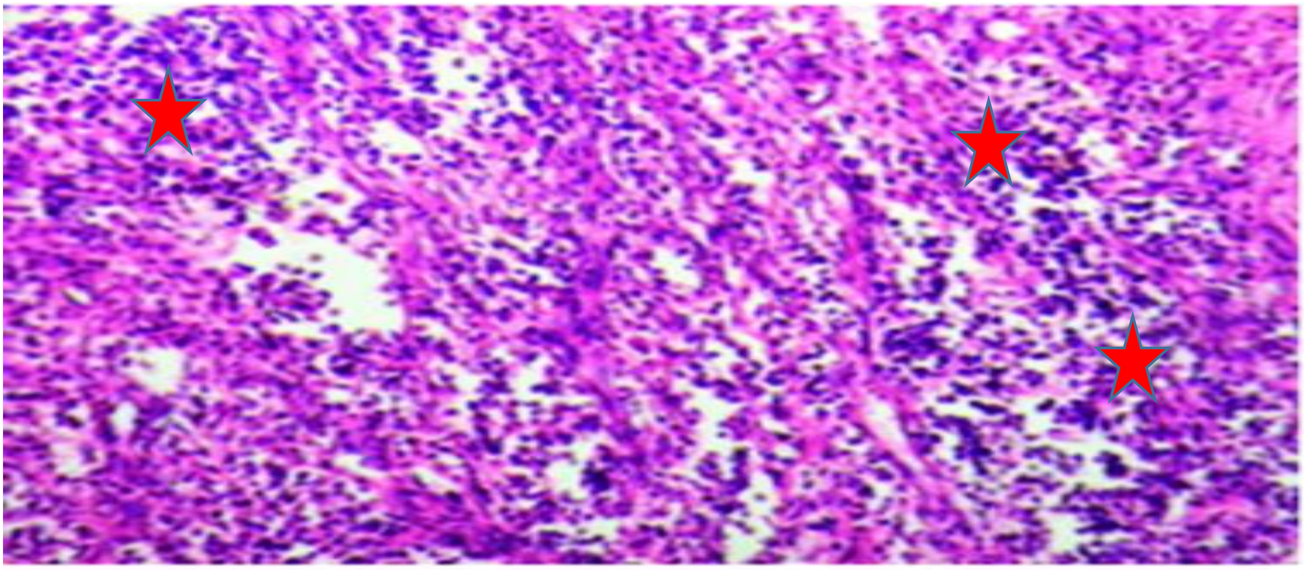

Figure 12. Histological appearances of lymphosarcoma in cattle (heifers). Tumor mass showing pleomorphic small to medium and round to oval neoplastic lymphocytes separated by a delicate collagenous fibrous tissue in lymphoma (red stars), Haematoxylin & Eosin, x40, Source: Habte (2022).

Melanoma

Melanoma is a benign tumor that arises from melanocytes, or pigment-producing cells (da Cruz Campos and Pimentel, 2023). The majority of melanoma cases occur on the skin surface of the head, neck, trunk, or legs; however, they can very rarely develop in the mouth, intestines, or eye (uveal melanoma) (Hunt, 2017). Despite being predominantly benign, there are rare reports of locally invasive tumors as well as metastasis to distant sites (Habte, 2022). The main cause of melanoma is exposure to UV light, particularly in individuals with low levels of the skin pigment melanin (da Cruz Campos and Pimentel, 2023).

Gross lesion appearance

The size of melanoma tumors in cattle varies widely, ranging from less than 5 cm to up to 25 cm (Constable et al., 2017). These tumors can appear as single or multiple, raised, firm masses that are typically black (Mathewos et al., 2020). The mass is composed of a proliferation of spindle to round-shaped cells that frequently contain abundant black pigment (Flores-Balcázar et al., 2020). On cross-section, melanoma appears as pigmented brown or black and oily (Figure 13).

Figure 13. Gross lesion of skin melanoma on the neck of cattle (red arrow), Source: Javanbakht (2014).

Histopathological appearance

Neoplastic melanocytes are arranged in sheets that resemble a band-like pattern (Mithila et al., 2020). Melanocytic tumors exhibit characteristic melanin-containing neoplastic cells, often mixed with heavily pigmented melanophages and arranged in nests and clusters, Cellular pleomorphism and mitotic activity are noted as variable features (da Cruz Campos and Pimentel, 2023).

In dendritic cell-type melanoma, dermal and/or hypodermal melanoma consists of cells with a dense, disordered, or band-like arrangement and an extremely high melanin content (Khalid et al., 2020). Cellular details can typically be observed only after discoloration (Mathewos et al., 2021). The cells are polyhedral or round, with numerous small dendritic cells present. Although mitoses are not abundant, necrotic foci are frequently observed (Mithila et al., 2020). As indicated in Figure 14. Microscopically melanoma has shown a proliferation of spindle to round-shaped cells containing abundant black glandular pigment (Khalid et al., 2020). As shown in Figure 15, Histological appearances of dermal melanoma in cattle, dermal melanocytoma, and round cell type occurred (Baba and Câtoi, 2007). Also, it shows, a proliferation of spindle to round-shaped cells (dendritic cell type) containing abundant brown glandular pigment (Figure 16) (Šitum et al., 2014). Moreover, Malignant melanoma shows, pleomorphic, and giant cell type proliferation (Figure 17) (Goldschmidt, 2016). Histological appearances of malignant melanoma, epithelioid cell type (Baba and Câtoi, 2007), as indicated in Figure 18.

In Ethiopia, various types of tumors from different origins are a common problem in domestic animals, including those of epithelial and mesenchymal origins (Feyisa, 2018; Mathewos et al., 2021). The most prevalent tumor in cattle among those of epithelial origin is squamous cell papilloma (Table 3). Similarly, among tumors of mesenchymal origin, cutaneous fibrosarcoma is observed on the dewlap of bulls (Habte, 2022). Cutaneous fibrosarcoma affects fibroblasts, a specific type of cell (Constable et al., 2017). Epithelial-origin tumors are the most frequently occurring tumor type in Ethiopia (Mathewos et al., 2020). A study conducted in Wolayita Sodo indicated that young animals are more susceptible to bovine papilloma than mature animals (Feyisa, 2018). This increased susceptibility has resulted in early culling or slaughtering of affected animals, leading to significant economic implications. As indicated in Figure 19, gross papilloma lesion on the mandibular, ocular, teat, shoulder, and cutaneous region (Mathewos et al., 2020).

The periocular squamous cell carcinoma (SCC) is located on the third eyelid of a bull (Mathewos et al., 2020). It can be grossly identified by its raised, irregular surfaces, with some portions being friable and soft, while most of the tumor is hard in consistency. The lesion is ovoid and varies in color from white to gray (Feyisa, 2018; Moharram et al., 2019). As indicated in Figure 20, both macroscopic and microscopic features of peri-ocular SCC (Mathewos et al., 2020). Figure 21, shows the Microscopic appearance of peri-ocular squamous cell carcinoma; Shows round masses of keratin pearls of peri-ocular SCC from the third eyelid of the local breed bull (Mathewos et al., 2020).

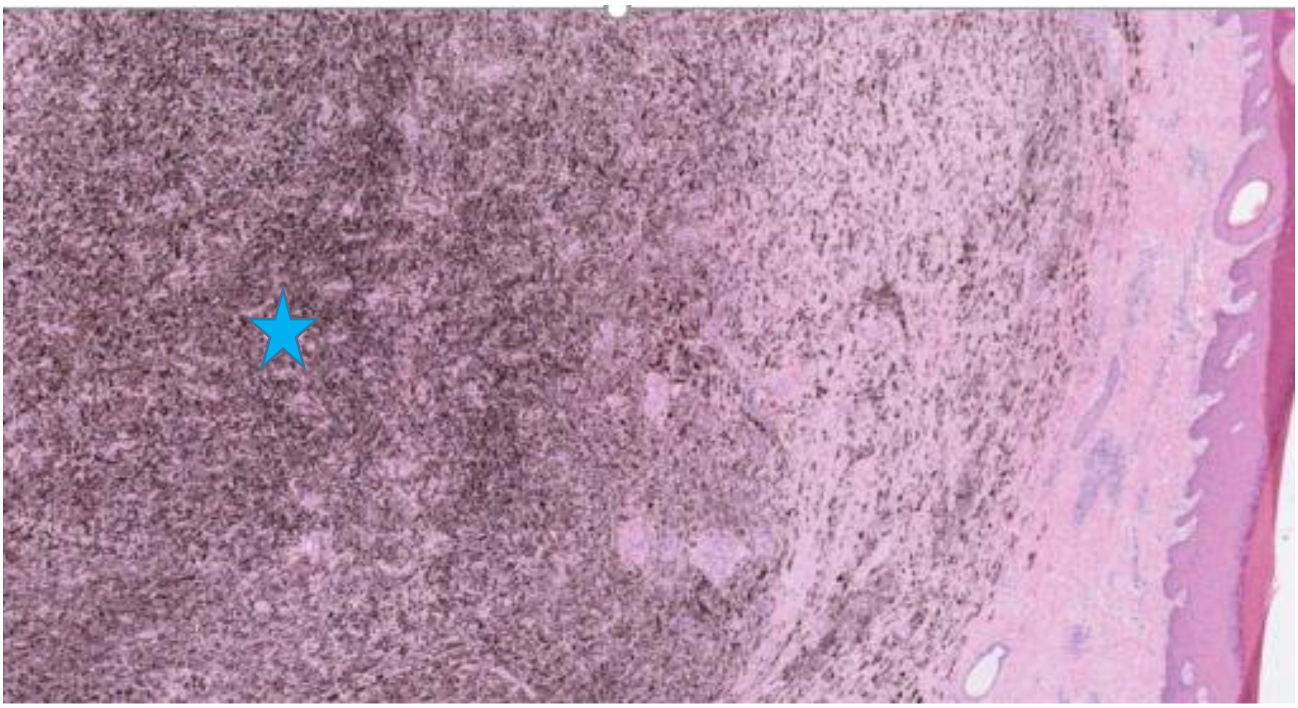

Figure 14. Microscopic appearance of a melanoma in heifer exotic breed. The Photomicrograph depicting a proliferation of spindle to round-shaped cells containing abundant black glandular pigment, 4x (blue star), Source: Khalid et al. (2020).

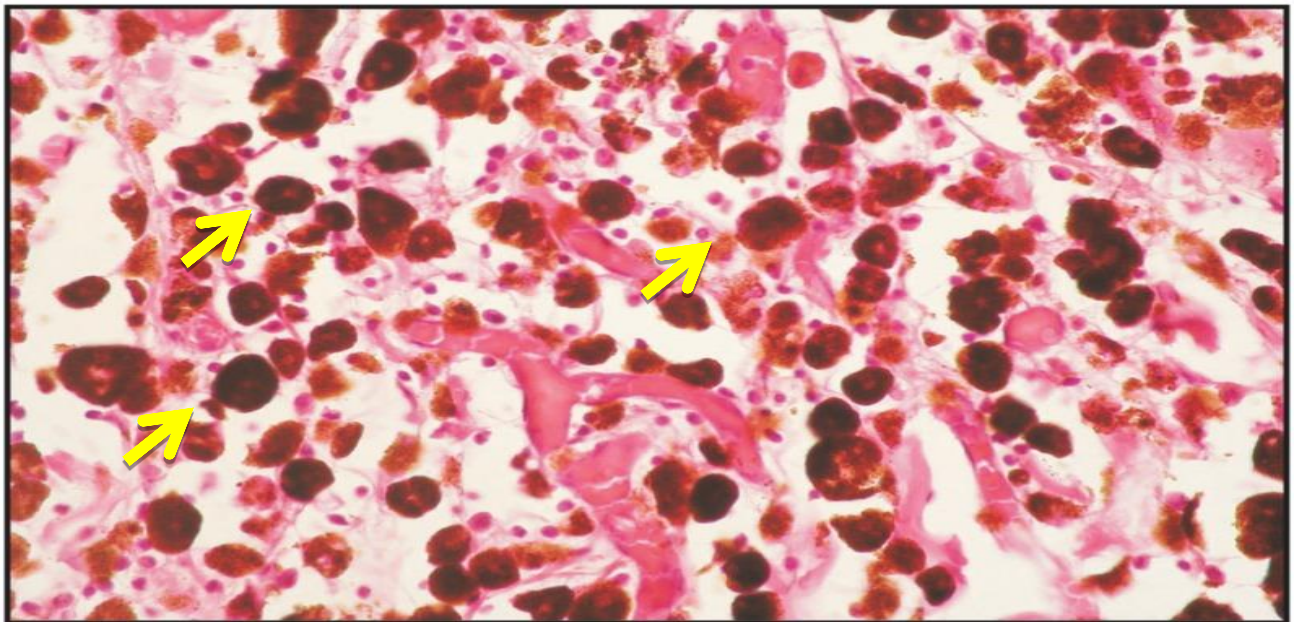

Figure 15. Histological appearances of dermal melanoma in cattle. Dermal melanocytoma, round cell type, 10x (yellow arrows), Source: Baba and Câtoi (2007).

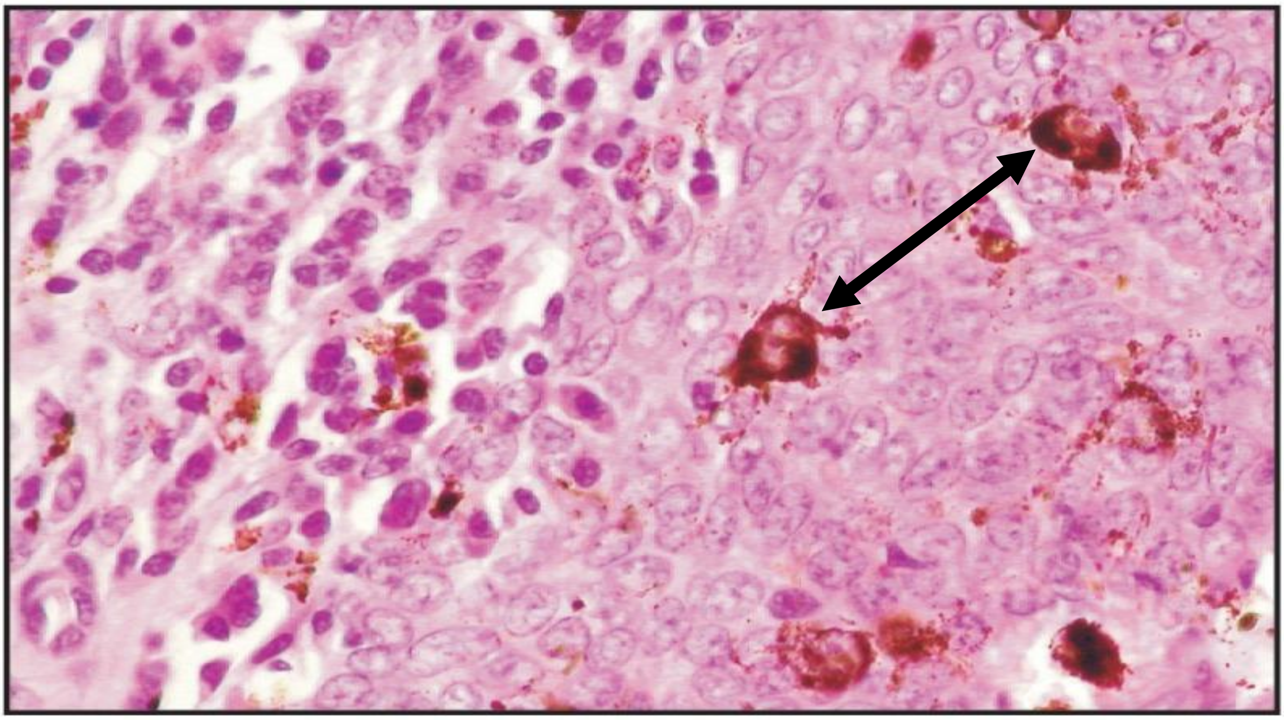

Figure 16. Histological appearances of melanoma in cattle. Photomicrograph depicting a proliferation of spindle to round-shaped cells (dendritic cell type) containing abundant brown glandular pigment, 10x (double black arrow), Source: Šitum et al. (2014).

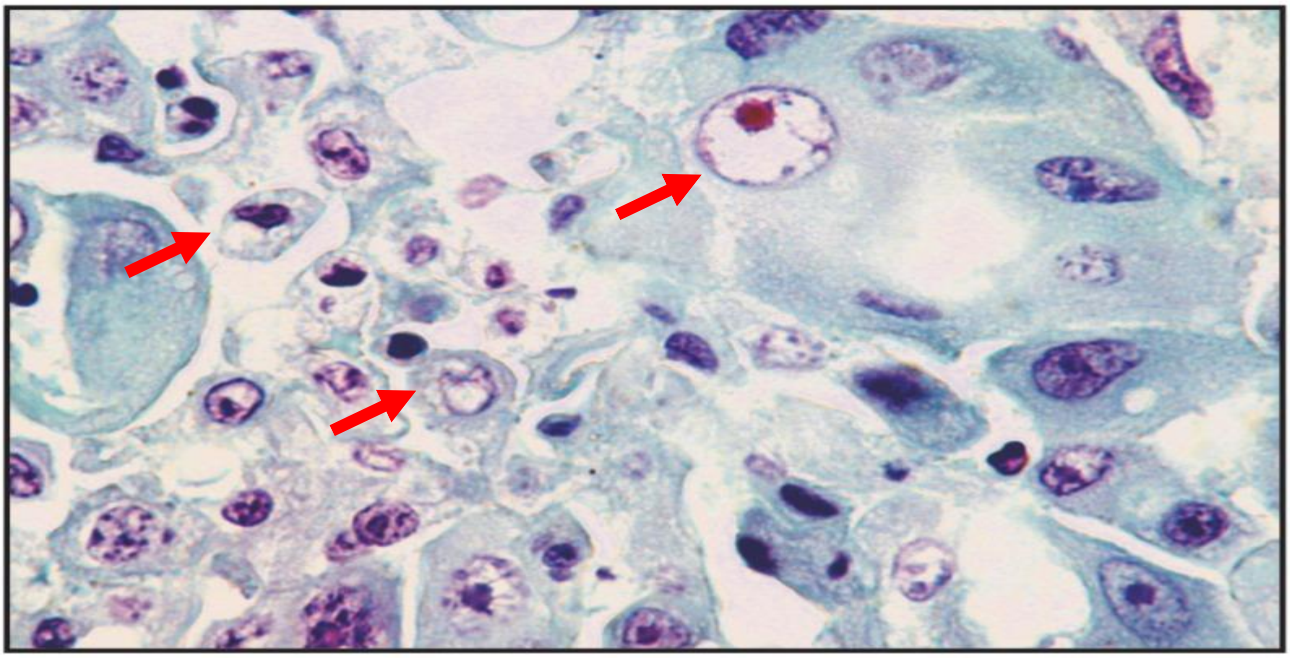

Figure 17. Histological appearances of melanoma in cattle. Photomicrograph depicting malignant melanoma, pleomorphic, and giant cell type, 10x (red arrows), Source: Goldschmidt (2016).

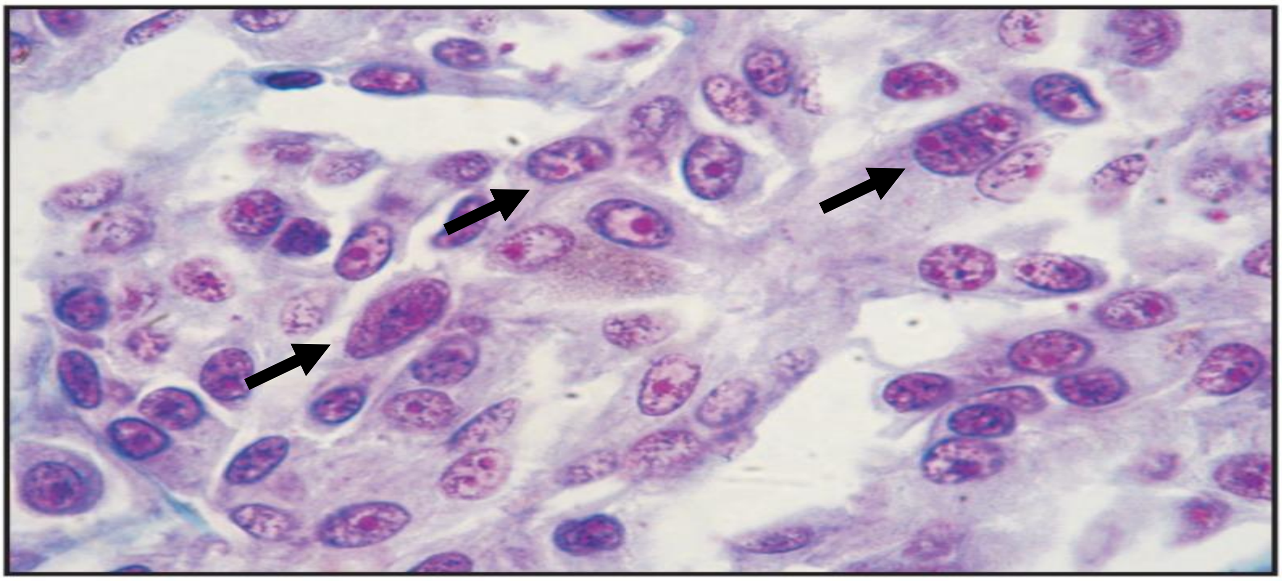

Figure 18. Histological appearances of melanoma in cattle. Photomicrograph depicting malignant melanoma, epithelioid cell type, 10x (black arrows), Source: Baba and Câtoi (2007).

Table 3. Frequencies of tumors of epithelial origin among domestic animals

Number	Tumor Type	Number of Cattle affected	Percent
1	Squamous cell papilloma	20	33.3
2	Ocular SCC	1	1.7
3	Basal Cell Carcinoma	-	
4	Mammary Gland Tumor Papillary Mammary Adenocarcinoma Carcinoma Mixed Type Mammary Adenocarcinoma	- - -	- - - -
5	Sertoli Cell Tumor	-	-
6	Atypical Anal Sac Adenocarcinoma	-	-
Total		21	35

Source: Feyisa (2018); Mathewos et al. (2020)

Figure 19. Gross appearance of papilloma on different body parts of cattle. **A**: gross papilloma lesion on the mandibular region (white arrow). **B**: gross papilloma lesion on the ocular region (white arrow). **C**: gross papilloma lesion on the leg region (white arrow). **D**: gross papilloma lesion on the teat region (white arrow). **E**: gross papilloma lesion on the shoulder region (white arrow). **F**: gross papilloma lesion on the cutaneous region (white arrow). **G**: gross papilloma lesion on the cutaneous region (white arrow), Source: Mathewos et al. (2020).

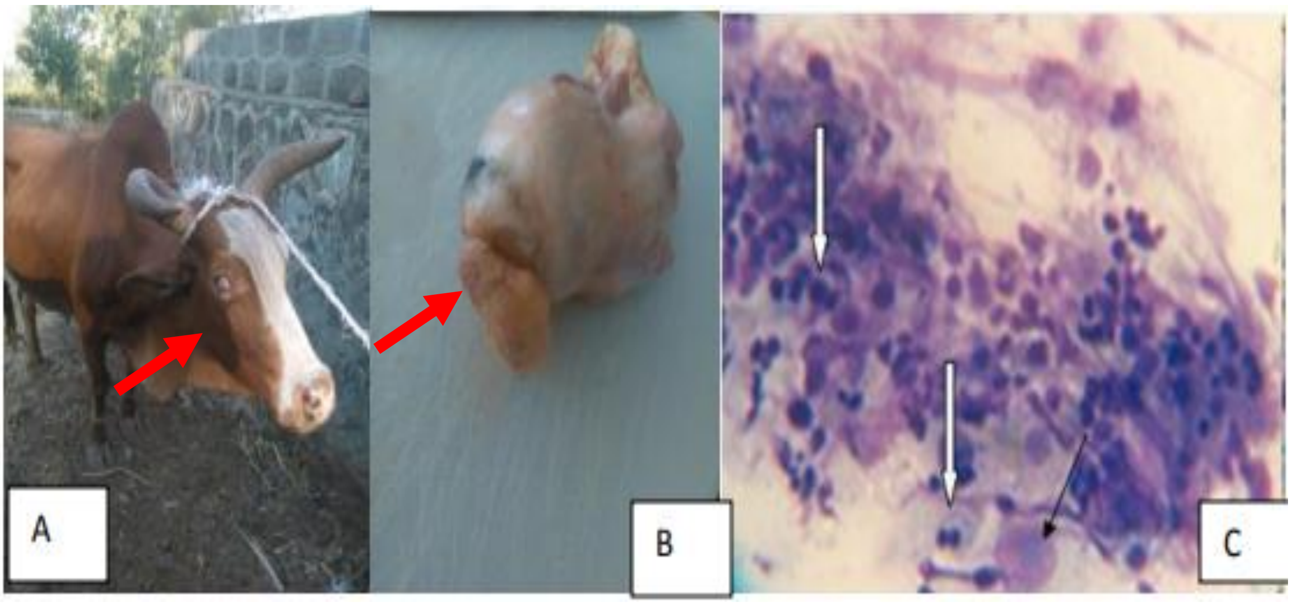

Figure 20. Gross and microscopic appearance of peri-ocular Squamous Cell Carcinoma (SCC). **A** and **B:** Represent the macroscopic features of peri-ocular SCC (red arrows). **C:** Shows the microscopic appearance of peri-ocular SCC from the third eyelid of the bull (white arrows), Source: Mathewos et al. (2020).

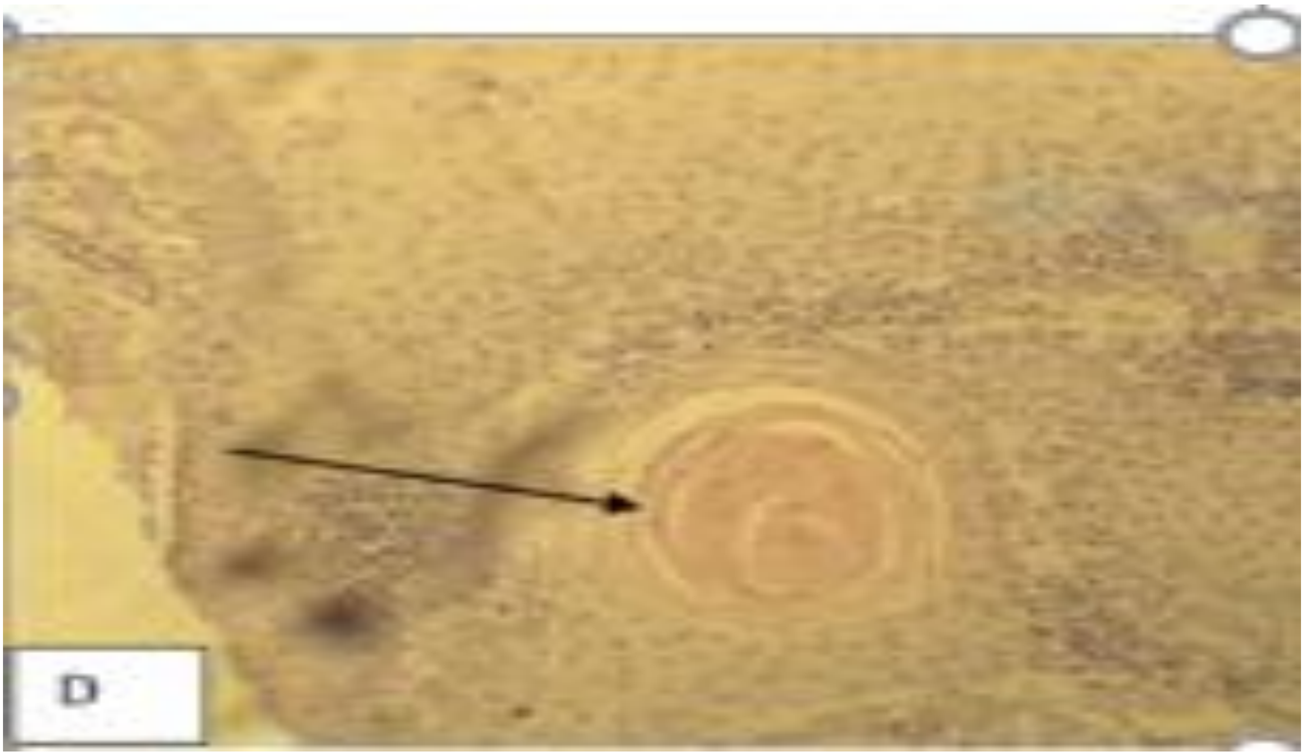

Figure 21. Microscopic appearance of peri-ocular squamous cell carcinoma. **D:** Show round masses of keratin pearls of peri-ocular SCC from the third eyelid of the local breed bull, 10x (black arrow), Source: Mathewos et al. (2020).

2.5. Cause and risk factors of skin tumor

Most tumors are linked to problems in gene expression (Mathewos et al., 2020). However, the specific causes of various skin tumors remain largely unknown (Hunt, 2017). Despite decades of research and advancements in early identification and therapy, the actual causes of most skin malignancies often associated with gene expression issues are still not fully understood (Kiupel, 2020). Some known tumor-inducing factors include excessive exposure to UV light, exposure to chemical toxins, for example; aflatoxins and reactive oxygen radicals, oncogenic viruses, and spontaneous changes in DNA replication (Habte, 2022). More than 90 percent of skin tumors are associated with UV radiation (Moharram et al., 2019). Additionally, factors such as skin color, species, lack of pigment, age, breed, sex, immune system disorders, and inherited conditions that increase sensitivity to sunlight all contribute to DNA mutations, potentially leading to either benign or malignant tumors (Moharram et al., 2019). In particular, cattle with white coats are more severely affected by skin tumors (Habte, 2022). Furthermore, exotic cattle breeds are more prone to tumors than indigenous breeds (Crespo et al., 2019).

Pathogenesis and development of skin tumor

Development

The mechanisms that lead to the formation and development of skin tumors are similar to those of other cancer types. Damage to a cell's genetic machinery is widely recognized as the etiology of all types of cancer (Khalid et al., 2020). Generally, the development of tumor lesions is a complex and often unpredictable phenomenon (Moharram et al., 2019). However, three phases are typically recognized in many tumors, including mutation (altered DNA replication), promotion, and irreversible tumor growth (Hunt, 2017).

The physiological process of tissue repair can sometimes lead to abnormal processes, especially when multiple foci of microdamage occur within the organism (Crespo et al., 2019). The pathophysiological mechanism involves multiple permanent (long-lasting) tissue microdamage, which, combined with sympathetic dominance, can sustain cell proliferation while inhibiting anti-tumor immunity (Hunt, 2017). The cancer reparative trap represents a resistant pathophysiological condition that contributes to the appearance, development, and progression of cancer (Bukhtoyarov and Samarin, 2015).

Skin tumor metastasis

Metastasis refers to the development of secondary cancer in locations other than the primary tumor (Khalid et al., 2020). The cells continue to proliferate in these new areas, eventually forming additional tumors composed of cells that resemble the tissue of origin (Mathewos et al., 2021). The spread of cancerous cells from a primary tumor to the skin is specifically referred to as skin metastasis (Kumar et al., 2015).

Genetic modifications in cancer cells provide advantageous properties, such as the ability to adhere to other cells, degrade the extracellular matrix, induce the secretion of normal cell-killing factors, increase cell motility, and spread through tissues (Timurkan and Alcigir, 2017). Additionally, these modifications allow for growth autonomy, resistance to anti-growth signals, evasion of apoptosis (immortality), and angiogenesis, all of which contribute to further cancer growth and dissemination in various tissues (Kumar et al., 2015). Several classes of molecules are involved in the metastatic cascade, including those that govern invasion (such as degradative enzymes and motility factors) and adhesion (including integrins, selectins, and cadherins, Khalid et al., 2020).

Diagnosis of skin tumor

Diagnosis of skin tumors can be performed clinically and histopathologically. Clinically, skin tumors can be identified through palpation and percussion of a raised, swollen, firm, nodular mass or any non-healing growth or lesion (Vasconcelos et al., 2023). Additionally, growths that are profusely bleeding should also be suspected as tumors (Habte, 2022). Histopathological diagnosis involves tissue biopsy and Fine Needle Aspiration Cytology (Khalid et al., 2020).

Histopathological examination

Histopathology is a method used to diagnose and understand abnormal cellular characteristics such as anaplasia, invasion, extreme mitosis, metastasis, and loss of polarity, all of which indicate malignancy (Timurkan and Alcigir, 2017). It is employed to differentiate between benign and malignant tumors (Vasconcelos et al., 2023). A skin or tissue biopsy is utilized to perform cytological and histological studies, and it is typically regarded as the gold standard for making a final diagnosis (Khalid et al., 2020).

Characteristics of cancer cells include high cellularity, cellular enlargement, an increased nuclear-to-cytoplasmic ratio, nuclear hyperchromasia, cell dis cohesiveness, and prominent, large nucleoli (Thomas et al., 2016). Additionally, cellular and nuclear pleomorphism, along with background tumor necrosis, are also important histological features of tumor cells (Mithila et al., 2020).

Application of immunohistochemistry for tumor diagnosis

Immunohistochemistry is the process of selectively identifying antigens (proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues (Mathewos et al., 2020). After tissue sections are incubated with the relevant antibodies, positive reactions (tumor antigen-antibody binding) are identified through the application of a detection system (Kabiraj et al., 2015).

This technique is used to understand the distribution and localization of biomarkers and differentially expressed proteins in various parts of biological tissue (Khalid et al., 2020). Tumor markers are biochemical indicators used to identify the presence of tumors (Ugochukwu et al., 2019). These markers can include cell surface proteins, cytoplasmic proteins, enzymes, or hormones (Mathewos et al., 2021). The system is highly sensitive because it allows for the attachment of a relatively large number of enzyme molecules, such as peroxidase, at the antigen site (Kabiraj et al., 2015). Specific molecular markers are characteristic of particular cellular events, such as proliferation or cell death (apoptosis), and examples include keratinocytes and various tumor antibodies and markers (Mithila et al., 2020).

Visualizing the antibody-antigen interaction can be accomplished in several ways. One method is chromogenic immunohistochemistry, where an antibody is conjugated to an enzyme, such as peroxidase (the combination is termed immunoperoxidase), which catalyzes a color-producing reaction (Mathewos et al., 2021). Common substrates for this reaction include diaminobenzidine (producing a brown color) or aminoethylcarbazole (producing a red color), with which the enzyme reacts (Kabiraj et al., 2015). Another method is immunofluorescence, where the antibody is tagged with a fluorophore, such as a fluorescent dye (Khalid et al., 2020).

Cytological examination

Cytological examination of tumors can be performed using the fine needle aspiration cytology (FNAC) technique (Ugochukwu et al., 2019). Cytology is an important tool that helps veterinarians distinguish tumors from inflammatory lesions (Mathewos et al., 2021). This process involves cell sampling by inserting a thin hollow needle into the tissue mass, followed by staining the collected cells and examining them under a microscope (Thomas et al., 2016). Other diagnostic techniques may include dermoscopy and various imaging modalities such as X-rays, computed tomography (CT) scans, positron emission tomography (PET), ultrasound, and magnetic resonance imaging (MRI, Mithila et al., 2020). Additionally, tests such as urine and blood analyses can provide valuable information for tumor diagnosis (Timurkan and Alcigir, 2017).

The economic impact of skin tumor

In Ethiopia, skin and hide account for 14–16% of all export revenue annually (Nigussu, 2014). However, the quality of raw materials poses significant challenges that hamper the leather industry (Vasconcelos et al., 2023). One of the primary causes of poor-quality skin is skin tumors, which lead to substantial economic losses (Kumar et al., 2015). Over time, the market share value of skin and hides has declined due to a decrease in leather prices on the global market, stemming from deteriorating skin quality (Mathewos et al., 2021). The economic losses associated with skin tumors are linked to the morbidity and mortality of domestic animals (Mathewos et al., 2020). Moreover, the morbidity of affected animals results in decreased body weight, reduced productivity and reproduction, difficulties during calving or milking, carcass condemnation, treatment costs, compromised skin quality, and decreased market value, as well as suckling problems and increased mortality (Kumar et al., 2015).

Periocular squamous cell carcinoma (SCC) can cause blindness in cattle, leading to early culling and accounting for approximately 12% of carcass condemnations (Mathewos et al., 2020). Another common skin tumor, lymphosarcoma, leads to extensive organ condemnation, contributing to 13.5% of beef cattle and 26.9% of dairy carcass condemnations (Mauldin, 2019). The estimated annual financial loss from carcass condemnations due to all types of tumors is approximately $2.2 million (Mathewos et al., 2020), highlighting the significant economic impact of skin diseases.

Skin tumors in the cattle industry lead to an increased culling rate due to metastasis to critical organs such as the lungs, liver, and draining lymph nodes, resulting in severe complications (Kumar et al., 2015; Mauldin, 2019). In the context of healthcare management for skin cancer, data from over 880,000 healthcare providers indicated that they received $77 billion in Medicare payments (Chen et al., 2016).

Management and medication of skin tumor

Prevention and management of tumors are challenging due to numerous environmental influences that can alter normal DNA replication (Mauldin, 2019). However, early diagnosis and treatment remain crucial for effective management before metastasis occurs (Khalid et al., 2020). Additionally, strengthening national policies and programs to raise awareness and reduce exposure to risk factors, such as prolonged UV radiation, is important (Achalkar, 2019).

The management and treatment methods for skin tumors may depend on the cancer's stage, the type of tumor, and the likelihood of cancer spreading or regressing (Thomas et al., 2016). Common management approaches for skin tumors include radiation therapy, chemotherapy, and surgical removal (Ugochukwu et al., 2019). Other methods may include electroporation, gene therapy, cryotherapy (using liquid nitrogen or carbon dioxide to freeze and destroy cancer cells, (Timurkan and Alcigir, 2017), and immunotherapy through the administration of inactivated tumor cells (Bukhtoyarov and Samarin, 2015). If the tumor is localized and confined to a specific area, surgery is prioritized; conversely, if it has widely spread, chemotherapy and radiotherapy become more significant (Xiao et al., 2020).

Chemotherapy

Chemotherapy can be administered subcutaneously, orally, or intravenously (Lotfalizadeh et al., 2022). Topical therapy drugs used for non-melanoma skin cancers, such as SCC and papilloma, include imiquimod and 5-fluorouracil (Timurkan and Alcigir, 2017). Systemic chemotherapy employs anticancer (cytotoxic) drugs that circulate through the bloodstream to target and destroy cancer cells (Ugochukwu et al., 2019). Common chemotherapy agents used to treat cancers like melanoma or to slow their growth include cisplatin and paclitaxel (Taxol, Xiao et al., 2020). Intravenous infusions of magnesium chloride have been reported to be effective in treating bovine cutaneous papillomatosis when lesions are few; this treatment is often combined with Ivermectin (Lotfalizadeh et al., 2022).

Drug therapy plays a crucial role in destroying cancer cells, slowing or halting their growth and spread (Khalid et al., 2020). It can also shrink tumors before surgical or radiation treatments, eliminate cancer cells that may remain post-surgery, and relieve or manage symptoms of advanced non-melanoma skin cancer (Mithila et al., 2020).

Nanophytosomes

Lipid-based nanocarriers called phytosomes combine phytoconstituents or plant extracts with phospholipids (Saeed et al., 2022). Through this conjugation, a complex with enhanced solubility, stability, and bioavailability is formed (Barani et al., 2021). The potential of phytosomes in cancer treatment has been documented in previous studies (Dubey et al., 2022). Curcumin, resveratrol, and quercetin phytosomes, for example, have demonstrated anticancer effects in a variety of *in vitro* and *in vivo* settings (Patra et al., 2021). Additionally, chemotherapeutic drugs including Paclitaxel, Docetaxel, and Camptothecin have been delivered via phytosomes with increased efficacy and decreased toxicity

(Alharbi et al., 2021). Several methods, such as solvent evaporation, thin-film hydration, and coacervation, can be used to create phytosomes (Alharbi et al., 2021).

A promising medication delivery method for enhancing the bioavailability and effectiveness of anticancer substances produced from plants is nanophytosomes (Alharbi et al., 2021). Compared to conventional delivery methods, these lipid-based nanocarriers have several benefits, including enhanced cellular absorption, higher bioavailability, and decreased toxicity (Saeed et al., 2022). The effectiveness of nanophytosomes in delivering phytoconstituents to cancer cells with little harmful effects on healthy cells has been demonstrated by recent research that has investigated the potential of nanophytosomes in cancer therapy (Saeed et al., 2022).

Silibinin has efficient anticancer properties against a variety of cancer cells, such as hepatocellular carcinoma, prostate cancer, breast cancer, and lung cancer, have drawn a lot of interest in recent years (Barani et al., 2021). The anticancer properties of silibinin have been explained by several different mechanisms (Saeed et al., 2022). One of the main strategies is to stop the growth of cancer cells by causing cell cycle arrest and death (Dubey et al., 2022). By targeting multiple signaling pathways, silibinin has also been demonstrated to prevent the angiogenesis, invasion, and metastasis of cancer cells (Saeed et al., 2022).

One of the most common forms of cancer is skin cancer, which is a serious global public health concern (Patra et al., 2021). An appealing method of treating skin cancers is the use of wound-healing substances that also have cytotoxic effects on cancer cells (Saeed et al., 2022). It has been demonstrated that sinigrin, a naturally occurring substance in the Brassicaceae family, has anticancer properties (Barani et al., 2021). The anticancer effects of Sinigrin's phytosomal formulation on A-375 melanoma cells and its wound-healing properties on normal human keratinocyte cells (HaCaT) were examined by Mazumder et al. in a novel study (Alharbi et al., 2021). The study found that when it came to cytotoxicity against A-375 cell lines, Sinigrin-loaded phytosomes significantly outperformed free Sinigrin (Saeed et al., 2022). Furthermore, normal cells (HaCaT) showed only mild cytotoxic effects (Patra et al., 2021). 50% more wound closure was observed at different doses and periods in the *in vitro* wound healing study using HaCaT cells (Dubey et al., 2022). These findings imply that phytosomes loaded with sinigrin might be a viable option for treating malignant wounds and cancer therapy (Saeed et al., 2022). It has been demonstrated that phytosomes, a novel delivery technology, increase the bioavailability of natural substances, including anticancer drugs (Barani et al., 2021). The lipid-based Sinigrin found in phytosomes is encased in a phospholipid bilayer (Dubey et al., 2022). This encapsulation improves the compound's stability and solubility, which raises its bioavailability (Saeed et al., 2022).

An innovative method of treating skin malignancies is the use of phytosomes loaded with Sinigrin as a therapeutic agent (Patra et al., 2021). It has been demonstrated that Sinigrin has anticancer effects by causing apoptosis and preventing cell division (Dubey et al., 2022). Sinigrin's phytosomal form may make it possible to deliver the drug to cancer cells more effectively while reducing its impact on healthy cells (Alharbi et al., 2021).

Mitomycin C (MMC) has demonstrated encouraging outcomes in the treatment of a variety of malignancies in addition to its strong anticancer properties (Patra et al., 2021). However, a significant barrier to MMC's therapeutic use has been its quick absorption into the systemic circulation (Barani et al., 2021). As a result, the drug's plasma concentration in the pertinent areas drops, which reduces the effectiveness of treatment (Saeed et al., 2022).

Turmeric, or *Curcuma longa*, is a long-used traditional herb that has been utilized for ages for its therapeutic qualities (Barani et al., 2021). It contains chemical substances known as curcuminoids and naturally occurring hydrophobic polyphenols, which have been demonstrated to have a wide range of pharmacological activity, including positive benefits in the treatment of various malignancies (Dubey et al., 2022). However, curcumin's poor oral solubility and bioavailability frequently impede its medicinal potential (Patra et al., 2021). To overcome these challenges and make its clinical application easier, several formulation techniques and other strategies have been developed (Saeed et al., 2022).

Vaccination

Vaccination remains the best prevention method against papilloma (Vasconcelos et al., 2023). Bovine papillomavirus (BPV) vaccine strategies typically involve the use of recombinant BPV L1 protein vaccines and the intradermal administration of autogenously produced wart vaccines (Ugochukwu et al., 2019). Due to the lack of available vaccinations, efforts to mitigate the risk of enzootic bovine lymphosarcoma focus on controlling the spread of the bovine leukemia virus and, in sporadic cases, reducing risk factors (Achalkar, 2019). Unfortunately, there is no curative treatment for viral infections or lymphosarcoma in cattle (Habte, 2022).

Radiation therapy

Radiation therapy involves exposing the cancerous part of the body to high doses of radiation, which can destroy rapidly growing cells and shrink tumors. This treatment is targeted specifically to the area where the cancer is developing

(Hennequin et al., 2016; Low and Sahi, 2016). Radiation can also be applied after surgery as an adjuvant therapy to eliminate any small areas of remaining cancer cells that may not have been visible during the procedure (Lotfalizadeh et al., 2022).

CONCLUSION

Skin tumors are the most frequently diagnosed neoplastic disorders in bovines, with bovine papilloma and squamous cell carcinoma being particularly prevalent. Bovine papilloma tumors, in particular, are among the most commonly diagnosed and economically significant tumors in cattle. Although the specific causative agent remains unknown, most skin tumors are associated with prolonged exposure to ultraviolet radiation. These tumors lead to substantial economic losses due to reduced productivity, decreased reproduction, calving, and milking difficulties, treatment costs, suckling problems, early culling, carcass condemnation, and management expenses. Given the economic significance of skin tumors in Ethiopia, skin tumors warrant greater attention from researchers and control centers. Early diagnosis and management of skin tumors are critical issues that need to be addressed.

DECLARATIONS

Competing interests

The authors declared that there is no conflict of interest.

Author's contributions

Mengesha Ayehu Getnet wrote the draft of the paper. Asnakew Mulaw Berihun supervised the drafts and revised the draft of the manuscript. All authors checked and approved the final draft of the manuscript.

Ethical considerations

All authors have contributed to the preparation of this paper. The authors observed the final version of the finished paper and evaluated any corrections and updates. They also checked the similarity index of article.

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Availability of data and materials

Since this manuscript has been prepared as a review article it has only used different journal papers that have been done on bovine skin tumors. Therefore, there is no Excel available data.

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