“Principles of Surgical Oncology”

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Introduction
Surgical oncology remains an evolving science using multiple diagnostic modalities and therapies. Whilst surgery remains pivotal in the treatment of neoplasia, it behoves clinicians to remain abreast of advancements being made in our understanding of tumour biology and in appropriate neoadjuvant and adjuvant treatments. Clinicians should ask themselves “How can I maximise the potential for effective palliation or cure, how can I maximize my patient’s quality of life and how can I minimise the side effects of my interventions?” Cancer is not a synonym for death and, even if cure is not possible, many cancers can be regarded as ‘survivable’ chronic disease. Providing quality of patient life is considered as paramount, the ultimate aim is to be on the extreme right arm of the survival bell curve. In the words of Stephen J Gould, who was diagnosed with abdominal mesothelioma and lived for 20 years after this diagnosis (having been told the median survival time was 8 months), “the median isn’t the message”.

Surgeons now have to be more than ‘cutters and sewers’; we have to be pathobiologists. Box 1 provides examples of areas in which the oncologist has to be proficient and this list is not exhaustive. It simple serves to demonstrate the vast breadth of knowledge needed and thus that we shouldn’t see ourselves working in isolation over these challenging cases but as part of a collegial team, utilizing our colleagues with different areas of knowledge and expertise. E-technology makes this easier to achieve, even if we find ourselves geographically isolated from our peers.

**BOX 1 Breadth of Knowledge for the Modern Day Oncologist**

- How to make a diagnosis
- How to stage neoplastic disease
- What surgical dose options exist and which should I apply
- Imaging technologies – Radiography, CT, MRI, Sonography, Scintigraphy, PET-CT, Contrast agents
- Surgical principles
- Reconstructive surgical techniques
- Palliation
- Value of cytoreduction prior to/after alternative therapies
- Neoadjuvant vs. Adjuvant therapies eg chemotherapy, radiotherapy, immunotherapy
- Nutrition – feeding the healthy body and starving the neoplasia
- Support surgeries eg feeding tubes, urinary diversion
- Pain pathways and Analgesia
- Preventative/Prophylactic surgeries
- Owner counselling
- Emergencies eg uroabdomen, haemoabdomen, pneumothorax
- Metastatic disease management
- Perioperative complications
- Paraneoplastic syndromes & Identifying co-morbidities
- Laboratory sample handling, processing and biomarkers
- Infection control and Antibiosis
- Metronomic therapy & Anti-Angiogenesis
**Diagnosis and Staging**

To treat effectively, we must begin by knowing what we are dealing with for it is better the devil you know than the devil you don’t. This means starting with the ‘basics’ of a thorough clinical examination supported by blood counts, serum chemistry and urinalysis – paraneoplastic syndromes and co-morbidities are not only clues, they are crucial deviations from homeostasis that we need to know about, examples of which are shown in Box 2.

**BOX 2 Examples of Paraneoplastic Syndromes & Co-Morbidities**

- Comorbidities: Anaemia, Cachexia, Hepatic Function, Renal Function, Cardiac Function
- Hypercalcaemia
  - Apocrine gland adenocarcinoma
  - Lymphoma
  - Multiple myeloma
- Hypoglycaemia
  - Insulinoma
- Hypertension
  - Phaeochromocytomas
  - Adrenocortical adenocarcinoma
- Hypotension
  - Mast cell tumour
- Coagulation disturbances
  - Mast cell tumour
  - Haemangiosarcoma
- Other neoplastic diseases in the same individual
  - Eg multiple mast cell tumours are reported in 14-20% of dogs and cats
  - Eg in dogs with adrenal phaeochromocytomas, it is estimated that 50% have additional and unrelated tumours

Similarly, biopsy and staging information is vital to optimize patient management. Bray (2013) states “An incomplete resection (‘dirty margin’) is consistently associated with significantly reduced survival times” yet in 490 cases of canine soft tissue sarcoma (Bray et al, 2011), more than 90% of soft tissue sarcoma resections performed in general practice had no prior investigations prior to the first surgery and less than 4% of cases had a grade determined prior to the first surgery. These are concerning statistics and we should strive to change them. Often extra cost and time is cited as a reason for not performing biopsies before definitive surgery yet this can be a very false economy and may turn a treatable disease into an untreatable one. Treatment without biopsy will be speculative at best & **usually** cannot be justified. Exceptions to this rule of course exist and include those situations in which knowing the tumour biology will not change the treatment recommendations (eg splenic tumours) and those in which the risk of biopsy is as great as definitive surgery (eg spinal cord tumours).
In this regard, three adages to remember are:

1. The first surgery offers the best chance of cure
2. Incomplete excision facilitates recurrence
3. Second surgeries are less successful and expensive

There are four main types of biopsy techniques: fine needle aspiration (FNA), needle-core biopsy, incisional biopsy and excisional biopsy. The biopsy technique chosen should be simple and safe and cost effective whilst maximizing the chance of achieving an accurate diagnosis. We aim to answer the following questions: 1) what type of tumour am I dealing with? 2) what is the likely biological behavior of the tumour? 3) what appropriate treatment options do I possess and, with respect to surgery, what is an appropriate surgical dose to apply; marginal, wide, radical? 4) what prognosis shall I give?

Generally, whilst FNA is economical (material costs are low, most animals do not require sedation) and can be diagnostic for certain tumour types (eg lymphoma, mast cell tumours), we improve our chances of an accurate diagnosis by obtaining a larger tissue volume. This larger volume can be used for cytological (eg impression smears) as well as histopathological testing, the latter giving us important information about the structure or architecture of a mass. Incisional biopsies usually include a junction between normal and abnormal tissue so that tumour invasion may be assessed; the assumption being that the tumour margins are the most representative of the disease and that the tumour’s centre may be necrotic and thus non-diagnostic. An exception to this rule is with bony neoplasia in which the margins of the mass may contain reactive rather than neoplastic tissue.

The role of excisional biopsy is controversial; it is attractive in that it has the potential to diagnose and treat at the same time but, without prior knowledge of tumour type, the chances of this diagnose-and-cure scenario are completely random. Therefore, it should only be done when it will not change nor compromise future definitive surgical procedures.

All biopsy techniques should be performed with definitive surgery in mind – this means that needle and biopsy tracts can be resected en bloc along with the primary tumour without compromising tumour control and functional outcome. Box 3 outlines some general biopsy rules.

For malignant neoplastic disease, clinical staging should be done to describe not only the extent and resectibility of the primary tumour but also to determine local and distant metastases. Many imaging modalities are available, including radiography, ultrasonography, nuclear scintigraphy, computed tomography, magnetic resonance imaging and positron-emission tomography. With respect to lymph node staging, whilst palpation of nodes is important in the clinical examination, lymph node size is not accurate in predicting metastatic disease. This is nicely demonstrated in the study by Williams and Packer (2003) in which 100 dogs with oral malignant melanoma were assessed, finding that 40% of dogs with palpably normal nodes had metastatic disease whilst 49% of dogs with enlarged nodes did not. Thus, FNA or incisional or excisional biopsy of regional lymph nodes is recommended in animals with malignant disease processes.

The concept of the sentinel lymph node is rather poorly defined in veterinary medicine at this time. In comparison, it is a significant concept in human oncology. It is based on the theory that metastatic disease occurs in an orderly fashion within the lymphatic system and that the sentinel (regional) node acts as an effective filter and barrier to tumour cell spread. Thus, if there is no
evidence of spread into the sentinel lymph node, there should be no distant metastatic disease. But, is this true? Two theories have evolved about what to do surgically with regional lymph nodes. In the Halsted theory, the sentinel node is removed with the expectation that it prevents further spread. In the Cady Fisher theory, the sentinel node is removed to assist with staging and may serve as a form of cytoreductive surgery but it does not prevent or predict metastatic disease.

The World Health Organisation Tumour Node Metastasis (TNM) staging system (1980) is frequently used by veterinary oncologists (Box 4). Other staging systems have been designed for specific tumour types. Regardless, staging schemes aim to standardise communications between oncologists and provide useful tools with which to discuss response to treatments and prognoses.

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**BOX 3 Some Rules of Biopsy**

- Ideally, advance image beforehand
- Locate FNA/biopsy with future definitive excision in mind
- Multiple samples (e.g., 6 needle cores) & locations within mass to improve diagnostic yield, think central vs. marginal
- Include LNs
- Minimise dissemination – Halsted tenets, uninvolved planes should not be breached, change instruments between different biopsy sites
- Avoid overzealous scrubbing for surgical preparation (applies to biopsy & definitive surgery)
- Submit all & think about fresh samples, culture & cytology; in house cytology can be helpful to ensure diagnostic sample has been obtained

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**BOX 4**

**WHO's TNM Classification Scheme for Tumours in Domestic Animals (Owen, LN. 1980)**

**Primary Tumour**

| T0 | No evidence of invasive growth |
| T1 | <1 cm diameter and not invasive |
| T2 | 1-3 cm diameter or locally invasive |
| T3 | >3 cm diameter, locally invasive or ulcerated |

**Regional Lymph Node**

| N0 | No evidence involved |
| N1 | Node firm and enlarged |
| N2 | Node firm, enlarged & fixed to surroundings |
| N3 | Nodal involvement beyond regional nodes |

**Distant Metastasis**

| M0 | No evidence of metastasis |
| M1 | Metastasis to one organ system |
| M2 | Metastasis to >1 organ system |
Surgery and Neoadjuvant and Adjuvant Therapies

Once diagnosis and staging has been established, we need to determine an optimal customized or individualized course of curative-intent or palliative-intent action for our patient and this, increasingly so, may well involve a multimodal attack combining surgery with concomitant treatments such as chemotherapy, metronomic chemotherapy, antiangiogenic chemotherapy, radiotherapy, immunotherapy, hormone therapy and or gene therapy. For solid tumours, surgery remains the mainstay of our armory against neoplastic disease. Considerations to co-morbidities (eg cardiac disease, renal disease, anaemia), paraneoplastic conditions (see Box 2), analgesia and anaesthesia, asepsis, antibiosis and nutritional support are beyond the scope of this lecture but this does not diminish in any way their importance and they are thoroughly discussed elsewhere in the wider literature. However, a brief revision of general surgical principles is appropriate. William Stewart Halsted (1852-1922), often referred to as “the father of surgery”, was the first chief of surgery at Johns Hopkins Hospital, Baltimore and he started the first formal surgical residency programme in the USA. We will all recall learning his ‘Tenets’ and it is remarkable that these remain as relevant today as ever (Box 5). They should be second nature to any surgeon. Further surgical tips relating to neoplastic disease are shown in Box 6.

**BOX 5 The Tenets of Halsted**

- Maintain Haemostasis
- Maintain Asepsis
- Careful Tissue Handling
- Approximation of Tissues – Close Dead Space
- Minimise Tension
- Minimise the Introduction of Foreign Materials

The biggest surgical error made in oncological surgery is applying too small a ‘surgical dose’. Classic surgical doses are categorized as radical, wide, marginal or intralesional. The latter, aka ‘debulking’ surgery, is rarely applicable as tumour regrowth is usually rapid, it is rarely palliative and adjuvant therapies are generally less effective in the presence of macroscopic disease.

Wide and radical resections are generally performed with cure of solid tumours in mind (curative-intent surgery). Surgical margins are influenced by tumour type, grade, biological behavior, size and anatomic location. The difficulty is in determining how much normal-appearing tissue should be removed en bloc with the gross tumour and precise guidelines for tumour margins have not been clearly defined. The metric approach (eg 3D cm-distances from the primary tumour) and the barrier approach (eg use of tissues resistant to neoplastic spread such as fascia, periosteum and bone and or removal of an entire anatomical compartment) are often cited with respect to mast cell tumours and soft tissue sarcomas. For example, 3cm lateral margins and one-two fascial planes deep is commonly applied to these tumours regardless of their location, size or grade. However, the origin of the 3cm rule is unknown and is being increasingly challenged. For example, Simpson et al (2004) demonstrated that all grade 1 mast cell tumours were completely excised with 1cm lateral margins...
and all grade 2 tumours were completely removed with 2cm lateral margins when the primary tumours were less than 5cm in diameter. So it may be true that in some situations we are overdosing with surgery and risking increased morbidity associated with wide or radical excisions. However, metric distances required to achieve tumour free margins for higher grade mast cell tumours, for those over 5cm in diameter and subcutaneous mast cell tumours has yet to be determined. With respect to soft tissue sarcomas, their pseudocapsular reactive zones are difficult to metrically define and even with ‘wide’ removal and ‘clean margins’, microscopic disease may be left behind.
BOX 6 Some Oncological Surgical Tips

- Always apply Halsted’s Tenets
- Wide clip – remove more hair than you think necessary
- Gentle skin preparation to reduce incidence of tumour cell exfoliation and or vasoactive substance release (e.g. MCTs)
- Use sharp, scalpel incisions to reduce tissue trauma
- Haemostasis: Ligate vessels and lymphatics early & always before severing to reduce release of tumour emboli and reduce risk of haematoma formation. Ligation of artery or vein first is controversial and no evidence currently to support one or the other
- Treat tumour like an abscess to protect normal tissues; isolate with moistened swabs, don’t grasp tumour itself, handle carefully with stay sutures or atraumatic instruments placed in nearby normal tissues, avoid contact with ulcerated areas
- Remove adhesions en bloc with the tumour
- Remove all previous biopsy tracts and drain holes
- Use monofilament suture materials (tumour cells can become trapped in interstices of multifilament sutures) and those with good tensile strength profiles
- Lavage is controversial – may dilute residual tumour cells and thus decrease risk of recurrence or it may spread tumour cells throughout the area of lavage
- Avoid the use of drains (if must, plan within future resection and or radiotherapy sites)
- Don’t be frightened of open wounds – they are better than leaving cancer behind
- Don’t be frightened of staged closure. Avoid reconstructive surgery at the time of initial tumour resection; better to manage an open wound, await histopathology reports and close at a later date
- If the tumour margin is breached, electrocoagulate the exposed surface, lavage the wound and change instruments, gloves and drapes
- Change instruments, gloves, drapes before closing
- Submit all tissues for histopathology: prior biopsy samples are small and may not be truly representative of the larger tumour.
- Talk to your pathologists about margins of concern & the availability of prognostic biomarkers
- Recurrent tumours should be considered as a new disease; recurrent tumours (even of the same grade) may have different phenotypic expression and may pose a more aggressive threat to the oncologist: the first surgery offers the best chance of cure.
BOX 7 Submitting Samples

- Entire tumour should be fixed in 10% buffered formalin at a tissue:formalin ration of 1:10
- Tumour should not exceed 1cm thickness but do not slice full thickness through the mass so that the orientation is maintained
- Talk to your pathologist: give full history, draw pictures
- For thin tissues, pin out on cardboard to reduce tissue shrinkage and curling which can skew margin assessments
- For solid tumours, may be helpful to suture through vertical layers to stop ‘tissue slip’ which can distort tissue orientation
- For a 1x2x3cm mass, a pathologist would need 4000 sections to examine margins adequately – most commercial laboratories rely on 3-6 sections so mark areas of concern
- Use sutures or ink (eg Alcian blue, India ink) to mark specific areas you’re worried about. If using ink, allow air drying before formalin fixation. Don’t use ink if performing hormone-receptor assays
- Submit separate pieces of the wound bed from sites of concern; neoplastic cells in this tissue more reliably predicts residual disease
Marginal resection is defined as incomplete tumour removal with residual microscopic disease anticipated. Planned marginal resection may be useful in limb-sparing techniques to decrease tumour burden to microscopic levels such that adjuvant therapies (eg radiation) are more efficacious. Unplanned marginal resections should be avoided as they can have a significant negative impact on future treatments. For unplanned resections, a decision needs to be made on what to do. No further treatment is an option for low-grade tumours that may not recur (local recurrence rates are not 100%) but the problem is predicting which will and which won’t recur and a waiting game is usually an uneasy silence. Therefore, consideration should be given to staged removal of the surgical scar; for example, by removing the original scar with 1cm margins and re-performing histopathology, it can be determined whether tumour cells remain present in the scar tissue and thus whether further treatment (wider surgical excision and or radiotherapy) is advisable.

**Multimodal Management**

Combining surgery with other therapies such as chemotherapy, metronomic chemotherapy (the palliative use of chemotherapeutic agents at lower but more sustained doses to control angiogenesis and invasion), radiation therapy and immunotherapy aims to maximize the chance for cure whilst minimizing the risks (morbidity and mortality) associated with any one procedure. Neoadjuvant therapy is that performed prior to surgery and, for example, aims to reduce tumour size to reduce surgical dose needed, make inoperable tumours operable and reduce risk of metastases. Adjuvant therapy is applied after surgery and aims to eliminate microscopic residual disease. Each have their specific advantages and disadvantages and these have been tabulated several times in the literature; a version of which has been reproduced in Boxes 8 & 9.
## BOX 8 Timing of Chemotherapy & Surgery

<table>
<thead>
<tr>
<th>Timing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td>◆ Fewer radioresistant or hypoxic cells present in field</td>
<td>◆ Delayed wound healing</td>
</tr>
<tr>
<td>(before surgery)</td>
<td>◆ Smaller RT field, normal tissues spared</td>
<td>◆ Increased risk of dehiscence</td>
</tr>
<tr>
<td></td>
<td>◆ Decrease risk of dissemination of cells during subsequent surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◆ Decrease surgical dose required</td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>◆ Accurate delivery</td>
<td>◆ Specialised facilities required, costs increased</td>
</tr>
<tr>
<td></td>
<td>◆ Larger fractional doses delivered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◆ Decreased exposure to normal tissue</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>◆ Staging, surgery &amp; wound healing are not delayed</td>
<td>◆ Decreased blood supply due to scar tissue, increases RT resistant cells</td>
</tr>
<tr>
<td>(after surgery)</td>
<td></td>
<td>◆ Efficacy RT difficult to determine when only microscopic disease present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>◆ Larger RT field required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>◆ Repopulation of T cells possible between surgery and starting RT</td>
</tr>
</tbody>
</table>

RT is considered more effective in the neoadjuvant setting but it does have deleterious effects on tissue vascularity and is associated with higher rates of delayed wound healing and wound complications. Therefore, it is advised to wait until acute radiation effects have passed (approximately 3-4 weeks post-RT). In the adjuvant setting, radiotherapy is generally recommended to start 7-21 days post-operatively.
<table>
<thead>
<tr>
<th>Timing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td>◦ Reduce T size to help its removal</td>
<td>◦ Delays surgery, risks T growth</td>
</tr>
<tr>
<td>(before surgery)</td>
<td>◦ No delay in treatment of M disease</td>
<td>◦ Delayed wound healing</td>
</tr>
<tr>
<td></td>
<td>◦ Determine T sensitivity to drugs for post-op planning &amp; prognosticating</td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>◦ Intralesional administration</td>
<td>◦ Delayed wound healing</td>
</tr>
<tr>
<td></td>
<td>◦ Increase local drug concentration without increasing systemic toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>◦ Treats microscopic disease</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>◦ Surgery &amp; wound healing are not delayed</td>
<td>◦ Decreased blood supply to T due to scar tissue may reduce efficacy</td>
</tr>
<tr>
<td>(after surgery)</td>
<td>◦ More effective when distant microscopic disease present</td>
<td>◦ Efficacy difficult to determine when only microscopic disease present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>◦ Repopulation of T cells possible between surgery and starting ChT</td>
</tr>
</tbody>
</table>

In the adjuvant setting, chemotherapy is generally recommended to start 10-14 days post-operatively, when the risk to wound healing is low, although ranges are reported (0-21 days).
References:

1. www.vssso.org
2. www.vetcancersociety.org
3. www.vetoncologyconsults.com.au