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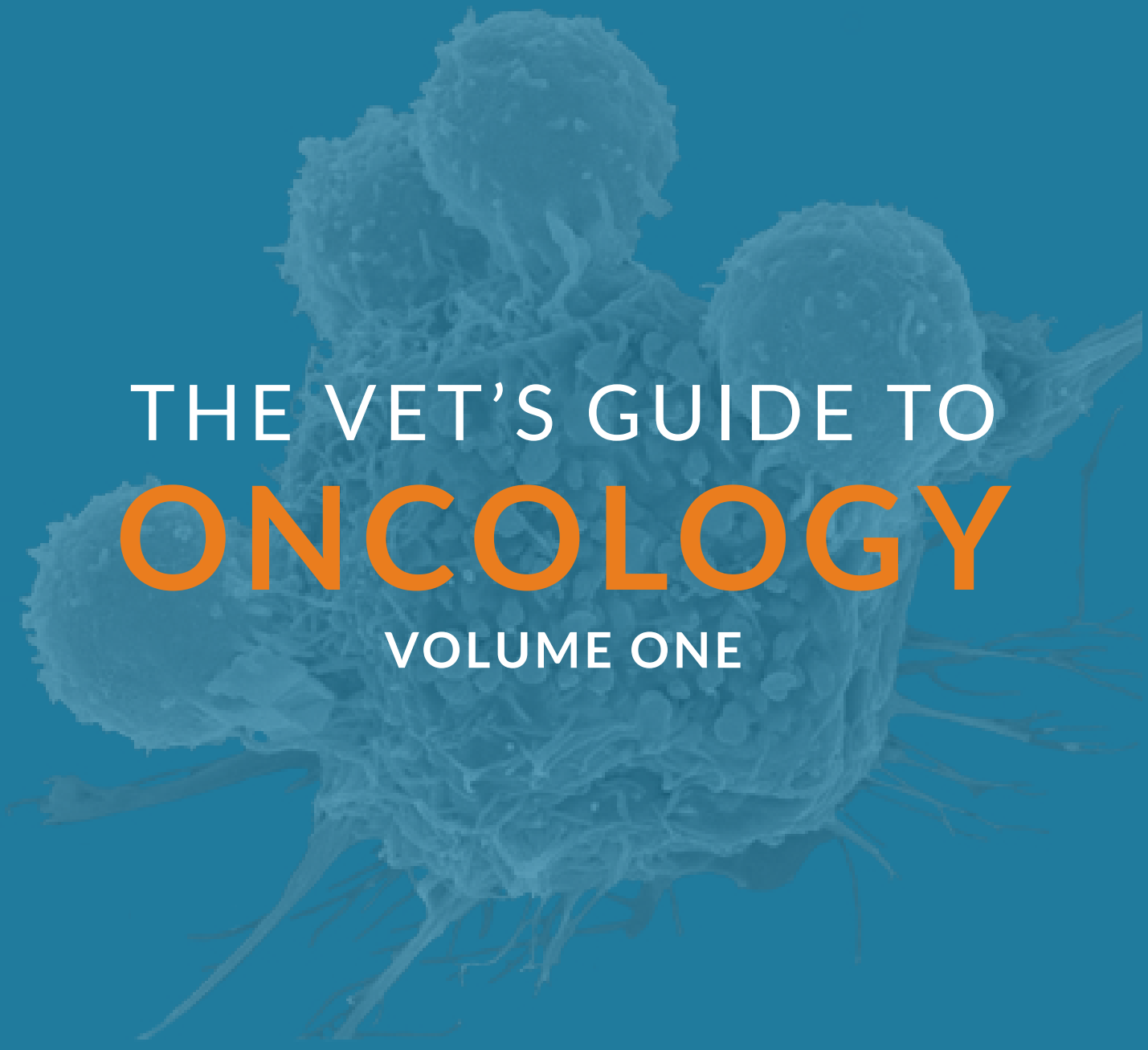

THE VET'S GUIDE TO ONCOLOGY

VOLUME ONE

www.sashvets.com

FOREWORD

With Justin Wimpole, CEO

Cancer is one of the most common conditions to affect our patients during their lifetime. Although cancer often affects our patients later in their life, it is also a condition which can affect younger pets. Pet owners have an unyielding bond with their pets and a diagnosis of cancer is devastating news. This is a situation where a family member has been diagnosed with a very serious and often life-threatening condition. As a result, our clients are after the highest quality of treatment for their pets.

Fortunately, there have been many advances in early detection, diagnosis, staging and treatment of many cancers. Technology is constantly evolving and there is a large amount of work to be done to bring the best diagnostic and treatment options to pets. The Small Animal Specialist Hospital (SASH) has been involved in advances such as targeted chemotherapy delivery, pioneering immuno-therapy and providing on-site state-of the-art radiation therapy. The future will most likely involve taking insights from the research bench to the "cageside" quicker, using large data sets to fuel these insights as well as advances in genomic profiling, precision medicine and patient specific medicine.

It is vital now and as we move into the future that as caregivers, veterinarians give accurate information and advice in a caring and compassionate way. At SASH our aim is to enable pets and their families to live their best life. This includes supporting our referring vet partners to be able to provide care to their patients to the best of their abilities.

The Vet's Guide To Oncology has been compiled by the dedicated SASH Comprehensive Cancer Centre team using the knowledge that they have developed from their many years of training and experience in treating pets with cancer. The purpose of this valuable resource is to act as a practical guide to assist general practitioners to diagnose cancer earlier, provide more accurate information to clients and deliver safe and appropriate treatment for the benefit of their patients and clients.

The SASH team aims to partner with the veterinary community to deliver care that ultimately helps pets and their families live their best lives whilst delivering excellence in animal health care.

Justin Wimpole, CEO
Small Animal Specialist Hospital

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CHAPTER ONE

DIAGNOSTICS IN ONCOLOGY

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1. DIAGNOSTICS IN ONCOLOGY

As cancer is one of the leading causes of death in older animals, early detection and diagnosis can play a significant role in improving outcomes for our veterinary patients. Most cancers are considered a chronic disease, and as such, can be treated to allow long term control. With appropriate treatment, we can delay the progression of clinical signs or provide palliative care, which results in the improvement of the patient's quality of life.

When cancer is suspected, it is important to perform appropriate diagnostic testing in a timely manner. In most cases, a fine needle aspirate and/or biopsy are the ideal diagnostic tests for suspected cancer cases. These tests can provide both a diagnosis and may even help predict the biological behaviour of a given cancer.

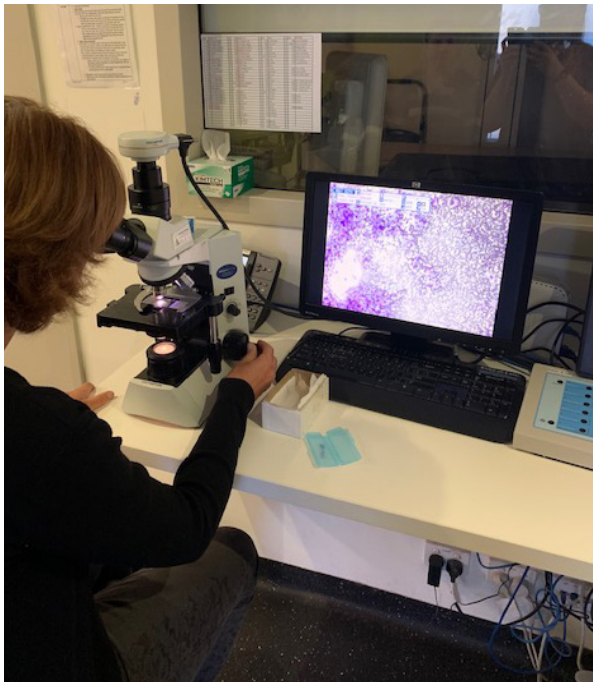
Fine Needle Aspirates and Cytology

A fine needle aspirate (FNA), followed by a cytological examination, is usually the first step in the diagnostic workup of a suspected tumour. A Fine needle aspirate has numerous advantages as a preliminary screening test. It is rapid, minimally invasive, and inexpensive, requiring little equipment and rarely requires patient sedation or anaesthesia. An aspirate can result in a quick turnover of results to allow for rapid follow up treatment.

Certain types of masses can be easily diagnosed with FNA. These include:

- Benign masses such as lipomas and sebaceous adenomas
- Neoplastic tumours (especially the round cell tumours) such as lymphoma, mast cell tumour, histiocytoma, plasma cell tumour, and transmissible venereal tumour

An aspirate taken well can be very helpful. Each of these masses has characteristic cellular features that are readily identifiable under a microscope.



It is important to understand that a FNA has some limitations. Some cell types do not exfoliate well on a FNA, leading to inconclusive results. A fine needle aspirate may also be non-diagnostic in the case of blood contamination or severe inflammation, or poor technique resulting in broken cells or a too-thick cell preparation which makes it difficult to be read by the pathologist.

Additionally, a FNA does not provide any information regarding tumour grade, tumour stage or the internal architecture of the tumour.

A fine needle aspirate is a valuable diagnostic tool, as long as its limitations are taken into consideration. Treatment decisions should only be made on the basis of a FNA if a definitive diagnosis can be made based on cytological examination and in many cases this will require review by a board-certified pathologist. If a definitive diagnosis cannot be obtained, the tumour can be further assessed with a biopsy.

Biopsy

A biopsy is not only a method for determining diagnosis, but also allows for the determination of the tumour's grade and internal architecture. A biopsy may be obtained in one of two ways: incisional biopsy or excisional biopsy.

Incisional Biopsy

An incisional biopsy is performed to collect information about the tumour before planning definitive treatment. Instead of attempting to remove the entire tumour, the attempt is made to collect small tissue samples that can be used to arrive at a histologic diagnosis.

Incisional biopsies are especially valuable in the following circumstances:

- When the diagnosis would change the type of treatment (for example, when deciding on margins needed for tumour removal)
- When a mass is in an area that would be difficult to reconstruct (for example, a skin mass that is not amenable to removal without aggressive reconstructive surgery on the limb)
- When the tumour type or prognosis would change the owner's willingness to treat (for example, when the top two differentials vary widely in prognosis and the owner is reluctant to pursue treatment for a guarded prognosis)
- When the tumour type will determine staging tests needed prior to an aggressive surgery

Incisional biopsies may be obtained using a variety of techniques. A simple wedge biopsy may be performed using a scalpel blade and forceps, or more specialised equipment such as a Tru Cut needle, biopsy punch, or endoscopic cutting forceps may be utilised. The best approach will depend on the characteristics of the mass and veterinarian preference.

When performing an incisional biopsy, it is important to take into account that the tumour may seed along the incision or needle tracts. It is good to avoid compromising healthy tissues while obtaining the sample and attempt to avoid dead space and the need for drain placement, as these can also facilitate local tumour spread. Keep in mind that the area of biopsy incision will also need to be removed at the time of definitive surgery and so it is vital to not create an incision larger than necessary.

Finally, it is important to obtain multiple biopsy samples from a single mass, when possible. Doing so will maximise the chances of obtaining an accurate diagnosis.

Excisional Biopsy

The limitations to excisional biopsy include that the mass may be removed with incomplete surgical margins for its specific tumour type (for example, an aggressive mast cell tumour may be removed with very narrow margins), incomplete margins (especially on some types of tumours) can lead to an increased likelihood of tumour recurrence. Patients may require additional local therapy (such as a second surgery or radiation therapy) and the opportunity to perform definitive treatment may be lost.

Excisional biopsies should be limited to small masses (less than 2 cm in diameter) that are freely moveable and non-invasive. Clients should be cautioned that an excisional biopsy may not be curative. Any mass that is removed should be submitted for histopathology and clients should be prepared for the fact that further interventions may be required.

Histopathology Submissions

All biopsy samples should be submitted to a veterinary pathology lab in 10% formalin. If small samples are obtained, cassettes or pieces of cardboard can be used to hold the pieces so that they are not lost. Each sample should be labelled, so that differences between samples can be identified and interpreted. Provide a complete patient signalment, history, and physical exam report on the histopathology submission form, in order to obtain the most accurate results from the pathologist.

Histopathology samples should always be submitted promptly. Although formalin is a preservative, samples still degenerate with storage.

Prompt submission is essential in order to allow for the most accurate results.

In the case of excisional biopsies, it is best to submit the entire tumour for histopathology. Samples should be no more than 1 cm thick, to ensure adequate formalin fixation. Large samples should be sliced like a loaf of bread, leaving the tumour base intact. This will allow the pathologist to provide information on tumour margins, or how much unaffected tissue was removed along with the tumour.

The width of tumour margins obtained can help predict the likelihood of tumour recurrence. In general, tumour margins are categorised as follows:

- Complete excision ('clean'): margins >5 mm
- Marginal excision ('clean but close'): margins 3–5 mm
- Incomplete excision ('dirty'): margins <3 mm

Tumour Grading

Histopathology also allows for tumour grading, which indicates a tumour's degree of malignancy. Criteria used to determine tumour grade include: tissue differentiation, mitotic activity, local invasiveness, and the extent of necrosis found within the tumour.

In many tumours, tumour grade has valuable prognostic significance. This is the case in mast cell tumours, lymphoma, soft tissue sarcomas, synovial cell sarcomas, primary lung carcinomas, and multilobular tumour of bone. In some tumours, however, tumour grade is not correlated with prognosis for example in chondrosarcomas, some endocrine carcinomas, plasmacytoma, and nasal adenocarcinoma.

CHAPTER TWO

BASIC RADIOTHERAPY

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2. BASIC RADIOTHERAPY

What is Radiation Therapy?

Radiation therapy, also known as RT or radiotherapy, involves the use of high-energy x-rays to treat cancer and other medical conditions. Radiation is delivered in a highly localised manner, targeting the tumour with the goal of only irradiating a small amount of healthy tissue.

Radiation therapy may be used alone, or in conjunction with other oncological treatments. Examples of how radiation therapy may be combined with other treatments include:

- Radiation therapy may be used to shrink a tumour prior to surgical removal, maximising the likelihood that the tumour can be completely excised with wide margins
- Radiation therapy may be used to eradicate microscopic disease after incomplete excision of a tumour
- Radiation therapy may be used in conjunction with chemotherapy drugs, which can increase cell susceptibility to radiation

The Mechanism of Radiation Therapy

In radiation therapy, radiation is delivered using a linear accelerator. High-intensity radiation is generated (using microwave technology that accelerates electrons towards a heavy metal target), shaped, and modulated in a customised manner for the specific patient and condition. This radiation is delivered to a specific region of the body, based on pre-treatment imaging.

Radiation damages the DNA within a cell, limiting the cell's ability to grow and divide. This damage eventually leads to cell death, contributing to tumour control, shrinkage, and/or eradication.

The Radiotherapy Process

The exact details of radiation therapy, from start to finish, depends on the individual patient's condition and overall health. In general however, the process involves five steps: an initial consult, simulation, planning, treatment and follow-up.

1. Initial Consultation and Consent

The client and patient will first see the Oncologist for an initial consult. The client is educated about the radiation therapy that is being proposed for their pet in detail, including risks, benefits and side effects.

At this visit, the client will receive a consent form that outlines the treatment plan and details associated with the planned therapy. Clients will also be provided with information regarding the cost of treatment. Clients will need to sign this consent form before treatment can proceed.

2. Simulation

At this visit, the pet will be anaesthetised. A CT scan will be performed, to allow radiation planning. The pet will then be positioned in the way that he or she will be positioned for each treatment. This may involve the use of positioning aids, such as custom-designed cushions. Measurements will be taken of the pet's tumour site. A point of reference for radiation therapy localisation will be determined, which may require clipping a small amount of hair.

3. Planning

The radiation oncology team will use the results of the CT scan, combined with radiation modelling software, to determine the best treatment plan for the patient. The radiation plan is designed to target the tumour, while minimising damage to healthy tissues.

4. Treatment

Radiation therapy typically involves one to twenty separate radiation therapy sessions. These sessions typically take approximately half an hour each. The pet is anaesthetised for each session, in order to prevent motion and damage to surrounding tissues.

These sessions may take place on an outpatient basis, with the pet brought in fasted for each visit, or the pet may be boarded with the Oncologist for the duration of treatment.

5. Follow-up

Follow-up plans are determined by the Oncologist based on the type of cancer and the patient's response to treatment. These follow-up visits are intended to monitor the response to treatment, as well as to monitor and address any side effects of radiation that may arise.

Radiation Therapy Types

There are several types of radiation therapy that may be used in the treatment of cancer. These radiation types vary in both their intent and how they are performed.

Definitive Radiation Therapy

Definitive radiation therapy is administered with the goal of achieving long-term control of cancer. Definitive radiation therapy is administered in multiple fractions, or prescribed doses of radiation. The most common protocols involve delivering radiation to the affected area once daily (Monday through Friday) for a period of two to four weeks. Splitting the radiation up in this way helps to reduce side effects.

Definitive radiation therapy is often used in the treatment of the following cancers:

- Nasal carcinomas
- Nasal sarcomas
- Nasal lymphoma
- Laryngeal lymphoma
- Brain tumours
- Pituitary tumours
- Oral squamous cell carcinomas in dogs
- Mast cell tumours (incompletely excised or non-surgical)
- Soft tissue sarcomas (incompletely excised or non-surgical)

Palliative Radiation Therapy

Palliative radiation therapy is not intended for long-term cancer control. Instead, palliative therapy is intended to alleviate pain and increase the patient's comfort level and quality of life.

Palliative radiation therapy treatments are typically administered as a small number of treatments, with a higher radiation dose delivered in each radiation fraction. Treatment protocols vary, with some patients receiving treatment once daily for a week, while other patients may receive once-weekly treatments over a longer period of time.

Cancers commonly treated with Palliative Radiation Therapy include:

- Oral melanoma
- Bulky soft tissue sarcomas

- Bulky carcinomas
- Oral squamous cell carcinomas in cats
- Osteosarcoma

Stereotactic Radiation Therapy

Stereotactic radiation therapy is a type of radiation therapy that is used for small tumours with narrow margins. These treatments involve delivering a high dose of radiation every other day for a total of three treatments. In many cases, these treatments are delivered during a single week (Monday, Wednesday, and Friday dosing).

Stereotactic radiation therapy is most commonly used in the treatment of well-defined brain tumours.

Multiple Treatments or One?

The type of radiation therapy that is administered depends on the type of cancer and individual patient factors. The Oncologist will determine an appropriate treatment plan for each patient.

In some cases, radiation therapy may be combined with other treatment modalities to achieve more effective tumour control. In other cases, radiation therapy may be recommended as the sole therapy to address a particular patient's cancer.

Common Side Effects of Radiation Therapy

The side effects seen with radiation therapy can vary considerably, depending on the protocol used. In general, side effects are typically mild with palliative protocols and more pronounced in pets receiving definitive radiation therapy, although there is significant variation between patients

Radiation therapy side effects are cumulative. In most cases, side effects begin to develop towards the end of the patient's treatment protocol. These effects often worsen during the first week after treatment and begin to show an improvement in two to three weeks after treatment. In some cases, however, radiation side effects may persist for up to six weeks after radiation therapy.

Radiation therapy side effects are often very localised, because radiation therapy is highly targeted to a specific region of the body. The most common side effects of radiation therapy are outlined below, however, there may be additional expected side effects based on the specific treatment performed.

Skin and Coat Side Effects

Most pets experience some degree of skin reaction within the irradiated area, although the severity of this reaction may vary depending on both individual patient factors and treatment-related factors. Common skin effects include localised alopecia, dermatitis, and hyperpigmentation

Alopecia typically resolves in cats, but may be permanent in dogs. In some cases, pets that lose hair may have white or grey hair in that area when the hair regrows. Moist dermatitis may occur, but typically resolves within one month.

Oral Side Effects

Oral treatments may result in tenderness or discomfort around the mouth, as well as decreased saliva production. In general, these effects are temporary and will resolve within a couple of weeks.

Nasal Side Effects

Pets receiving radiation therapy to the nasal area may experience sneezing or nasal discharge. Additionally, pets may be painful in this area and head-shy.

Ocular Side Effects

Radiation therapy near the eyes can lead to conjunctivitis, ocular discharge, and keratoconjunctivitis sicca. Medications and an Elizabethan collar may be required.

The eyes are also especially susceptible to late side effects of radiation therapy. Cataracts may occur in pets that receive radiation near the eyes, typically developing approximately one year post-treatment. In some cases, enucleation may be required due to

late side effects of radiation therapy on the eyes

Brain Side Effects

Radiation of brain tumours can result in acute delayed inflammatory reactions. These reactions are observed in approximately 15% of cases treated with definitive radiation and 30% of patients treated with stereotactic radiation. Common signs of acute delayed inflammatory reactions in the brain include worsening of neurologic signs. These changes are typically transient and often respond well to steroid treatment.

Serious Side Effects

Rarely, more serious late side effects may occur. These late side effects may include a radiation-induced secondary tumour at the radiation site, or localised bone necrosis. It is important to note, however, that less than 5% of patients experience these effects in the 5 years following radiation therapy.

CLIENT EDUCATION: Radiation Therapy

Why is my pet losing hair at the radiation site? What should I do?

Hair loss and skin reactions at the radiated sites are normal. In most cases, these changes are only temporary. Use an e-collar to prevent self-trauma to irritated skin and schedule an examination to determine whether additional treatment is necessary.

My pet's mouth is sore after radiation treatments. What can I do to help?

Radiation to the mouth may cause discomfort and decreased saliva production, which may make it difficult for your pet to eat. Try offering tasty, warmed, soft food.

Pain medication can be prescribed if necessary. The good news is that your pet's discomfort should resolve within a few weeks.

Why are my pet's eyes inflamed after radiation therapy?

Short-term effects of radiation near the eyes may include redness, itching, discharge and decreased tear production. If your pet's eyes are uncomfortable, apply an Elizabethan collar to prevent self-trauma and schedule a veterinary appointment as soon as possible. Your pet may need medication to address the effects of radiation on his or her eyes.

My pet's neurologic signs seemed to improve after radiation af a brain tumour, but now the neurologic signs are Rreturning. What's happening?

Brain radiation may cause delayed signs associated with the inflammation triggered by radiation. In this case, you might see worsening of your pet's neurologic signs. Typically, these changes can be treated with steroids, which decrease inflammation within the brain.

If your pet doesn't improve with steroid treatment, the next step would be to repeat diagnostics to ensure that the initial tumour has not recurred.

Does my pet emit radiation after treatments?

No. Once the linear accelerator has been turned off, there is no residual radiation that remains within your pet. You are free to cuddle and snuggle your pet as you normally would.

CHAPTER THREE

BASIC CHEMOTHERAPY

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3. BASIC CHEMOTHERAPY

What is Chemotherapy?

Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells.

There are a wide variety of chemotherapy drugs that may be used in pets, each with a different mechanism of action and side effect profile.

How does Chemotherapy work?

Chemotherapy interrupts cell division. The exact mechanism by which this interruption occurs varies between individual chemotherapy agents, with different drugs acting on different stages of the cell cycle and via differing mechanisms.

Some specific mechanisms employed by chemotherapy drugs include:

- Causing direct damage to DNA, preventing replication
- Altering the DNA in a specific way that slows growth and replication
- Interfering with chromosome replication
- Directly preventing mitosis
- Triggering apoptosis
- Anti angiogenic

It is important to note that most chemotherapy agents are not specific for cancer cells, but they also have effects on any rapidly dividing cells within the body. This accounts for some of the more common side effects that can be seen with chemotherapy such as bone marrow suppression and gastrointestinal signs. Fortunately, the changes that occur in healthy cells are typically reversed once the chemotherapy drugs have been excreted and normal cells have a greater capacity to repair the damage caused by chemotherapy agents.

When is Chemotherapy used to treat cancer?

In some cases, chemotherapy is used as the sole treatment for cancer. For example, lymphoma is often treated with chemotherapy alone.

In other cases, chemotherapy is used in conjunction with other treatments, such as surgery or radiation. Chemotherapy may be used to shrink a tumour prior to surgery, in order to allow the tumour to be removed with clean margins (neoadjuvant therapy). In cancers with a high risk of metastasis, chemotherapy is often used after radiation or surgery to reduce the likelihood of metastasis to other parts of the body (adjuvant therapy).

Chemotherapy Treatment Goals

The primary goal of veterinary chemotherapy is to improve the pet's quality of life.

While curing cancer may seem to be the ideal outcome of chemotherapy, it is often not possible to cure cancer. Even without the goal of being a cure, treatment can be successful. Quality of life can be significantly improved by minimising the discomfort associated with tumour growth and/or slowing the progression of cancer by months to years.

Oncologists can provide clients with information regarding the average life expectancy for their pet's cancer, with and without treatment. Owners can use this information, in conjunction with their own practical and financial considerations, to determine whether chemotherapy is a beneficial option for their pet.

Common Side Effects of Chemotherapy

Veterinary chemotherapy uses far lower drug doses than those used in human chemotherapy. Therefore, pets experience fewer and less severe side effects than those observed in human chemotherapy. While severe side effects can occur, they affect less than 5% of all pets receiving chemotherapy. Chemotherapy affects all rapidly dividing cells within the body, not just cancer cells. The most commonly-affected patient tissues in chemotherapy include the digestive tract, bone marrow and hair follicles.

Digestive side effects

The most common digestive effects associated with chemotherapy are decreased appetite, vomiting and diarrhoea. These effects typically occur 3–5 days after chemotherapy drugs are administered. Signs are typically mild and self-limiting or respond well to supportive medications. Some pets may require hospitalisation for intravenous fluid therapy. When a pet is given a drug that is known to cause nausea, anti-emetics may be administered concurrently in order to minimise side effects. In general, the use of anti emetics and antidiarrhoeals early on should be encouraged in order to reduce the chance of dehydration and hospitalisation.

Bone marrow side effects

Chemotherapy is often associated with bone marrow suppression, which may result in leukopaenia and thrombocytopaenia. Patients typically receive regular routine complete blood cell count (CBC) monitoring while receiving chemotherapy. The frequency of CBC monitoring is dependent upon the exact chemotherapy protocol being used. Low white blood cell counts may lead to chemotherapy administration being postponed, until the CBC has improved. Additionally, pets with severe leukopaenia, or those with evidence of infection, may be treated with antibiotics on an outpatient basis or hospitalised for intravenous fluids and injectable antibiotics.

Coat side effects

The coat effects of chemotherapy are most pronounced in dogs belonging to wire-haired or non-shedding breeds, such as Terriers and Poodles. These dogs may experience some degree of hair loss after treatments and most will lose their whiskers and guard hairs. Pets that have hair clipped during chemotherapy will not regrow hair until after chemotherapy is completed.

Chemotherapy Administration

Chemotherapy protocols vary significantly depending on the type of cancer, the extent of the disease, and the overall health of the patient.

Chemotherapy can include any combination of oral medications that are given at home, injectable medications given during outpatient appointments, and slower infusions also given on an outpatient basis.

The frequency and duration of chemotherapy depends on the particular patient, drug and disease. Some patients will remain on chemotherapy for the rest of their life, though many chemotherapy protocols only include several weeks to months of treatment, assuming that remission is achieved. If cancer recurs after a period of remission, chemotherapy may be resumed.

CLIENT EDUCATION: Handling Chemotherapy Medications at Home

In some cases, clients may be sent home with chemotherapy medications to administer orally. These medications have the potential to cause damage to healthy cells in both pets and humans, so it is important that clients be instructed to handle these drugs with correct personal protective equipment (PPE). Pregnant and nursing women and small children are at the highest risk of effects from handling chemotherapy agents and should not be handling them or the wastes from pets on chemotherapy. Chemotherapy drugs are not only found within the tablets or capsules themselves, but also within the blood, saliva, urine and faeces of pets undergoing treatment. Therefore, it's important to handle the excrement of treated pets with correct PPE during chemotherapy. While the Oncologist will review this information with the client, here are the answers to some commonly-asked questions about oral chemotherapy.

How do I administer chemotherapy medications at home?

Follow these steps to administer your pet's chemotherapy medications at home:

- Read the instructions thoroughly.
- Wear gloves.
- Administer the medication in an area where the surface is easy to clean and away from food preparation areas.
- If possible, place the medication at the back of your pet's throat and encourage him or her to swallow. If that is unsuccessful, you can place the tablet in a small amount of a soft treat (such as cheese, peanut butter, or canned food).
- Used gloves and empty medication bottles should be returned to the Oncologist for safe disposal.
- Contact the Oncologist if you have difficulty administering medications.

How do I clean up after a medication spill (or a urine/faeces accident)?

If a chemotherapy drug is spilled at home (or your pet has an accident within 48 hours of receiving medication), the area is considered contaminated and it should be cleaned promptly.

Use the following technique for cleaning spills:

- Wear gloves
- Use a dilute bleach-soaked paper towel or cloth to clean up the spilled medication
- Work in a circular fashion, from the outside in to the center, to avoid further spreading the medication on your floors or countertops
- Throw away contaminated cloth or paper towels, placing them in a separate waste bag that is double-bagged in a second waste bag. This can be disposed of in the outside garbage container

If your pet has spat out or vomited the medication, do not attempt to repeat dosing. There is no way to know how much of the medication your pet may have ingested/absorbed and you do not want to overdose your pet. Contact the oncology department for instructions on what to do in this situation.

If contamination of your pet's bedding occurs, the bedding should be handled with gloves. Be careful to avoid dripping urine through your home on the way to the laundry room. Soiled bedding should be washed twice (first with cold water, then with warm water) with regular laundry detergent. After this washing, the bedding is considered safe to handle without any special precautions.

Can I still interact with my pet while they are receiving chemotherapy?

There is no known safe amount of chemotherapy for us to be exposed to. There is a small amount of chemotherapy found in urine, saliva and faeces, up to 21 days after chemotherapy is administered. For this reason you should avoid contact with urine, saliva and faeces from pets on chemotherapy and wash the area thoroughly if you come into contact with these wastes.

CHAPTER FOUR

COMMON CHEMOTHERAPY DRUGS

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4. COMMON CHEMOTHERAPY DRUGS

The exact chemotherapy protocol for each patient is determined by the patient's cancer, the extent of cancer spread and the patient's health status. The following chemotherapy medications are those that are commonly used in veterinary patients

Carboplatin

Carboplatin is a platinum-containing alkylating agent that inhibits DNA replication in a cell-cycle nonspecific manner. Carboplatin is used to treat a variety of tumours in pets. Common diseases that are treated with carboplatin include osteosarcoma, nasal carcinoma and squamous cell carcinoma

Administration

Carboplatin is an intravenous injection. It is typically administered during an outpatient visit every 3–4 weeks. Unlike cisplatin, this drug does not require aggressive fluid diuresis.

Side Effects

Observed Adverse Effects Include The Following:

- Neutropaenia: This typically occurs 7–21 days after treatment and resolves with time. All patients receiving carboplatin should have a CBC checked one, two and three weeks after treatment. For some patients, their nadir may be late, or they may have two nadir's occur
- Thrombocytopenia: This typically occurs 7–21 days after administration and can put a patient at risk of bruising or haemorrhage
- Inappetence, nausea, vomiting, diarrhoea: Gastrointestinal (GI) effects are uncommon with carboplatin, but can occur. In the absence of fever, GI effects can be managed conservatively with symptomatic treatment (withhold food for 12–24 hours and then gradually reintroduce a bland diet, giving anti-emetics and anti-diarrhoeals.)

CCNU (Lomustine)

Lomustine is an alkylating agent that is used to treat a number of veterinary cancers, including lymphoma, brain tumours, mast cell tumours and sarcomas.

Administration

Lomustine is given orally, in capsule form, typically in a bolus dose, but in some circumstances a dose may be divided over a number of days. It is typically administered every 3 weeks in dogs and every 3–6 weeks in cats.

Side Effects

- Nausea and vomiting: May be seen after administration. This medication should be given on an empty stomach, 3–4 hours after a meal
- Neutropaenia: In dogs, this typically occurs 7 days after treatment and resolves within 1–3 days. In cats, neutropaenia may occur 1–6 weeks post-treatment and persist for up to six weeks. Performing weekly CBCs for monitoring in cats is recommended
- Thrombocytopaenia: A cumulative, irreversible thrombocytopaenia can occur up to four weeks after treatment and the likelihood increases with repeated treatment. Monitor CBCs post-treatment
- Hepatotoxicity: ALT is monitored closely in patients receiving CCNU, and if the ALT increases then the therapy is discontinued. Concurrent administration of denamarin is recommended
- Lethargy: Occasional side effect. This effect typically resolves within a few days; no treatment is needed other than allowing the pet to rest
- Fever: May occur in conjunction with infection, or may occur spontaneously Notify Oncologist if a fever develops.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that interferes with DNA replication. It is used to treat a wide range of tumours, including lymphoma, mammary carcinoma and hemangiosarcoma. It is used in both conventional chemotherapy protocols and metronomic chemotherapy. Cyclophosphamide can also be used to ablate bone marrow prior to a stem cell transplant.

Administration

Cyclophosphamide may be administered orally (in a tablet or capsule) or as an injection. There are a wide variety of available protocols, depending on the cancer to be treated. Some protocols utilise a single maximum dose of cyclophosphamide, and others use cyclophosphamide long-term as a component of metronomic chemotherapy.

Side Effects

- Sterile haemorrhagic cystitis: Cyclophosphamide metabolites such as acrolein are excreted by the kidneys and can cause bladder inflammation if held in the bladder for prolonged periods of time. Recommend administration in the morning with a diuretic, followed by free access to water and frequent opportunities to eliminate throughout the day. Similar to other chemotherapy agents, cyclophosphamide can cause neutropaenia 7 days after administration

Doxorubicin

Doxorubicin is an anthracycline antibiotic antineoplastic drug, used to treat a number of cancers including lymphoma, sarcomas, carcinomas and multiple myeloma.

Administration

Doxorubicin is a bright red, injectable chemotherapy drug that is administered IV as a slow infusion over 15 minutes. The rate of administration is vitally important, too fast, and patients are at risk of an anaphylactoid like reaction including severe arrhythmias, immediate gastrointestinal signs and urticaria. If given too slowly, there is a significant increase in risk for severe gastrointestinal signs after treatment. Doxorubicin is markedly vesicant and any amount of drug extravasated from the vein can cause catastrophic tissue damage and necrosis. Many patients who have doxorubicin extravasation injuries require amputation of the limb.

Side Effects

- Cardiac effects: These effects may be acute or cumulative and can lead to congestive heart failure. Echocardiogram is often recommended prior to treatment in any patient of increased risk of cardiac toxicity
- Renal failure in cats: Typically associated with higher cumulative doses especially in feline patients. Patients receiving doxorubicin should receive routine bloodwork monitoring
- Extravasation injury: even a small amount of doxorubicin extravasated outside of a vein can cause extensive progressive tissue necrosis and often requires aggressive surgical intervention (frequently amputation)
- Hypersensitivity reactions: Hives can be seen immediately after treatment, but can typically be prevented with the use of antihistamines or anti-inflammatories
- Gastrointestinal effects: Typically seen 2–5 days after treatment and resolved within 24–48 hours. Fasting prior to doxorubicin administration and for a period of time after treatment can reduce the likelihood of this side effect
- Neutropaenia: Typically seen 5–7 days after treatment, white blood cell counts typically rebound by 8–9 days post-treatment
- Alopecia: Mild hair loss or delayed hair regrowth, rarely significant

Chlorambucil (Leukeran)

Chlorambucil is a nitrogen mustard derivative antineoplastic agent, often used to treat leukaemia and lymphoma.

Administration

Chlorambucil is an oral medication. Protocols vary, and this drug can be given as a bolus dose in substitution for other alkylating agents, or can be given on a daily basis.

Side Effects

- Alopecia: Mild hair loss or delayed hair regrowth, rarely significant
- Neutropaenia and/or thrombocytopaenia: Typically seen 7–14 days after treatment, lasting 1–3 days before cell counts normalise
- Nausea, vomiting, and diarrhoea: Uncommon side effects; treat symptomatically

Melphalan (Alkeran)

Melphalan is a nitrogen mustard derivative antineoplastic agent, used to treat multiple myeloma and other neoplastic diseases

Administration

Melphalan is an oral medication, typically given on a continuous basis for multiple myeloma but can be administered in a bolus dose as part of combination chemotherapy protocols for lymphoma.

Side Effects

- Neutropaenia and/or thrombocytopaenia: Typically seen 5–7 days after treatment, lasting 1–3 days prior to normalising. In cats the thromboctopaenia can be profound and long lasting
- Anorexia, nausea, vomiting, and diarrhoea: Rare, treat symptomatically

Metronomic Chemotherapy

Metronomic chemotherapy utilises low dosages of chemotherapy given on a daily or every other day basis and is often combined with non-steroidal anti-inflammatory drugs. This therapy aims to control tumours by stopping angiogenesis in the tumour.

Administration

Metronomic chemotherapy is typically administered on a consistent, long-term basis, depending on the drugs used. This type of chemotherapy is administered by owners at home, in the mornings on a daily or every other day basis.

Side Effects

Side effects depend on the particular drugs used. Cyclophosphamide and chlorambucil are the most common.

Mitoxantrone

Mitoxantrone is a synthetic anthracenedione antineoplastic. It is used in the treatment of a number of neoplastic diseases, including anal sac adenocarcinomas and other carcinomas.

Administration

Mitoxantrone is a bright blue liquid that is administered as an IV injection.

Side Effects

- Anorexia, vomiting, diarrhoea: Usually self-limiting and responsive to symptomatic treatment, these effects typically occur 2–5 days post-treatment
- Neutropaenia. Typically occurs 7–8 days week post-treatment, then resolves
- Urine may take on a blue colour as the drug is cleared in the urine; this is not clinically significant

Toceranib phosphate (Palladia)

Palladia is a tyrosine kinase inhibitor, inhibiting a number of cell surface receptors that play important roles in cell signalling, cell growth, and cell division. Palladia is very effective against mast cell tumour disease, as well as a number of other tumours, usually carcinomas.

Administration

Palladia is an oral medication, typically dosed on an every other day or three times per week basis. This medication is usually administered by owners at home.

Side Effects

- Muscle cramping: This is sometimes seen during the first few weeks of Palladia. Affected pets may demonstrate lameness or reluctance to move. Signs typically resolve within 1–2 days, but pain medication or anti-inflammatories can be given for symptomatic treatment if necessary
- Hypertension: Increases in mean and systolic blood pressure are not uncommon after starting Palladia. As many patients with cancer are hypertensive due to their disease, it is important to measure blood pressure prior to starting therapy and then regularly throughout treatment. Treatment of hypertension is often required
- Anorexia, vomiting, diarrhoea: Usually self-limiting, responds to symptomatic treatment
- Neutropaenia: A decrease in total white blood cell count and specifically neutrophils, is commonly seen. This may require a dose reduction of the medication and is particularly common when combining this medication with other anti-neoplastic agents

Piroxicam (Feldene)

Piroxicam is a non-steroidal anti-inflammatory medication (NSAID) that is used in the treatment of a number of cancers, including transitional cell carcinoma.

Administration

Piroxicam is an oral medication, typically administered at a dose of 0.3 mg/kg once daily

Side Effects

The side effects of piroxicam are similar to those seen with any other NSAID:

- Renal and hepatic effects: Blood work should be done prior to starting piroxicam and monitored during treatment
- Intestinal ulceration: Monitor pets for gastrointestinal signs, especially tarry stools
- Clotting disorders: Monitor for any signs of bruising or bleeding. If noted, stop medication

Prednisolone

Prednisolone is a steroid that is used as an adjunct treatment in a variety of cancers.

Prednisolone should not be given with NSAIDs, due to the risk of gastrointestinal ulceration. Interactions may also be seen with diuretics, phenobarbital, cyclophosphamide, mitotane, and anticholinesterase agents. Prednisolone may also increase insulin requirements in diabetic pets

Administration

Prednisolone is typically given orally, at a dose of 0.5–1 mg/kg/day

Side Effects

- Polyuria/polydipsia: Clients should be instructed to provide unlimited access to water and give their pets frequent opportunities to eliminate
- Increased appetite: Clients should take care to continue feeding a consistent amount; do not increase food intake to match the increased appetite
- Increased panting: Not clinically relevant
- Gastrointestinal ulceration: This is primarily a risk in pets receiving concurrent NSAIDs. Owners should be instructed to monitor for black/tarry stool

Vinblastine

Vinblastine is a vinca alkaloid antineoplastic agent that is often used to treat mast cell tumours in dogs and cats.

This drug can also be substituted for vincristine in cats being treated with lymphoma.

Administration

Vinblastine is a clear liquid that is given IV, typically on an outpatient basis.

Side Effects

- Gastrointestinal issues, such as anorexia, vomiting, or constipation: These signs are most likely to occur 3–5 days post-treatment and typically respond well to a bland diet and supportive medications
- Lethargy: Typically self-limiting, resolving within a couple of days
- Neutropaenia: This can be severe and is most often seen 7 days after administration
- Skin damage at the injection site, if extravasation occurs

Vincristine

Vincristine is a vinca alkaloid antineoplastic that is often used to treat lymphoma in dogs and cats.

Administration

Vincristine is a clear liquid that is given IV, typically on an outpatient basis.

Side Effects

- Gastrointestinal issues, such as anorexia, vomiting, diarrhoea, or constipation: These signs are most likely to occur 2–7 days post-treatment and typically respond well to a bland diet. Ileus is more likely in feline patients and can be severe
- Lethargy: Typically self-limiting, resolving within a couple of days
- Neutropaenia: This is most often seen 7 days after administration
- Skin damage at the injection site, if extravasation occurs

CHAPTER FIVE

SURGICAL ONCOLOGY

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Animal Cancer Centre

5. SURGICAL ONCOLOGY

An integral part of oncology therapy is surgery. Surgery helps to provide tumour diagnosis and for many types of cancer, it's treatment.

It has been widely recognised that well performed first instance surgery provides the best chance for cure. Therefore, cooperation between the Oncologist and oncology trained surgeon is crucial for thorough surgery planning, considering the patient's general health status, lifestyle and its activity level, tumour stage and possible adjuvant therapies. There are many factors to consider when deciding on the level of surgical intervention and postoperative management. Current comorbidities related to the tumour such as vomiting, dehydration, anaemia or hypercalcaemia or tumour unrelated such as renal, hepatic or cardiac compromise can all increase the anaesthetic risk and surgical morbidity and will likely influence the adjuvant therapeutic options.

The goal of surgery (therapeutic or curative intent, cytoreduction or palliation), the prognosis of the patient and the underlying health of the patient should all be discussed with the owners beforehand to ensure they are fully informed. The biology of the tumour can be highly variable between the types and grades, and as a result, the objectives of surgery may be different for each patient.

Surgical Margin

The rim of grossly normal tissue removed with the tumour is called the surgical margin. Based on the extent of margin removed during the surgery we recognise four levels of surgical resection – radical surgery, wide, marginal and debulking (or intralesional) surgery.

Surgical margins are three-dimensional and the lateral and deep margins must be considered and well planned during the surgery. The extent of lateral margins should be guided by the tumour type and its biological behaviour. Deep margin is usually represented by separate tissue planes (connective tissue such as muscle fascia) and wide surgical resection should include at least one tissue plane below the tumour.

Surgery as a Diagnostic Option

Diagnostic surgery or biopsy aims to remove some, or all, of the tumour to allow for laboratory diagnostics by veterinary pathologists. There are two benefits to this; to understand the prognosis of the tumour, and to formulate a treatment protocol for the future.

Fine needle aspirate is the simplest and least invasive diagnostic procedure, providing small sample for cytology and the goal of FNA being to separate between non-neoplastic (e.g. inflammatory, infectious) and cancerous process. When compared to histopathology, fine needle aspiration appeared to be in agreement in close to 91% of cases and was 98% specific for diagnosing neoplasia.

Larger diagnostic biopsy samples for histopathology can be obtained via needle core biopsy (Tru-cut), punch biopsy or through incisional or excisional biopsy. When compared to fine needle aspirate, larger histopathology sample allows for tumour grading and immunohistochemistry staining.

Tru-cut biopsy can often be performed under sedation, using a local anaesthetic at the biopsy site.

Incisional surgery removes a biopsy tissue from the tumour usually in a wedge shape, whereas excisional surgery removes the whole tumour. Incisional biopsy should be from the tumour itself

and must avoid the healthy surrounding tissue to protect the margin.

Excisional biopsy, or removal of the tumour close to its pseudocapsule, could be considered marginal surgery. This level of excision aims to remove the entire tumour, but without sufficient margin and will be unlikely curative. Marginal resection is reserved for diagnostic purposes but could be used as primary surgery in an area of limited tissue availability (distal extremity, on a skin overlying joints etc) and should be complemented either with subsequent wide resection of the scar or accompanied by adjuvant therapy.

Any biopsy approach should be well planned because the biopsy track or biopsy scar must be incorporated in the final curative intent resection.

Regional lymph node biopsy is performed as part of the staging for prognosis or as a therapeutic option. Diagnostic lymph node biopsy can be performed using Tru-cut needle but more commonly, the entire lymph node is excised. The excision of mandibular, retropharyngeal, prescapular, inguinal, popliteal, or medial iliac node is often executed with the aim to reduce the amount of gross disease.

Surgery as a Therapeutic Option

Well planned and well executed surgical removal can represent single stage curative treatment for some types of cancer. With curative intent surgery, the entire tumour must be removed with sufficient margin clear of any neoplastic cells.

A radical excision represents tumour removal outside of its anatomical compartment (body part removal), e.g. limb amputation for osteosarcoma or splenectomy for hemangiosarcoma.

Wide surgical excision incorporates margin consisting of 1–3 cm of tumour free tissue in all directions as well as deep margin. The deep margin can be less than 1 cm providing one tissue plane is involved in the excision. Historically, 3 cm margin and one to two deep tissue planes have been prescribed for most malignant tumours but recent studies shown that 2 cm margin allows for complete excision of 91–100% of grade 2 MCTs and 1 cm margin appears enough for complete excision of grade 1 MCT. Wide surgical margin recommended for soft tissue sarcomas remains at least 3 cm laterally and one tissue plane deep.

Radical and wide margin surgery is considered curative intent surgery and when well executed, it can remain as the sole treatment.

Marginal surgery refers to tumour removal with narrow margin laterally and deep, and the mass is removed usually outside of its pseudocapsule ('shelled out', extracapsular removal). This level of excision usually leaves microscopic disease behind. It is suitable for rather benign tumours such as lipoma but will not be sufficient for malignant soft tissue sarcoma or mast cell tumour. Marginal surgery could be considered in a situation where the lack of tissue prevents wide excision and radical surgery is not acceptable. A great example is soft tissue sarcoma of the extremity. In such a situation, marginal surgery should be followed by adjuvant therapy, such as radiation or intralesional or systemic chemotherapy.

Debulking or intracapsular surgery is performed within the tumour capsule or within the tumour plane and gross or microscopic neoplastic tissue remains in situ. This is the least acceptable surgical option because presence of a gross tumour renders any adjuvant therapy less effective. Examples of these scenarios include tumours which are attached to vital organs, or very close to important blood vessels. This cytoreductive surgery aims to reduce the tumour to a smaller size. This enables it to potentially be responsive to chemotherapy or radiation.

Unfortunately, not all tumours are suitable for curative or marginal surgery, and therefore palliative surgery may be considered. This type of surgery aims to improve the quality of life of the patient, but it may not necessarily increase the survival time. Examples include splenectomy with a ruptured and bleeding tumour or amputation for pathological fracture where the primary tumour has already metastasis. Partial removal of an obstructive mass could temporarily improve quality of life in some cases.

Intraoperative Considerations

Proper surgical technique and tissue handling is the key to a successful outcome. Gentle skin preparation is mandatory because excessive rubbing and tumour handling increases risk of metastasis because of the risk of tumour cell exfoliation.

Tumour handling should be minimised to prevent seeding of the cancer cells. The tumour should be isolated with moist laparotomy sponges to protect contact with normal tissue. Haemostasis with early ligatures or electrocautery should prevent tumour emboli into circulation (especially in highly vascular tumors of the liver, spleen or lung).

Atraumatic tumour handling will prevent tumour fragmentation and exfoliation of the tumour cells.

Use of multifilament suture materials has been implicated in increased local recurrence rates.

Drains should be avoided in oncological surgery as they penetrate the margins and potentially increase tumour cell extension outside of the planned margins. If a drain is required, it should be placed in such a manner, that any egress contaminated tissue can be readily removed during potential revision surgery or it could be placed subsequently, once the histological margin becomes known.

If the tumour capsule has been intraoperatively disrupted, the defect should be sutured, stapled or electrocoagulated with the entire wound sutured, instruments and gloves changed and a new clean margin of excision established.

It is essential that a set of new instruments and new gloves be used for any subsequent tumour removal on the same patient to prevent tumour cells seeding to another anatomical location.

Postoperative Considerations

The entire resected mass should always be submitted for histopathological evaluation of the tumour type, grade and surgical margins. A Pathologist will then evaluate the tumour margins for presence or absence of residual cancer cells. The margin of the excised sample should be stained with tissue ink or marked with suture prior to fixation in 10% buffered formalin to aid the Pathologist in orientation.

The sample for histopathology should be clearly labelled with name and anatomic location.

For more information please visit

www.sashvets.com

Alternatively, please call our helpful Animal Cancer Centre team on

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