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Neoplasias in Fish: Review of the Last 20 Years. A Look from the Pathology

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Authors' contributions

This work was carried out in collaboration between both authors. The author LAR managed the writing and diagnoses reported in LIPOA and the author VFP collaborated with the literature search. Both authors read and approved the final manuscript.

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ABSTRACT

In fish there is an innumerable variety of neoplasias that arise essentially from all cell types. Neolasia here, we will focus on the neoplasias that appear spontaneously in these animals and will not cover the experimentally induced neoplasias and/or the animal models of neoplasias. As for diagnosis, in general, specialists in aquatic organism pathology are not so familiar with the diagnosis of neoplasias. Infectious pathology, as opposed to non-infectious pathology, is the predominant condition in this area and, of course, these are of greater importance because some infectious diseases generate great economic losses, while neoplasias are isolated pathologies, with some exceptions.

In the last 20 years, 10 neoplasias in different species have been diagnosed in our laboratory, and we reported their characteristics in this paper. We also made a detailed bibliography review and observed how 90 neoplasias among 56 species of teleosteal fish were reported.

Neoplasias in fish, unlike other diseases, do not generate great losses to aquaculture. However, the true value of neoplastic pathology compared is to better understand the histiogenesis and biological behavior of neoplasias in mammals and humans. Carcinogenesis is generally complex and in most neoplasias in both mammals and fish, the origin is unknown, and it seems that there are many factors that contribute to the onset and growth of neoplasias.

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1. INTRODUCTION

Neoplasia literally means "new growth" and neoplasm is the result of this new growth. The term 'tumor' originally was applied to the swelling caused by the inflammation. Neoplasias can also induce swelling, but for a long time the term neoplastic has barely been used, so the term is now equivalent to neoplasia. Cancer, in turn, is the common and generic term for all malignant tumors, but in reality, it refers to carcinoma, a type of malignant neoplasia originating in epithelia. Although the ancient origins of this term are somewhat uncertain, it is probably derived from the Latin 'crab', cancer, presumably because a cancer "adheres to any part that stubbornly grabs like a crab" [1,2].

2. NEOPLASMS IN TELEOST FISH

In this review, we will adopt the term neoplasia in general and carcinoma and sarcoma in specific situations, with some exceptions, when unavoidable. Although all pathologists know what they mean when they use the term neoplasia, it has been surprisingly difficult to develop a precise definition. The eminent British oncologist Rupert Allan Willis [3] provided one of the most acceptable definitions: “A neoplasm is an abnormal mass of tissue, whose growth exceeds and is not coordinated with that of normal tissues and persists in the same excessive manner after the stimuli that triggered it have ceased”. To this characterization we could add that the abnormal mass has no purpose, feeds on the host, and is virtually autonomous and, besides invading organs and interfering with their normal function and negatively impacting the immune system of a host, the neoplasias have their own histocompatibility antigens [4,5]. In fact, recent advances in cancer therapy in mammals and humans have shown clear benefits in stimulating the immune system. The inhibition of immune control points, whose efficacy requires that tumor antigens be recognized by T cells, favors neoplasia growth. This critical step is mediated by interactions of the Major Histocompatibility Complex (MHC) with T-cell receptors. Class I MHC molecules are expressed by the majority of nucleated cells and contain mainly peptidic antigens derived endogenously from CD8 T cells [6].

When we say that neoplasias "feed on the host" it is because the neoplastic tissue competes with normal cells and tissues for supplying energy and the nourishing substrate for their growth. As these masses can multiply in an individual who is debilitated, they are to some extent autonomous. Further on, it becomes evident that this autonomy is not complete. All neoplasias ultimately depend on the host for their nutrition and vascular supply; many forms of neoplasias require endocrine support [7,8]. Some neoplastic cells are "immortal"; they die when the host dies, which indicates the intimate and intricate neoplasia/host relationship [9,10].

The process of neoplasia is not limited to mammals; it can also develop in most vertebrates and in some insects and plants, and its occurrence in these other life forms has been useful to study its histiogenesis and its biological behavior [11-15].

In fish there is an innumerable variety of neoplasms that arise essentially from all cell types. In this review, we will focus on the neoplasms that appear spontaneously in these animals and we will not cover the experimentally induced neoplasias and/or the animal models of neoplasias, for which the fish has been of great scientific importance [16]. The frequency of neoplasias in fish is not negligible; only one author compiled 407 neoplasias in several species of fish and of various tissue origins a few decades ago [17]. On the other hand, several books on fish pathology dedicate some chapter to this theme [18-24].

All neoplasms, benign and malignant, have two basic components: first, neoplastic cells in proliferation that constitute their parenchyma and second, supporting stroma formed by connective tissue and blood vessels. Although the parenchymal cells represent the "vanguard" proliferation of neoplasias and, therefore, determine their nature; the growth and evolution of neoplasias critically depend on their stromatous environment [25]. An adequate stroma allows the supply of necessary blood to the stromatous connective tissue and provides a basis for the growth of neoplastic cells [26,27]. In some neoplasias, the stromatous support is scarce, causing it to be soft and fleshy. Sometimes parenchymal cells stimulate the formation of an abundant collagen stroma, called desmoplasia and therefore macroscopically are hard [28]. However, the nomenclature of

neoplasms is based mainly on the parenchymatous component.

In general, benign neoplasias are designated by adding the suffix "oma" to the cell of origin. Mesenchymal cell neoplasias generally follow this rule. For example, a benign neoplasia that arises from fibroblastic cells is called fibroma [29], while a cartilaginous neoplasia is a chondroma and an osteoblast neoplasia is an osteoma [30-32]. In contrast, the nomenclature of benign epithelial neoplasms is more complex. They are classified in several ways, some based on their cells of origin, others on microscopic architecture and still others on their macroscopic patterns. A benign epithelial neoplasm arising from glandular cells would be called adenoma [33,34]. Benign epithelial neoplasias that produce projections in the form of fingers or warts, visible microscopically or macroscopically, from the epithelial surfaces, are called papillomas [35]. Those that form large cystic masses, as in the ovary, are called cystoadenomas [36]. Some tumors produce papillary patterns that stand out through the cystic spaces and are called papillary cystoadenomas [37].

The nomenclature of malignant neoplasms follows essentially the same scheme used for benign ones, with some additions. Those arising from mesenchymal tissue are usually called sarcomas, such as fibrosarcoma, liposarcoma and leiomyosarcoma for smooth muscle neoplasms, and rhabdomyosarcoma for striated muscle neoplasms [38-41]. Epithelial cell derivatives are called carcinomas. Thus, the neoplasia that appears in the epidermis of ectodermal origin is a carcinoma, similar to the neoplasias that appear in the mesodermically derived cells of the renal tubules and endodermically derived cells of the lining of the gastrointestinal tract [42]. Carcinomas can also be qualified by their pattern and architecture; the glandular growth microscopically identified is called adenocarcinoma, and the one that produces recognizable squamous cells, which appears in any epithelium of the body, is called squamous cell carcinoma or epidermoid carcinoma. It is an additional common practice to specify, the source organ where possible [34]. However, it is not uncommon for a neoplasia to consist of undifferentiated cells and must be designated simply as a malignant neoplasia with little or no differentiation [43,44].

In most neoplasias, parenchymal cells look very much like each other, as if they were all derived from a single cell. Less frequently, the divergent differentiation of a single lineage of parenchymal cells creates what are called mixed neoplasias. The best example is the so-called carcinosarcomas; these tumors contain scattered epithelial components within a sarcomatous stroma which sometimes contain apparent cartilage islands or even bone [45]. The vast majority of neoplasias, including mixed neoplasias, are composed of cells representing a single embryonic layer. The teratoma, by contrast, is formed by a variety of parenchymal cell types representative of more than one germ layer, generally all three. They arise from totipotential cells and, therefore, are found mainly in the gonads, even if, on rare occasions, they are found in remnants of primitive cells abducted elsewhere. These totipotential cells differentiate themselves along several germinal pathways, producing, for example, tissues that can be identified as skin, muscle, fat, dental structures and, in fact, any body tissue [46-48].

The nomenclature of neoplasias is important because specific designations have specific biological implications. In the most common forms of neoplasia their name is related to histiogenesis and its biological behavior (benign or malignant). However, there are some inappropriate but deeply rooted uses. For generations, melanocyte neoplasias have been called melanomas, although they should be correctly called melanocarcinomas [49]. Similarly, lymphomas that are malignant, from different biological behaviors, are called with the suffix "oma", which would seem to imply benignity [50].

Similarly, aberrant differentiation can produce a mass of disorganized but mature specialized cells where the particular site is known as hamartoma. Therefore, a hamartoma may contain small islands of cartilage, blood vessels and lymphoid tissue. Sometimes the lesion is purely cartilaginous or purely angiomatous. Even if they can be interpreted as benign neoplasias, the total similarity of the tissue to cartilage or normal blood vessels and the occasional mixing of other elements favors a hamartomatous origin. In any case, hamartoma is totally benign [51,52].

In the vast majority of cases, the differentiation between a benign and a malignant neoplasia can be made morphologically with considerable

accuracy; sometimes, however, a neoplasia challenges categorization. It has already been said: "it is not necessary that all neoplasias be classified as benign or malignant". Certain histological characteristics may suggest innocence, while others point to an aggressive potential. Ultimately, every morphological diagnosis is subjective and constitutes a prediction of the future course of a neoplasia [53]. In some cases, this prediction is confused by a marked discrepancy between the morphological appearance of a neoplasia and its biological behavior. However, such deception or ambiguity is not the rule; in general, there are criteria by which benign neoplasias can be distinguished from malignant ones, which will behave according to such definition. These differences are related to differentiation and anaplasia of the cells that compose the neoplasia, their growth rate, invasion capacity, and ability to produce metastasis [54].

The terms 'differentiation' and 'anaplasia' apply to the parenchymal cells of neoplasia. Differentiation refers to the degree to which parenchymal cells resemble normal comparative cells, both morphologically and functionally. Therefore, well differentiated neoplasias are composed of cells that resemble the normal mature cells of the tissue of origin of the neoplasia. Poorly differentiatedor undifferentiated neoplasms have unspecialized cells of primitive appearance. In general, benign neoplasias are well differentiated. Smooth muscle neoplasia, a leiomyoma, resembles so much the normal cell that it is impossible to recognize it as a tumor cell in a high-resolution examination. Only by the massification of these cells, by counting and cell differentiation in a nodule, the neoplastic nature of the lesion is revealed, and it is possible to get closer to the 'tree that has lost sight of the forest' [55].

Malignant neoplasias, in turn, vary from well differentiated to undifferentiated. It is said that malignant neoplasias composed of undifferentiated cells are anaplastic. The lack of differentiation, or anaplasia, is considered a distinctive seal of malignant transformation. Literally, anaplasia means "reverse formation", which implies a reversion from a high level of differentiation to a lower level. However, there is substantial evidence that neoplasias arise from mother cells present in all specialized tissues. A well differentiated neoplasia evolves from a maturation or specialization of undifferentiated cells as they proliferate, while an undifferentiated neoplasia evolves without maturation of the transformed cells [56]. Thus, the lack of differentiation is not a consequence of 'dedifferentiation'. The lack of differentiation, or anaplasia, is marked by a series of morphological and functional changes. In a characteristic way, both the cells and the nuclei present a variation of pleomorphism in size and shape. It is possible to find cells that are many times larger than their neighbors and others that can be extremely small and primitive looking, and this is called anisocytosis. Characteristically, the nuclei of these cells contain a great amount of DNA and have a very dark coloration (hypercromatic). They are disproportionately large in relation to the cell and the proportion of the nucleus to the cytoplasm may reach 1:1, instead of the normal proportion of 1:4 or 1:6. The shape of the nucleus can be extremely variable, and the chromatin is usually grouped and roughly distributed along the nuclear membrane and this is called anisocytosis. Large nucleoli are usually present in these nuclei [57].

Compared to benign neoplasias and some well differentiated malignancies, undifferentiated ones generally have many mitoses, which reflects the greater proliferating activity of parenchymal cells [58]. The presence of mitosis, however, does not necessarily indicate malignancy or even that it is neoplastic tissue. Many normal tissues that exhibit a rapid change, such as the lymphohematopoietic cells of the pronefros, have numerous mitoses and the non-neoplastic proliferations, such as hyperplasia, contain many cells in the mitosis process [59]. More important as morphological characteristics of malignant neoplasia are the strange and atypical mitotic figures that sometimes produce tripolar, quadripolar or multipolar spindles. Another characteristic of anaplasia is the formation of giant tumor cells, where some have only one huge polymorphic nucleus and others have two or more nuclei. These giant cells should not be confused with those that are inflammatory, such as the enormous cells present in a foreign body or the typical Langhans cells of mycobacteria. In the neoplastic giant cell, the nucleus is hypercromatic and is large in relation to the cell [60]. Besides the cytological anomalies described here, the orientation of the anaplastic cells is markedly altered, that is, they lose their normal polarity, observing large masses of neoplastic cells that grow anarchically and in a disorganized manner [61]. Although these growing cells obviously require a blood supply, often the vascular stroma is scarce, and in many

anaplastic neoplasias, large central areas suffer ischemic necrosis [62].

It may be generalized that most benign neoplasms grow slowly over a period of years, while most malignancies grow rapidly, sometimes at an erratic rate, and eventually can spread and kill their hosts. At the other extreme are the neoplasms that grow more slowly and can also enter periods of lethargy that last for years.

A characteristic of many benign neoplasias is the development of a compression edge of connective tissue, sometimes called a fibrous capsule, which separates them from the host tissue. This capsule is largely derived from the stroma of native tissue as the parenchymal cells atrophy under the pressure of the expanding neoplasia. Such an encapsulation process tends to contain benign neoplasia as a discrete mass. Although there is this well-defined excision plane around most benign neoplasias, in some cases this process is not present. Therefore, hemangiomas (neoplasms composed of entangled blood vessels) are often not encapsulated and may appear to impregnate the site where they appear [63]. The growth of malignant neoplasias is accompanied by infiltration, invasion, and progressive destruction of surrounding tissue. The histological examination of these apparently encapsulated masses almost always reveals small neoplastic growth that penetrates the margin and infiltrates the adjacent structures [64].

Most malignant neoplasias are obviously invasive and can be expected to penetrate the surrounding tissue. Along with the development of metastasis, the degree of invasion is the most reliable feature that differentiates malignant from benign neoplasias.

Metastases are implants of discontinuous neoplastic tissue with the primary tumor. Metastasis unequivocally marks a neoplasia as malignant because benign ones do not cause metastasis [65].

It is therefore evident that the properties of invasion and metastasis are separable. In general, the more aggressive, faster growing, and greater the primary neoplasia, the greater is the probability that it already has metastasis. However, there are countless exceptions. Small, well differentiated, and slow growing lesions sometimes have a wide metastasis and, on the contrary, some fast-growing lesions may remain localized for years. The probability of metastasis cannot be judged from the pathological examination of primary neoplasia [66-68].

As for diagnosis, experts in aquatic organism pathology are generally not so familiar with diagnosing neoplasias. Infectious pathology, as opposed to non-infectious pathology, is the predominant one in this area and, clearly, these are of greater importance because some infectious diseases generate great economic losses, while neoplasms are isolated pathologies, with some exceptions, such as the case of melanomas in Xiphophorus, which have a genetic implication that can alter the production of these ornamental fish in aquaculture [69,70].

Although histopathology is a very useful tool for the diagnosis of diseases in general, in the case of neoplasias it has a fundamental role in diagnosis [71]. First, for the differential diagnosis, when observing the tissues, the first question is whether it is an inflammatory or neoplastic pathology. With some exceptions, such as certain inflammatory pseudotumors, the histopathological difference is clear, presenting no problem in differentiating between these pathologies [72]. When it is determined that it is a neoplasia, two questions immediately arise about its histogenesis and its biological behavior: from which tissue did this neoplasia originate? is it a benign or malignant neoplasia? In a high percentage of cases, with optical microscopy with H-E and other complementary techniques with dyes, the question is resolved [73]. In other cases, where the neoplasias are little differentiated or undifferentiated, the problem is aggravated. In our laboratory, in the last 20 years, 10 neoplasias were diagnosed in different species, whose characteristics can be seen in Table 1.

We performed a detailed bibliography review and observed how 90 neoplasias were reported among 56 species of teleosteal fish (Table 2-13).

Coinciding with Stoskopf [21], we observed that cyprinids are the ones that present more neoplasias. The author associates this to the fact that they have a very long life.

The vertiginous development of diagnostic methods and techniques in human medicine was immediately transferred to veterinary medicine and therefore to the pathology of aquatic organisms, which is a branch of veterinary medicine.

Table 1. Spontaneous neoplasms in teleost fish related in LIPOA between 2000-2020

Neoplasm	Species	Year	Diagnosis			References
			OM	IHQ	EM	
Thymoma	*Cyprinus carpio*	2004	Yes	No	Yes	Romano and Marozzi, 2004 [74]
Carcinosarcoma of mandible	*Onchorhyincus mykiss*	2010	Yes	Yes	No	Romano et al., 2010 [45]
Neoplasia of the sertoli cells	*Cyprinus carpio*	2013	Yes	Yes	Yes	Romano et al., 2013 [75]
Borderline ovarian cystadenoma	*Carasius auratus*	2014	Yes	Yes	No	Romano et al., 2014[64]
Multiple neurofibromas of the heart	*Cyprinus carpio*	2015	Yes	Yes	Yes	Romano et al., 2015 [76]
Alveolar rhabdomyosarcoma	*Carasius auratus*	2016	Yes	Yes	Yes	Wicki et al., 2016 [41]
Melanoma	*Carasius auratus*	2018	Yes	Yes	Yes	Romano et al., 2018 [77]
Haemangioma esclerosante	*Paralichthys orbignyanus*	2018	Yes	No	No	Klosterhoff et al., 2018[63]
Lymphoma	*Rachycentron canadum*	2019	Yes	Yes	No	Klosterhoff et al., 2019 [50]
Melanoma	*Xiphophorus hellerii*	2020	Yes	Yes	Yes	Romano et al., 2020 [78]

**OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 2. Spontaneous neoplasms in teleost fish related between 2000-2020

Family				Diagnosis			
	Neoplasm	Species	Year	OM	IHQ	EM	References
Acipenseridae	Haemangioma	*Acipenser baerii*	2018	Yes	No	No	Rezaie et al. 2018 [79]
	Nephroblastoma	*Huso huso x Acipenser ruthenus*	2018	Yes	Yes	No	Rahmati-Holasoo et al. 2018 [80]
Adrianichthyidae	Lymphoma	*Oryzias latipes*	2008	Yes	No	No	Hayashi et al. 2008 [81]
Anguillidae	Stomatopapillomatosis	*Anguilla anguilla*	2010	Yes	Yes	No	Marino et al. 2010[a] [82]
	Myxoma	*Anguilla anguilla*	2014	Yes	Yes	No	Gjurcevic et al., 2014 [83]
Ariidae	Fibrosarcoma	*Hemiarius dioctes*	2015	Yes	No	No	Dennis and Diggles, 2015 [40]
Callichthyidae	Skin nodular neoplasm	*Callichthys callichthys*	2003	Yes	No	No	Caruso et al. 2003 [84]
Characidae	Cutaneous ossifying fibroma	*Paracheirodon innesi*	2016	Yes	No	No	Murphy and Imai, 2016 [29]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 3. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				MO	IHQ	ME	
Cichlidae	Lymphoma	Hua Luo-Han	2008	Yes	No	No	Lin et al. 2008 [85]
	Adenoma	*Astronotus ocellatus*	2010	Yes	No	Yes	Hochwartner et al. 2010 [86]
	Squamous cell carcinoma	*Astronotus ocellatus*	2010	Yes	No	No	Rahmati-holasoo et al. 2010 [87]
	Liposarcoma	Flower horn fish	2016	Yes	No	No	Rahmati-Holasoo et al. 2016 [88]
Clariidae	Rhabdomyosarcoma	*Clarias gariepinus*	2017	Yes	No	No	Okorie-Kanu et al. 2017 [89]
Clinidae	Chromatophoroma	*Gibbonsia montereyensis*	2011	Yes	Yes	Yes	Camus et al. 2011 [90]
Clupeidae	Leiomyoma	*Sardina pilchardus*	2003	Yes	No	No	Ramos and Peleteiro, 2003 [91]
Congridae	Angioleiomyoma	*Conger conger*	2016	Yes	Yes	No	Marino et al. 2016 [92]

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Table 4. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				MO	IHQ	ME	
Cottidae	Squamous cell carcinoma	*Cottus gobio*	2016	Yes	Yes	No	Quaglio et al. 2016[93]
Cyprinidae	Melanoma	*Cyprinus japonicus*	2003	Yes	No	No	Ramos and Peleteiro, 2003[91]
	Haemangioma	*Carassius auratus*	2006	Yes	No	No	O'Hagan and Raidal, 2006[94]
	Ovarian carcinoma	*Cyprinus carpio*	2006	Yes	Yes	No	Raidal et al. 2006[95]
	Branchioblastoma	*Cyprinus carpio*	2007	Yes	No	No	Knüsel et al. 2007[96]
	Branchioblastoma	*Cyprinus carpio*	2010	Yes	No	No	Sholichah et al. 2010[97]
	Nephroblastoma	*Cyprinus carpio*	2010	Yes	No	No	Stegeman et al. 2010[98]
	Haemangioma	*Puntius sarana*	2012	Yes	No	No	Sahoo et al. 2012[99]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 5. Spontaneous neoplasms in teleost fish related between 2000-2020

Family				Diagnosis			
	Neoplasm	Species	Year	MO	IHQ	ME	References
Cyprinidae	Schwannoma	*Danio rerio*	2012	Yes	Yes	No	Marino et al. 2012[100]
	Haemangiosarcoma	*Cyprinus carpio*	2013	Yes	No	No	Hyatt et al. 2013[101]
	Ocular glioneuroma	*Carassius auratus*	2014	Yes	Yes	No	Mandrioli et al. 2014[102]
	Leiomyoma	*Carassius auratus*	2015	Yes	Yes	No	Oryan et al. 2015[103]
	Intestinal carcinoma	*Danio rerio*	2015	Yes	Yes	No	Paquette et al. 2015[104]
	Schwannoma	*Carassius auratus*	2015	Yes	Yes	Yes	Sirri et al. 2015a[57]
	Papilloma	*Carassius auratus*	2016	Yes	Yes	No	Lanteri et al. 2016[105]
	Chondroma	*Ctenopharyngodon idella*	2016	Yes	No	No	Mesbah et al. 2016[31]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 6. Spontaneous neoplasms in teleost fish related between 2000-2020

Family				Diagnosis			
	Neoplasm	Species	Year	MO	IHQ	ME	References
Cyprinidae	Rhabdomyosarcoma	*Hypophthalmichthys molitrix*	2016	Yes	No	No	Rezaie et al. 2016[106]
	Fibroma	*Carassius auratus*	2016	Yes	No	No	Shokrpoor et al. 2016[107]
	Myxoma	*Carassius auratus*	2016	Yes	No	No	Shokrpoor et al. 2016[107]
	Haemangiopericytoma	*Cyprinus carpio*	2016	Yes	Yes	Yes	Sirri et al. 2016[108]
	Fibrosarcoma	*Carassius auratus*	2017	Yes	No	No	Rezaie et al. 2017a[109]
	Chromatophoroma	*Cyprinus carpio*	2019	Yes	Yes	No	Siniard et al. 2019[110]
	Chromatophoroma	*Carassius auratus*	2019	Yes	Yes	No	Siniard et al. 2019[110]
	Papilloma	*Abramis brama*	2019	Yes	Yes	No	Iaria et al. 2019[111]

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Table 7. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Cyprinidae	Schwannoma	*Carassius carassius*	2019	Yes	Yes	No	Iaria et al. 2019[111]
Goodeidae	Ovarian teratoma	*Zoogoneticus tequila*	2016	Yes	Yes	No	Romanucci et al. 2016[48]
Lepisosteidae	Ovarian cystadenoma	*Lepisosteus oculatus*	2000	Yes	No	No	Thiyagarajah et al. 2000[36]
Lutjanidae	Neurofibroma	*Lutjanus griseus*	2000	Yes	No	No	Williams et al. 2000[112]
Moronidae	Fibropapiloma	*Dicentrarchus labrax*	2003	Yes	No	No	Ramos and Peleteiro, 2003[91]
	Lipoma	*Dicentrarchus labrax*	2011	Yes	No	No	Marino et al. 2011[113]
Mugilidae	Neurofibroma	*Mugil cephalus*	2010	Yes	Yes	No	Marino et al. 2010b[114]
Osphronemidae	Rhabdomyosarcoma	*Colisa fasciata*	2001	Yes	No	No	Iwanowicz et al. 2001[115]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 8. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Osphronemidae	Nephroblastoma	*Betta splendens*	2010	Yes	No	No	Lombardini et al. 2010[116]
	Melanoma	*Betta splendens*	2014	Yes	Yes	No	Rahmati-Holasoo et al. 2015[117]
	Iridophoroma	*Betta splendens*	2019	Yes	No	No	Rahmati-Holasoo et al. 2019[118]
Ostraciidae	Iridociliary melanoma	*Lactoria cornuta*	2010	Yes	No	No	Da Silva et al. 2010[119]
Percidae	Fibrosarcoma	*Perca flavescens*	2005	Yes	No	No	Bowser et al. 2005[120]
Poeciliidae	Melanoma	*Xiphophorus nezahualcoyotl*	2008	Yes	No	No	Fernandez and Bowser, 2008[70]
	Lipoma	*Poecilia velifera*	2012	Yes	No	No	De Stefano et al. 2012[121]
	Congenital teratoma	*Poecilia reticulata*	2014	Yes	No	No	Rahmati-holasoo et al. 2014[122]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 9. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Poeciliidae	Squamous cell carcinoma	*Xiphophorus maculatus*	2017	Yes	No	No	Rezaie et al. 2017b[123]
	Melanoma	*Xiphophorus* sp.	2019	Yes	Yes	No	Iaria et al. 2019[111]
Pomacentridae	Odontoma	*Amphiprion ocellaris*	2018	Yes	No	No	Vorbach et al. 2018[52]
Salmonidae	Renal carcinoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]
	Renal cystadenoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]
	Biliary cystadenoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]
	Leiomyoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]
	Rhabdomyosarcoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 10. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Salmonidae	Peri-hepatic teratoma	*Oncorhynchus tshawytscha*	2003	Yes	No	No	Lumsden and Marshall, 2003[124]
	Leiomyosarcoma	*Salmo salar*	2012	Yes	Yes	No	Bowser et al. 2012[38]
	Rhabdomyosarcoma	*Salvelinus fontinalis*	2015	Yes	Yes	Yes	Sirri et al. 2015b[125]
Sciaenidae	Sarcoma thymic	*Argyrosomus regius*	2012	Yes	No	Yes	Soares et al. 2012[126]
Scombridae	Lipoma	*Thunnus thynnus*	2006	Yes	No	No	Marino et al. 2006[127]
	Lipoma	*Thunnus maccoyii*	2008	Yes	Yes	No	Johnston et al. 2008[128]
	Neurofibrosarcoma	*Thunnus maccoyii*	2008	Yes	Yes	No	Johnston et al. 2008[128]
Serranidae	Seminoma	*Centropristis striata*	2002	Yes	No	No	Weisse et al. 2002[129]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 11. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Sparidae	Lymphoma	*Pagrus major*	2000	Yes	No	Yes	Miyazaki et al. 2000[65]
	Melanoma	*Plectropomus leopardus*	2012	Yes	No	Yes	Sweet et al. 2012[130]
	Schwannoma	*Sparus aurata*	2008	Yes	Yes	No	Marino et al. 2008[131]
Sparidae	Lipoma	*Lithognathus mormyrus*	2009	Yes	No	No	Gómez, 2009[132]
Sparidae	Lymphoma	*Rhabdosargus sarba*	2017	Yes	No	Yes	Singaravel et al. 2017[133]
	Iridophoric osteoma	*Rhabdosargus sarba*	2017	Yes	No	Yes	Singaravel et al. 2017[133]
	Osteoma	*Rhabdosargus sarba*	2017	Yes	No	Yes	Singaravel et al. 2017[133]
	Psammomatoid Ossifying fibroma	*Rhabdosargus sarba*	2017	Yes	No	Yes	Singaravel et al. 2017[133]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 12. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Sparidae	Fibroma	*Lithognathus mormyrus*	2019	Yes	Yes	No	Iaria et al. 2019 [111]
Sphyraenidae	Leiomyosarcoma	*Sphyraena jello*	2017	Yes	No	No	Singaravel et al. 2017 [133]
Syngnathidae	Fibrosarcoma	*Hippocampus erectus*	2004	Yes	No	No	Willens et al. 2004 [134]
	Renal adenoma	*Hippocampus kuda*	2012	Yes	No	No	LePage et al. 2012 [135]
	Renal adenocarcinoma	*Hippocampus kuda*	2012	Yes	No	No	LePage et al. 2012 [135]
	Exocrine pancreatic carcinoma	*Hippocampus kuda*	2012	Yes	No	No	LePage et al. 2012 [135]
	Intestinal carcinoma	*Hippocampus kuda*	2012	Yes	No	No	LePage et al. 2012 [135]
	Rhabdomyosarcoma cardiac	*Phyllopteryx taeniolatus*	2012	Yes	No	No	LePage et al. 2012 [135]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

Table 13. Spontaneous neoplasms in teleost fish related between 2000-2020

Family	Neoplasm	Species	Year	Diagnosis			References
				OM	IHQ	EM	
Syngnathidae	Adenoma	*Hippocampus erectus*	2018	Yes	Yes	No	Stilwell et al. 2018 [136]
Trichiuridae	Osteoma	*Trichiurus lepturus*	2002	Yes	No	No	Lima et al. 2002 [137]

**The names of the neoplasms included in table 2 are those used by the authors cited in the references. The terminology of neoplasms diagnosed in our laboratory often differs from those used by the authors mentioned in the table. OM: Optical Microscopy; IHQ: Immunohistochemistry; EM: Electron Microscopy*

In the 1970s, electronic microscopy clearly collaborated in the precise diagnosis of neoplasias [138]. This technique has proved to be essential for the diagnosis of certain diseases; however, its application to the diagnosis of neoplasias in general has been relatively neglected and remains primarily as a research tool. The reasons for this seem to be multiple. First, the complexity of preparing tissue samples for electron microscopy may have discouraged pathologists from attempting such an effort routinely. Although it is correct that tissues should be handled with care for good ultrastructural conservation, some reports show satisfactory conservation of ultrastructure in tissues fixed in 10% buffered formalin, which is also the routine fixation technique for optical microscopy. Second, the opinion that electron microscopy is not useful or essential for the diagnosis of neoplasias arose from the belief that there are no reliable ultrastructural criteria for the diagnosis of various neoplasias [139,140].

In the 1980s, the emergence of poly and monoclonal antibodies brought solutions to almost every type of differential diagnosis in oncologic pathology. The overwhelming growth in the development of these antibodies has provided a very valuable tool for diagnosis [141,142]. The availability of a monoclonal antibody panel to evaluate function, structure, differentiation, and histogenesis at the morphological level can help overcome diagnostic problems while advancing our understanding and appreciation of neoplasias. Imonohistochemistry is a useful tool, easy to perform and of great specificity [143,111]. It is important to note that many monoclonal antibodies used in mammals and humans are useful for the immunomarking of fish cells and tissues [144,145].

3. CONCLUSION

Neoplasias in fish, unlike other diseases, do not generate great losses to aquaculture. However, the true value of neoplastic pathology compared is to better understand the histiogenesis and biological behavior of neoplasias in mammals and humans. Carcinogenesis is generally complex and in most neoplasias in both mammals and fish, the origin is unknown, and it seems that there are many factors that contribute to the onset and growth of neoplasias.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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