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MODERN METHODS OF DIAGNOSIS OF MAMMARY TUMOR AND TUMOR-LIKE LESIONS IN CATS

Abstract: The paper provides an overview of the classification and diagnosis of feline mammary tumors (FMT) in cats. The clinical stage of neoplastic process is one of the driving prognostic factors. In accordance with the WHO recommendations 1980, it is determined by the TNM system: the size of neoplasm, the state of regional lymph nodes and the presence/absence of distant metastases.

The clinical stage of the disease is defined based on the obtained data during the examination, surgery and study of the postoperative material (excised tumor, the edges of the resection and regional lymph nodes).

It was found that tumors larger than 3 cm have a significantly worse prognosis than tumors smaller than 3 cm.

The median survival with a tumor size of less than 3 cm is 1.75 times greater (21 months versus 12 months) than with a tumor size of more than 3 cm. The most significant morphological prognostic factor is the histological type of malignant tumor and the histological gradation of tumor tissue. Among carcinomas, the most invasive are micropapillary, solid and cribriform carcinomas, the most unaggressive is carcinoma in situ.

Adverse prognostic factors of mammary cancer in cats are a high Ki67 index of proliferative activity, hyperexpression of Her-2 epidermal growth factor, cyclooxygenase-2, absence or low level of expression of receptors to estrogen and/or progesterone by tumor cells (less than 10%), as well as a high level of expression by tumor cells of VEGF (vascular endothelial growth factor).

Key words: cats, mammary glands, pathology, feline mammary tumors (FMT), mammary cancer (MC), diagnosis, prognostic factors

Introduction. The analysis of domestic and foreign literature shows that feline mammary tumors (FMTs) are the 3rd most common oncological pathology in cats. The incidence rate is significantly influenced by gender, age, breed, ovarian status, application of progestin-based contraceptives [1].

FMTs represent a group of neoplasms that is heterogeneous in terms of tissue belonging, histological structure and biological behavior. Malignant tumors occur most frequently and compose from 80 to 96% of all tumors and tumor-like lesions of mammary glands. Mammary cancer (MC) prevails, accounting for 91.4% of all cases of malignant tumors. Invasive mammary cancer is much more common than carcinoma in situ. Among histological types of mammary cancer, cribriform, solid, and tubulopapillary carcinomas prevail; mucinous, tubular, and papillary carcinomas are less common.

Research methods. The work is of analytical nature. It is based on the study and analysis of domestic and foreign literature on the diagnosis and differential diagnostic procedure of tumor and tumor-like lesions of the mammary glands in cats. Materials on the impact of the clinical stage of the neoplastic process, the histological type of tumor, the histological gradation of tumor tissue, as well as the histochemical features of tumor cells on the curability and outcome of invasive forms of mammary cancer were analyzed and summarized.

Research results. Diagnosis of mammary tumor and tumor-like lesions is based on anamnesis data (breed, sex and age, reproductive status, taking drugs with progestogenic and/or estrogenic properties, symptoms and duration of disease, etc.), the results of examination and palpation of the mammary gland and regional lymph nodes, X-ray and ultrasound examinations of the thoracic and abdominal organs, cytological analysis of the punctate of the primary node and enlarged lymph nodes, tissue smears from the declared surface of the primary tumor; cytology of pleural and/or peritoneal exudate (with hydrothorax

and ascites, respectively). Postoperative histological verification of tumor is mandatory, since the results on the nature of the neoplastic process according to biopsy data are often insufficient or erroneous [2].

Digital radiography (DR) and ultrasound investigation (US) play a key role in the diagnosis of metastatic lesions of the thoracic and abdominal organs [3, 4]. The efficiency of visualization of metastatic lesions depends on the magnitude of the pathological process.

When the size of a metastatic tumor is 0.5–1 cm or less, the DR and US sensitivity is low [5]. Recently, computed tomography (CT) has been used to visualize metastatic tumors in thoracic organs. CT allows more clearly determination of the localization, size, and shape of a secondary metastatic tumor, the extent of its spread to the pleura, diaphragm, ribs, blade or thoracic vertebrae [4].

Histopathological studies are the gold standard for the diagnosis and differential diagnosis of mammary tumors and tumor-like lesions [6, 7]. They make it possible to define not only the tumor histotype, but also to carry out the histological grading of carcinoma invasive forms.

With no treatment, the survival rate of sick cats with malignant mammary tumors is approximately 12 months [3, 7, 8, 9]. The death of animals is mainly associated with the progressive growth and destruction of the primary malignant tumor, cancerous cachexia, metastases and/or concomitant pathology [8]. The prognosis of the life of sick with malignant mammary tumors is determined by many factors, among which the tumor size and histotype, the presence of regional and distant metastases, the age and general health of the sick cat, the presence and degree of curability of concomitant pathology.

The clinical stage of neoplastic process is one of the driving prognostic factors. In accordance with the WHO recommendations 1980, it is determined by the TNM system: the size of neoplasm, the state of regional lymph nodes and the presence/absence of distant metastases (table 1).

The clinical stage of the disease is defined based on the obtained data during the examination, surgery and studies of the postoperative material (excised tumor, the edges of the resection and regional lymph nodes).

It was found that tumors larger than 3 cm have a significantly worse prognosis than tumors smaller than 3 cm.

The median of age in postoperative survival rate with a tumor size of less than 3 cm is 1.75 times greater (21 months versus 12 months) than with a tumor size of more than 3 cm [12]. S.W. Millis et al [13] report that when the tumor size is less than 2 cm, the median survival is 16 months, with a size from 2 to 3 cm - 14 months, more than 3 cm - 11 months. According to other sources [8], regardless of the volume of surgical intervention, the median of age with a tumor volume (adenocarcinoma) from 1 cm^3 to 8 cm^3 is 54 months, from 9 cm^3 to 27 cm^3 - 24 months, more than 28 cm^3 - only 6 months. A significant worsening of the survival rate of sick cats with an increase in tumor size was also traced in the works of a number of other authors. [9, 14, 15].

The presence of metastases in regional lymph nodes is an aggravating prognostic factor. The median survival of sick cats with feline mammary cancer is 5-9 months in the presence of metastases in regional lymph nodes and 13-16 months without them [3, 13].

The median survival of sick also clearly depends on the localization of metastases. With localization of metastases in regional lymph nodes, it is 1543 days, in the lungs and pleura - 332 and 188 days, respectively [16].

Table 1 - Classification of the stages of the mammary tumor process in cats according to the TNM system [10, 11]

Stage	Tumor size	Conditions of regional lymph nodes	Metastases
1	T1	N0	M0
2	T2	N0	M0
	T1,2	N1 (+)	M0
	T3	N0 or N1 (+)	M0
	All T options	All T options	M1

Notes: T1 – tumor no more than 2 cm in the largest diameter; T2 – tumor reaches 2... 3 cm in the largest diameter; T3 – tumor more than 3 cm in the largest diameter; N0 – metastases in regional lymph nodes are not detected; N1 – metastases are clinically detected in regional lymph nodes on the affected side; M0 – no signs of distant metastases; M1 – distant metastases are detected

The most significant morphological prognosis factor is the histological type of malignant tumor and the histological gradation of tumor tissue. Sarcomas and carcinosarcomas are generally more malignant than most carcinomas [9].

Among carcinomas, micropapillary, solid and cribriform carcinomas are considered the most invasive, while carcinoma in situ is the most unaggressive [17]. The biological behavior of invasive forms of carcinomas directly depends on the degree of differentiation of tumor cells. To determine the degree of their malignancy, the Nottingham system of histological gradation of invasive forms of carcinomas and their modifications is used. [13].

Following the Nottingham system, the degree of malignancy of invasive carcinoma is assessed by three signs: the degree of development of glandular structures in tumor tissue, the severity of nuclear polymorphism and the generation number. Each sign is evaluated in points from 1 to 3. The sum of the

points determines the histological degree of tumor malignancy (table 3).

Based on materials from S.W. Millis et al. [13] the median and overall survival rate (over 18 months of observation) in cats with mammary cancer (MC) with the I degree of malignancy (high differentiation of tumor tissue) is 31 months and 82%, with the II degree of malignancy (moderate differentiation of tumor tissue) - 14 months and 37%, with the III degree of malignancy (low differentiation of tumor tissue) - 8 months and 18%, respectively.

Table 3 - Histological staging of invasive carcinoma according to the Nottingham system [18, 19]

Sign	Points	Notes
Formation of glandular structures > 75% of the tumor area 10–75% of the tumor area <10% of the tumor area	1 2 3	The estimation of formation of glandular structures is carried out at low microscope magnification. The mammary glands should have a distinct luminal lumen around which cells with radially oriented nuclei are located.
Nuclear polymorphism Small similar nuclei Moderate increase in size Extensire polymorphism	1 2 3	Nuclear polymorphism of tumor cells is assessed at high magnification (x40). The nuclei of tumor cells are compared with the nuclei of the luminal duct epithelium located in the surrounding mammary tissue.
Mitotic activity (number of mitotic figures) 0-8 9-16 17	1 2 3	Calculation is done at high magnification (x40). Tumor mitotic activity is defined as the number of mitotic figures found in 10 consecutive visual fields in the most proliferatively active part of the tumor. Only completely unambiguous, clearly defined mitotic figures are suitable for calculation. Hyperchromic, karyorectic, or apoptotic nuclei should not be calculated
Degree of malignancy 1 2 3	Total points 3–5 Total points 6 or 7 Total points 8 or 9	

Low survival rate is also clearly associated with local invasion of tumor cells into lymphatic and blood vessels. With the signs of lymphovascular invasion in the tumor tissue, the median of age is 8 months, without it - 18 months. [13].

R. Preziosi et al. [20] recommends to divide malignant tumors of epithelial origin, according to the nature of tumor growth and the prevalence of the neoplastic process, into three groups: stage 0 (carcinoma in situ), stage I (invasive carcinoma without signs of metastasis into regional lymph nodes and/or lymphovascular invasion) and stage II (invasive carcinoma with metastases in regional lymph nodes and/or with signs of lymphovascular invasion). Using small clinical material (n=33), the authors showed that the overall survival rate according to the data of both one-factor and multifactor analyzes with an increase in the stage of oncological disease significantly worsens. Unfortunately, the 3-stage system of histological classification of malignant epithelial tumors in cats described by Italian scientists does not take into account such an important prognostic factor as the pathological tumor size.

Recently F. Chocteau et al. [21] suggested taking into account the pathological tumor size (pT1,- ≤20 mm; pT2 - >20 mm), the presence/absence of signs of lymphovascular invasion in the tumor tissue and the state of regional lymph nodes while the histological assessment of carcinomas and their gradation into non-invasive and invasive forms. In the proposed 5-stage histological classification, carcinomas are divided into stage 0 (carcinoma in situ), stage I (invasive carcinoma, pathological tumor size (pT1) ≤20 mm, nodular status negative or unknown (pN0 – pNX), signs of lymphovascular invasion not expressed (LVI–), stage II (invasive carcinoma, tumor size> 20 mm (pT2), nodal status negative or unknown (pN0 – pNX), no lymphovascular invasion (LVI–), stage IIIA (invasive carcinoma, pT ≤20 mm (pT1), nodular status positive (pN +)), severe lymphovascular invasion (LVI +) and stage IIIB (invasive carcinoma, pT> 20 mm (pT2), LVI+ and/or pN+). Using big clinical data (n=395), the authors showed that with step up in the stage, the median and overall survival rate (over 12 months of observation) and the cancer-specific survival rate significantly decrease. According to the authors' data, the median cancer-specific survival for stage 0 (n=55 or 13.92%), I (n=103 or 26.07%), II (n=56 or 14.17%) IIIA (n=83 or 21.01%) IIIB (n=98 or 24.81%) reaches 1484, 808, 377, 448 and 207 days, respectively. The authors sumed up that the risks of death of sick cats with mammary cancer during the first year after diagnosis at stages I, II, IIIA and IIIB of the disease are respectively 1.78, 2.86. 3.34 and 5.24 higher than in the reference group of cats (with mammary cancer in stage 0).

The scientific literature data on the impact of age on the clinical course of mammary cancer and the disease outcome are contradictory. According to some sources [23], old age is an unfavorable prognostic factor. Along with that in the work of E.G. MacEwen et al. [8] the median survival in cats with mammary cancer under the age of 10 years and

older was almost the same and amounted to 15 and 14 months, respectively.

Several studies [8, 23] have shown that Siamese cats have a significantly worse prognosis in terms of survival rates than domestic short-wooled cats.

The histochemical characteristics of tumor also effect significantly on the survival of sick with mammary cancer. Adverse prognosis factors of MC in cats are a high Ki67 index of proliferative activity [17], hyperexpression of Her-2 epidermal growth factor [24, 25], cyclooxygenase-2 (COX-2) [31], the absence or low level of expression of receptors by tumor cells to estrogens and/or progesterone (less than 10%) [26], as well as a high level of vascular endothelial growth factor expression by tumor cells (VEGF> 72.1%) [27]

Conclusions. For diagnosis and differential diagnosis of mammary tumor and tumor-like diseases, a determination of the cancer stage, prognosis and substantiation of the therapy method, along with the anamnesis data and clinical and instrumental examination, the results of cytological analysis of punctates of the primary tumor node and enlarged lymph nodes as well as pathomorphological examination of the operating material (excised tumor) with the defining of the histochemical neoplasm profile.

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МЫСЫҚТАРДАҒЫ СҮТ БЕЗІНІҢ ІСІК ЖӘНЕ ІСІК ТӘРІЗДІ АУРУЛАРЫН ДИАГНОСТИКАЛАУДЫҢ ЗАМАНАУИ ӘДІСТЕРІ

Аннотация: Мақалада мысықтардың сүт безі ісіктерінің жіктелуі мен диагнозына шолу жасалады (СБІ). Ісік процесінің клиникалық кезеңі жетекші болжамды факторлардың бірі болып табылады. ДДҰ-ның 1980 жылғы ұсыныстарына сәйкес СБҚІ жүйесі бойынша анықталады: неоплазманың мөлшері, аймақтық лимфа түйіндерінің жағдайы және алыс метастаздардың болмауы.

Аурудың клиникалық кезеңін зерттеу операция және операциядан кейінгі материалды зерттеу кезінде алынған мәліметтер негізінде анықталады (кесілген ісік, резекцияның жиектері және аймақтық лимфа түйіндері). Мөлшері 3 см-ден асатын ісіктердің мөлшері 3 см-ден аз жаңа өскіндерге қарағанда нашар болжанатыны анықталды. Ісік мөлшері 3 см-ден аз болған кезде операциядан кейінгі өмір сүрудің орта шамасы мөлшері 3 см-ден асатын ісікке қарағанда 1,75 есе көп (12 айға қарсы 21 ай).Болжамның маңызды морфологиялық факторы қатерлі ісіктің гистологиялық түрі және ісік тінінің гистологиялық градациясы болып табылады. Обырлардың арасында ең инвазивті болып микропаппилалы, қомақты және крибриформалы карциномалар саналады, ең озбыр емесі - situ карциномасы.

Мысықтардағы сүт безі қатерлі ісігі болжамының жағымсыз факторлары-бұл Ki67 пролиферативті белсенділігінің жоғары индексі, her-2 эпидермальды өсу факторының гиперэкспрессиясы, циклооксигеназдар-2, рецепторлардың ісік жасушаларының эстрогендерге және прогестеронға дәлдігінің болмауы немесе төмен деңгейі (10-нан кем%), сондай-ақ VEGF ісік жасушалары дәлдігінің жоғары деңгейі (васкулярлық эндотелиальды өсу факторы).

Түйін сөздер: мысықтар, сүт бездері, патология, сүт бездерінің ісіктері (СБІ), сүт безінің қатерлі ісігі (СБҚІ), диагностика, болжам факторлары.

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СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ ОПУХОЛЕВЫХ И ОПУХОЛЕПОДОБНЫХ ЗАБОЛЕВАНИЙ МОЛОЧНОЙ ЖЕЛЕЗЫ У КОШЕК

Аннотация: Проведенная научно-исследовательская работа о влиянии клинической стадии опухолевого процесса, гистологического типа опухоли, гистологической градации опухолевой ткани, а также гистохимических характеристик опухолевых клеток на курабельность и исход инвазивных форм рака молочной железы.

Клиническую стадию болезни устанавливают на основании данных, полученных во время обследования, операции и исследования послеоперационного материала (удалённой опухоли, краёв резекции и региональных лимфатических узлов). Установлено, что опухоли размером больше 3 см имеют достоверно худший прогноз, чем новообразования размером менее 3 см. Медиана послеоперационной выживаемости при размере опухоли менее 3 см в 1,75 раза больше (21 мес против 12 мес), чем при размере опухоли более 3 см. Самым важным морфологическим фактором прогноза является гистологический тип злокачественной опухоли и гистологическая градация опухолевой ткани. Среди карцином наиболее инвазивными считаются микропапиллярная, солидная и крибриформная карциномы, самой неагрессивной - карцинома in situ.

Наличие метастазов в региональных лимфатических узлах является отягчающим прогностическим фактором. Медиана выживаемости больных кошек при раке молочной железы составляет 5-9 мес при наличии метастазов в региональных лимфоузлах и 13-16 мес при их отсутствии. Медиана выживаемости больных отчетливо зависит также и от локализации метастазов. При локализации метастазов в региональных лимфоузлах она составляет 1543 сут, в легких и плевре - 332 и 188 сут соответственно.

Неблагоприятными факторами прогноза при раке молочной железы у кошек являются высокий индекс пролиферативной активности Ki67, гиперэкспрессия эпидермального фактора роста Her-2, циклооксигеназы-2, отсутствие или низкий уровень экспрессии опухолевыми клетками рецепторов к эстрогенам и/или прогестерону (менее 10%), а также высокий уровень экспрессии опухолевыми клетками VEGF (васкулярного эндотелиального фактора роста).

Ключевые слова: кошки, молочные железы, патология, опухоли молочных желез (ОМЖ), рак молочной железы (РМЖ), диагностика, факторы прогноза.

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