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Approach to the cancer case: staging - how and why

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Introduction

The diagnostic evaluation of a patient with a suspected tumour requires a holistic approach and must include:

- A histological or cytological diagnosis of the tumour to determine the tissue of origin and grade of tumour. Cytology can usually differentiate neoplastic from non-neoplastic lesions and can tell you broadly which type of tumour you are dealing with, but accurate histogenesis and tumour grading requires histology. ('What is it?')
- Determination of the extent of the disease, both locally and at distant sites. ('How far has it got?')
- Identification of any tumour related complications
- Investigation of any concurrent disease which may alter the patient's prognosis or ability to tolerate treatment

It is impossible to treat a tumour optimally without knowing both the histogenesis and the anatomical extent of the tumour. Failure to appreciate the extent of the disease or the true nature of the lesion often results in inadequate treatment of the tumour and patient, a missed opportunity for cure and client misinformation.

Clinical staging of small animal neoplasms

To stage tumours, we assess the size and extent of the:

- primary tumour (T)
- the presence or absence of metastatic disease in both the local and regional lymph nodes (N)
- the presence or absence of metastatic disease within the rest of the body (M)

This 'TNM' approach can be used for virtually all solid tumours, and has been adapted for tumours which are by their nature usually disseminated, like lymphoma. The World Health Organisation (Owen, 1980) has published guidelines for the clinical staging of many animal tumours. While it is not necessary to use these classifications verbatim, the principles of the TNM approach should always be applied, as it is the best way of thinking about tumours.

A basic knowledge of the biological behaviour of tumours of different histological types is also required. In some cases, the detectable tumour stage does not reflect the true stage, because of the limitations of the techniques available in assessing the extent of the disease, e.g. even in the absence of detectable metastatic disease, all cases of long bone osteosarcoma are assumed to have metastatic spread at first presentation and are treated as having disease at a more advanced stage than clinical staging indicates. In contrast, with a tumour with limited invasive potential and/or low metastatic potential, treatment of the clinically detectable disease is often all that is indicated.

For individual patients, factors other than clinical staging are also important in determining treatment and prognosis: for example, the presence of paraneoplastic syndromes or significant intercurrent disease.

Solitary/Solid tumour: T

A histological diagnosis based on biopsy material (or cytological diagnosis based on aspirates/other samples) must be made. Extent is assessed by clinical examination and diagnostic imaging techniques including plain and contrast radiography, ultrasonography, endoscopy and computed tomography (CT) or magnetic resonance imaging (MRI) as appropriate, dependent on the tumour site. The sensitivity of these techniques varies, e.g. clinical examination of an oral squamous cell carcinoma may suggest a less extensive tumour than radiography, which in turn is less sensitive than CT. CT is an x-ray based technology, and is good for bone. MRI is a water based technology, and gives better discrimination between different soft tissues.

Solitary/Solid tumour: N

The local and regional lymph nodes must be thoroughly evaluated, especially in animals with carcinomas, oral malignant melanomas, or mast cell tumours as these commonly metastasise by the lymphatic route. However, soft tissue sarcomas (including so-called synovial cell sarcomas) will occasionally metastasise in this way.

Superficial nodes should be assessed by palpation/imaging and fine needle aspiration. Nodes affected by metastatic disease are not always grossly enlarged, and firmness on palpation should always raise suspicion. Palpation is insensitive to metastatic disease. (Reactive nodes are often painful on palpation and aspiration.) Single lateral views of the thorax may be adequate for suprasternal, cranial mediastinal and tracheobronchial lymphadenopathy, but sensitivity to thoracic nodal enlargement is greater if a dorsoventral (DV) view is also taken. Abdominal radiographs may reveal superficial iliac (sublumbar) or, if enormous, mesenteric lymphadenopathy, but ultrasonography is more useful. Ultrasound guided aspirates of nodes can often provide a rapid diagnosis.

Fine needle aspirates, if carried out well and examined by a good cytologist, are more sensitive to metastatic disease than palpation or Trucut type needle biopsies. However, negative cytological result does not rule out metastatic disease. Where clinical suspicion is high, repeat aspiration, nodal biopsy (wedge) or treatment assuming that the node is affected should be carried out based on clinical judgement.

Solitary/Solid tumour: M

The lung is the most common site of distant metastatic disease, but other sites include liver, skin, bone, brain, spleen, kidneys and distant nodes. Metastases may be evident on physical examination (e.g. cutaneous metastases). For pulmonary metastases, both lateral inflated views of the thorax provide the most sensitive combination of two views and are the minimum acceptable. A third view (DV) will slightly increase sensitivity and is recommended, and use of all four inflated views is the most sensitive of all. CT scans of the thorax are more sensitive than radiographs in detecting metastatic disease, but it is sometimes difficult to know how to interpret this information: for example, we do not really know the prognostic relevance of CT positive/ radiograph negative met status for patients planned to receive adjunctive chemotherapy.

Abdominal radiographs may show changes in the shape/ size/ outline of the liver, spleen or kidneys but ultrasound, as indicated by radiographic/ clinical/ biochemical findings and known biological behaviour of tumour, is often more sensitive in the detection of metastases e.g. to the liver. However, lots of older dogs will have benign nodular lesions in the liver or spleen. FNA/biopsy is required for diagnosis.

More sophisticated techniques include thoracic CT for pulmonary metastases or MRI, e.g. to detect CNS metastases brain and technetium-99 bone scans for bony metastases, e.g. osteosarcomas or chondrosarcomas.

Laboratory evaluation may show organ dysfunction secondary to metastatic disease (or paraneoplastic disease), but is very insensitive.

Example: TMN classification of canine/ feline tumours of the oral cavity

Using this classification, worsening survival has been reported with advancing stage for dogs with oral tumours (White et al, 1985) (see Table below):

The process of tumour metastasis

Metastasis is the transfer of disease from one organ to another organ, which is not in direct connection with it. Metastasis is a multistep process. The tumour itself must become vascularised and invade the local tissues and penetrate blood vessels and/or lymphatic vessels. Cells are then detached and released from the primary site, and disseminated to distant sites. They must evade host immunity during this dissemination (it is estimated that less than 0.01% of cells gaining access to the circulation survive to form a metastasis). Disseminated cells must then extravasate by invading the vascular walls, infiltrate into the tissue and proliferate. The metastases then becomes vascularised. Metastasis is therefore a highly selective process resulting from survival of cells that show unique properties. For this reason, metastatic tumour deposits may not show the same sensitivity to chemotherapeutic agents (or radiotherapy) as the primary tumour. Factors which influence the ability to metastasise include tumour vascularity, biochemical and immunological characteristics of tumour cells and host immune responses.

Tumour spread by direct extension along tissue planes or by shedding of tumour cells into a body cavity with

Primary tumour	Regional lymph nodes	Distant metastasis
Tis: pre-invasive carcinoma (carcinoma in situ)		
To: no evidence of tumour	No: no evidence of RLN involvement	Mo : no evidence of distant metastasis
T1: T < 2cm max diameter	N1: movable ipsilateral node N1a: nodes not considered to contain mets N1b: nodes considered to contain mets	M1: distant metastasis present (including distant nodes)
T2: T 2-4 cm max diameter	N2: movable contralateral or bilateral nodes (a/b as above)	
T3: T >4 cm max diameter	N3: fixed nodes	
T?a: no bone invasion T?b: bone invasion		

Table 1: TMN classification of oral tunours

direct serosal implantation does not involve invasion, or lymphatic and venous permeation. It is a different biological process.
Dissemination of disease in lymphoma patients is a feature of the normal behaviour of the cells, and is also not a truly metastatic process.

Regional lymph nodes

Normal lymph nodes can be an effective barrier to tumour spread, but it is controversial whether nodes containing detectable metastases fulfil this role. The immunological response seen in reactive nodes may be important in the early stages in slowing down metastases. However, once a local node is grossly affected by metastatic disease (i.e. FNA-positive) it probably does not contribute much to defence against metastases. Enlarged nodes draining an area affected by malignancy are probably an ineffectual immunological barrier, so can be resected. Removal of uninvolved nodes early in the disease course is controversial as it may promote metastasis.

Metastasic patterns

Malignant tumours are sometimes divided into tumours which metastasise by the lymphatic route (to local and regional lymph nodes) and those which metastasise by the haematogenous route (to lungs and parenchymatous organs). This division is not absolute.
Tumours which metastasise commonly by the lymphatic route include mast cell tumours, most carcinomas, and malignant melanomas. Tumours which commonly metastasise by the haematogenous route include most sarcomas and malignant melanoma.

Tumour behaviour: some examples

The various malignancies which we see in the dog and cat show a wide range of biological behaviour, both in terms of the degree of local invasion they exhibit and the rate and frequency with which they metastasise. Some tumours which have the same histological diagnosis behave differently if they arise in different sites, or in different species. Summarised below are some of the common tumours. These are, of course, sweeping generalisations, and the list is not comprehensive!

References

Available on request from the author.

Rapidly metastasising	oral/mucosal malignant melanoma visceral and subcutaneous haemangiosarcoma osteosarcoma of long bones (dog) poorly differentiated (grade III) mast cell tumours tonsillar squamous cell carcinoma poorly differentiated mammary tumours most mammary carcinomas in cats (adenocarcinoma of the anal sacs) (prostatic carcinoma)
Variably metastasising	thyroid carcinoma oral osteosarcoma/osteosarcoma of flat bones (lots of these are aggressive) osteosarcoma of long bones (cats) intermediate and high grade sarcomas synovial cell sarcoma anaplastic sarcoma insulinoma other mammary carcinoma apocrine adenocarcinoma in skin anal sac carcinomas intermediately differentiated mast cell tumours (lots don't) GIT carcinomas transitional cell carcinoma of bladder subungual malignant melanoma (dog)
Lower metastatic potential	oral fibrosarcoma (possibly around 20%) oral squamous cell carcinoma (around 10%) most soft tissue sarcomas (around 20%) sebaceous adenocarcinoma well differentiated mast cell tumours multilobular osteoma/osteosarcoma of bone canine intranasal tumours
Don't metastasise	oral basal cell tumours (old name acanthomatous epulids) haemangiopericytoma schwanomma/neurofibroma BENIGN TUMOURS