



University Zurich
Small Animal Surgery Clinic

Orthopedic and neurologic examination
Physiotherapy
Tibia tuberosity advancement
Oncosurgery
Case discussion



5th Continuing Education Course for Japan Small Animal Surgeons at the Small Animal Surgery Clinic, Vetsuisse Faculty, University Zurich, University
August 23 – 27, 2004

Contents

Contents	2
Program	3
Examination of the orthopedic patient	4
Examples, x-rays	9
Physical therapy	12
Cases and revisions	13
Introduction to neurophysiology	30
Localisation of neurologic disorders	32
Prevention and revision of perioperative and postoperative complications with Zurich cementless canine hip prosthesis	35
Cranial cruciate ligament rupture: pathogenesis, diagnosis, overview methods	38
Tibial tuberosity advancement (TTA) for the treatment of cranial cruciate disease in dogs: evidences, technique and initial clinical results.	40
Oncosurgery	42
Biopsy	42
Tumor staging	47
Surgical oncology	51
Chemotherapy	57
Canine mast cell tumor	63
Tumors of the skeletal system	67
Reconstructive surgery	90
Mammary gland tumors	92
Perianal tumors	98
Cancer of the oral cavity	101
Paraneoplastic Syndromes	126

Program

Orthopedic examination, physical therapy, cases

Monday, Aug	0800	Gait analysis	Venzin
23 rd 2004	0900	Examples	Venzin
	1000	x-rays	Koch
	1200	Lunch	
	1300	Physical therapy	Koch, Mouwen
	1500	- Cases and revisions from Japan	Voss, Keller
	1700	veterinarians and Zurich faculty including biomechanics, failures, problems	
	1700	Champagne party	

Neurologic examination, cases, THP complications

Tuesday,	0800	Introduction to neurophysiology	Riediger
Aug 24 th	0900	Exam of the normal and pathological neuropatient	Steffen
2004	1100	Electrodiagnosis	Steffen
	1200	Lunch	
	1300	THR cup and stem loosening: introduction and discussion, morphometry hip joint	Tepic, Montavon
	1500-1700	Cases and revisions /ctd)	Voss, Keller

Tibia tuberosity advancement (TTA)

Wednesday,	0800	ACL rupture: introduction, pathogenesis, diagnosis, overview methods	Koch
Aug 25 th	0900	TTA: principles, technique	Montavon
2004	1000	TTA: video, comments	Guerrero
	1045	TTA: Wet lab	Montavon, Faculty
	1200	Lunch	
	1300	Excursion	De Robillard

Oncosurgery

Thursday,	0800	Introduction to oncosurgery	Rod Straw
Aug 26 th	1000	Organ specific lectures	Rod Straw
2004	1200	Lunch	
	1300	Cases	Rod Straw
	1400	Wet lab	Rod Straw, faculty
	1700	End of wetlab	

Oncosurgery

Friday, Aug	0800	Organ specific lectures	Rod Straw
27 th 2004	0900	Wet lab	Rod Straw, faculty
	1200	Lunch	
	1300	Paraneoplastics	Rod Straw
	1400	Wet lab	Rod Straw, faculty

Examination of the orthopedic patient

Claudio Venzin, Dr. med. vet.

A full orthopedic examination should only be performed once a thorough **history** (Signalement: breed, age, size, history: how long is the problem, progressive.) and **physical examination** has been completed. Manipulation of the affected limb should be left until the end of the examination in order to avoid sensitizing the animal. Cats are more difficult to examine than dogs, as they do not stand still and are less tolerant of manipulation and restraint.

Gait

standing: Certain visual will help you determine the site of involvement. The body weight often shifted towards the normal limb. The normal limb may appear to be held closer to the midline or under the body, while the affected limb is held out to the side or away from the body. (Toes of the unaffected leg may appear to spread further apart due increased weight bearing). The back may arch dorsally as weight is shifted to the front or rear limbs. Hip joint dysplasia or CrCL rupture both side then the weight will be forward, causing the elbows to appear abducted, the head and neck to be carried low, back to arch dorsally. Nails will get longer in limbs not bearing full weight.

Gait: Gait should be observed at walk and trot. The head and neck move upward as the affected forelimb touches the floor, and downward when the normal forelimb touches the floor. (say „yes“ to the normal foreleg). The stride is shortened on the affected side and the animal spends less time on the affected limb. Audible clicks may sometimes be heard in young dogs with hip subluxation and in dogs with medial meniscal tears secondary to cranial cruciate ligament ruptures.

Palpation

A complete knowledge of structure and function helps you decide how to perform specific tests and how to interpret the results. Comparing one side with the other may help you detect specific abnormalities.

Palpation standing:

Important to exclude neurologic problems (proprioceptive positioning, head turning, spinal cord pain) Palpation to detect swelling, pain, muscle atrophy, bone deformities and effusion or subtle differences in periarticular soft tissue.

Palpation lateral recumbency:

Examination is started at the level of the digitis and proceeds proximally. Response to palpation, manipulation and range of motion is assessed at this time.

forelimb:

digitis:

- nail beds (inflammation, infection, neoplasia)
- phalanges, phalangeal joints (swelling, pain, bony abnormalities)
- footpads (laceration, infection, pododermatitis, neoplasia, sesamoid fractures or rheumatoid arthritis)

metacarpals:

- soft tissue swelling, crepitus from fracture or subluxation

carpus:

- performed in slight flexion, allowing for palpation of the radiocarpal joint and intercarpal joints
- flexion and extension in addition to stressing the joints medially and laterally to evaluate the collateral ligaments stability.

antebrachium:

- examination for any evidence of growth disparity between the radius and ulna.
- pain (panostitis, fracture, hyperthrophic osteodystrophy, premature growth plate closure, osteomyelitis, neoplasia)

elbow joint:

- Direct pressure applied over the medial coronoid process of the ulna is a useful method of eliciting a painful response in dogs having fragmented coronoid process. Other common causes for elbow pain are OCD, DJD, articular fracture, luxations, elbow incongruity and ununited anconeal process.

humerus:

- some of humeral bone pain include panosteitis, osteomyelitis, fracture and neoplasia.

shoulder:

- extension of the shoulder puts pressure onto the cranial lip of the glenoid cavity and tension on the triceps muscle. Flexion puts pressure on the caudal surface of the humeral head (OCD). Abduction exacerbates pain due to joint capsule lesion. Extrinsic causes of shoulder pain can include brachial plexus tumors, infraspinatus contracture, triceps tendon avulsion, medial displacement biceps brachii tendon and cervical disc disease.
- Biceps stretch test: The shoulder is slowly flexed to maximum flexion with the dog's elbow held 90° to the humerus.

hindlimb:

digitis:

- same as for forelimb examination

tarsus:

- The tarsus should be palpated in extension and flexion for any medial or lateral instability.

tibia/fibula:

- Bone pain can include; panostiteis, osteomyelitis, fracture and neoplasia

stifle:

- The joint should be taken through a full range of motion repeatedly to assess for any crepitus or patellar luxation. Collateral instability is examined with the joint in extension and flexion. The drawer sign is used to test for stability of the cruciate ligament. The tibial compression test can also be used to test for cruciate ligament instability in dogs that resent stifle palpation (Fig. 2). Since in some patients there may be only partial tear of the cranial cruciate ligament, the drawer test should be performed with the stifle in both extension and flexion (Fig.3). With partial tears of the craniomedial band of the cranial cruciate ligament, there will be drawer in flexion and no drawer in extension. The patella should be examined for any evidence of medial or lateral luxation in extension and flexion.

femur:

- Bone pain can include; panostiteis, osteomyelitis, fracture and neoplasia

hip joint:

- The hip is evaluated by putting the joint through a full range of motion including flexion, extension, adduction, abduction internal and external rotation. Marked subluxation is occasionally associated with an audible clicking sound as the dog walks, caused by the femoral head snapping in and out of the acetabulum. This can be felt by placing your hand over the greater trochanter as the animal walks. Hip luxation can also be checked with the Barden or Ortolani sign (Fig.1). The hip should also be evaluated for luxation, by checking the alignment of the ilial wing, greater trochanter and ischium.

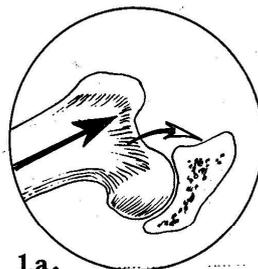
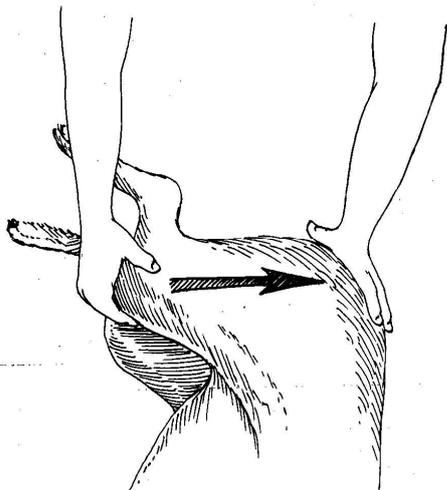
pelvis:

- palpation is difficult due to the gluteal musculature. The wing of the ileum and ischium are easy palpable. Evaluation of symmetry of the greater trochanter ileum and ischium may indicate the presence of acetabular, ilial wing or ischial fractures and hip luxation (Fig4).

Additional diagnostic tools:

Neurologic examination
X-Ray
Ultrasound
CT
MRI
Arthroscopy
Biopsy

1. Subluxation

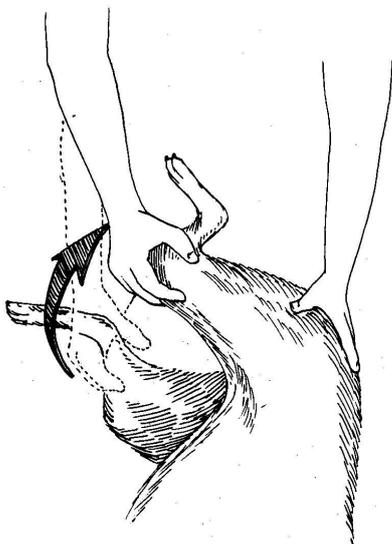


1a.

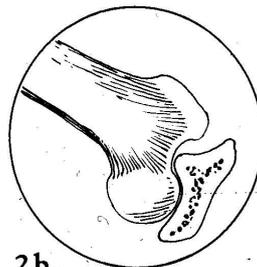


1b.

2. Reduction



2a.



2b.

Fig. 1

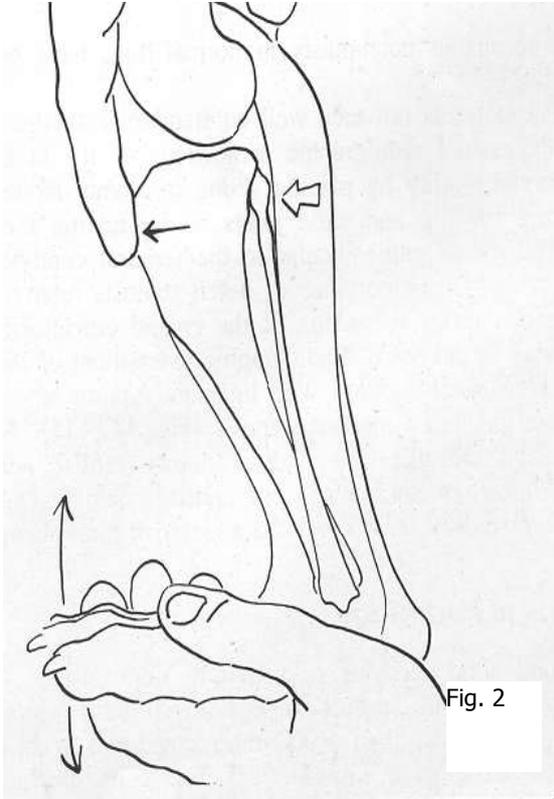


Fig. 2

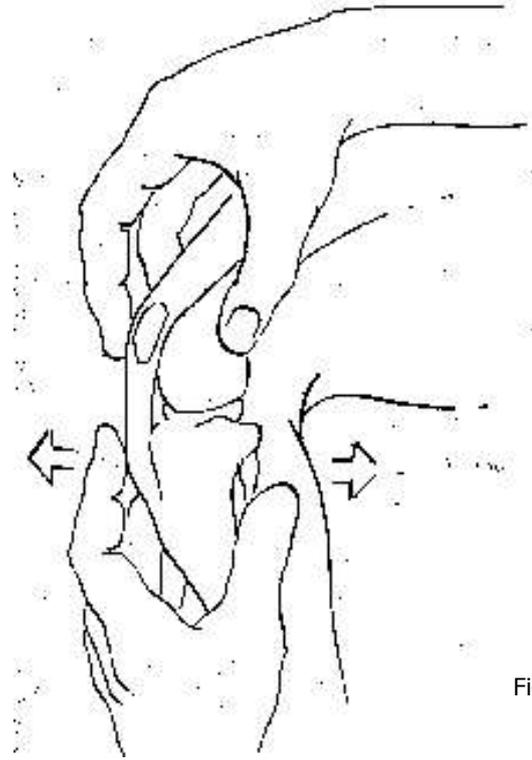


Fig. 3

Examples, x-rays

Daniel Koch, Dr. med. vet. ECVS

Case	Additional information from diagnostic imaging	Additional information from orthopedic examination	Differential diagnosis and remarks

Physical therapy

Marco Mouwen

Daniel Koch, Dr. med, vet. ECVS

Cases and revisions

Katja Voss, Dr. med. vet. ECVS

Marcel Keller, Dr. med. vet.

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Internal splinting of dorsal intertarsal and tarsometatarsal instabilities in dogs and cats with the ComPact UniLock 2.0/2.4™ System^a

K. Voss, M. Keller, P.M. Montavon

Summary

Dorsal intertarsal and tarsometatarsal instabilities are considered to be uncommon in dogs and only few cases have been reported in cats. Treatment usually consists in partial arthrodesis. Internal splinting of the affected joints represents an alternative surgical method with the goal of preserving joint function. In the present study, 13 animals (10 cats and three dogs) with dorsal, dorsomedial or dorsolateral intertarsal or tarsometatarsal instabilities, treated with an internal fixator (ComPact UniLock 2.0/2.4™ System) in bridging function, were reviewed. The joint cartilage was left intact. Follow-up time ranged from one month to one year postoperatively. Clinical outcome was considered good or excellent in 12 of the animals and moderate in one cat. Implant removal was performed in three patients. Follow-up radiographs were available for 10 of the patients. Joint space narrowing or joint fusion occurred in three cases. A broken screw in one cat and in one dog did not affect the stability of the joints involved.

The described technique is simple and less invasive than partial arthrodesis and the present results suggest it as valuable alternative to partial arthrodesis. Early implant removal could possibly prevent cartilage damage and joint fusion due to prolonged immobilization.

Introduction

The tarsus is a composite articulation, consisting of four joint rows, the tibiotarsal joint, the proximal and distal intertarsal joints and the tarsometatarsal joints. The tibiotarsal joint has the greatest range of motion (5). Although classified as rigid joints, the proximal intertarsal and talocalcaneal joints allow some degree of movement and should rather be considered low-motion joints (5, 7). Intertarsal and tarsometatarsal ligaments are numerous (5). For functional reasons they can be divided into short dorsal, short lateral and medial, and plantar ligaments. Second and third degree sprain of these ligaments causes joint instability of the affected side.

Partial tarsal arthrodesis is usually recommended for treatment of both plantar and dorsal intertarsal and

tarsometatarsal instabilities (3, 14, 18). Because the short dorsal ligaments are not under tensile stress during weight bearing, fibrous healing of the dorsal ligaments can lead to sufficient joint stability (4, 8, 14), and arthrodesis might not be necessary in cases with dorsal instabilities. External or internal immobilization of the affected joints must be provided during the healing period (4, 14). Temporary cross pinning, plating and a tension band repair using screws and wire are reported internal stabilization methods (4, 8, 10, 14, 16). Because prolonged joint immobilization causes malnutrition of the cartilage with subsequent degeneration (3, 13, 15), the implants should ideally be removed after periarticular fibrosis has stabilized the joint.

The present study describes internal splinting of thirteen consecutive cases with dorsal, dorsomedial or dorsolateral intertarsal and tarsometatarsal ligament injuries, with an internal fixator (ComPact UniLock 2.0/2.4™ System (Fig. 1)), available in two sizes (9). The 2.0 system can be used in cats and small dogs and the 2.4 system in larger dogs. The described technique is easy to perform and does not require an extensive surgical approach or debridement of the articular cartilage.

Material and methods

Medical records of 13 consecutive cases (10 cats and three dogs) with dorsal, dorsomedial or dorsolateral intertarsal or tarsometatarsal ligament injuries, treated by open reduction and internal adaptation with the ComPact UniLock 2.0/2.4™ System, were reviewed. Species, bodyweight of the patients, cause of injury, type and localization of the lesion, concurrent injuries, size, number and positioning of implants, duration of postoperative joint immobilization, clinical and radiological outcome were evaluated (Table 1). Presurgical evaluation included clinical examination and plain as well as stress radiographs of the affected tarsus in all of the cases. The instabilities were classified as follows: dorsal proximal intertarsal instability, presence of talocalcaneal luxation, dorsal distal intertarsal instability, or dorsal tarsometatarsal instability (Table 1).

One or two short ComPact UniLock 2.0/2.4TM plates were applied across the affected joints in bridging function (Table 1). The ComPact UniLock 2.0TM System was used in the cats and in one small dog (< 9 kg BW), and the ComPact UniLock 2.4TM System in the two larger dogs (> 33 kg BW). The surgical approach was performed directly over the lesion. Affected joints were evaluated for degree of soft tissue trauma, instability and cartilage damage, and then flushed in order to remove debris. Joint cartilage was left intact. One or two ComPact UniLock 2.0/2.4TM plates were cut to the desired shortest length, and contoured. The plates were applied across the unstable joint row after manual reduction. When possible, the screw holes were drilled monocortically and perpendicular to the plate. Care was taken to drill the hole within one single tarsal or metatarsal bone, in order to avoid penetration of adjacent joint surfaces. The depth of the screw holes was measured and appropriate self-tapping locking screws were inserted. A distance of 1 to 2 mm was left between the plate and the bone while tightening the screws (Fig. 2). This distance was aimed to preserve vascularity and encourage fibrous tissue healing underneath the plate. Subcutaneous tissue and skin were closed with single interrupted sutures.

Positioning of the implants was evaluated on postoperative radiographs. Either a soft padded bandage was applied during the first three to five days postoperatively to protect the wound, or a splinted bandage was used as external support for a variable duration. The decision for external splinting was based on the presence of concurrent injuries to the tarsus or foot (Table 1), or on surgeon's preference. The owners were encouraged to have the implants removed after four to six weeks.

Follow-up was performed in a time period between one month and one year postoperatively, either by clinical and radiological examination at our institution or at the private veterinarian, and/or by telephone inquiry of the owners (Table 1). Clinical outcome was graded as excellent if no visible lameness was detected at home by the owner and during the clinical examination. Outcome was considered good if owners reported an intermittent slight lameness, but lameness could not be confirmed during clinical examination. Outcome was moderate, when a weight-bearing lameness was detected at the clinic and the owners reported it to be consistent. Implant positioning, signs of joint instability, and width of the joint spaces was assessed on the follow-up radiographs. Radiographs taken by the private veterinarians were sent to our institution for evaluation.

Results

Ten cats and three dogs were presented with dorsal, dorsomedial or dorsolateral intertarsal or tarsometatarsal instabilities between April 2002 and June 2003. Bodyweight of the patients ranged from 3.5 to 35.7 kg (Table 1), with a mean of 9.3 kg. Clinical examination findings at admission included mild to non-weight bearing lameness, soft tissue

swelling, pain on manipulation and tarsal instability in all of the cases. Definitive diagnosis was achieved by performing stress radiographs under general anesthesia. Four animals were diagnosed with dorsal proximal intertarsal instability, three cats with dorsal proximal intertarsal instability and talocalcaneal luxation, one cat sustained a dorsal distal intertarsal instability and five animals had a dorsal instability at the level of the tarsometatarsal joints (Table 1). Concomitant medial or lateral instability at the affected joint level was further diagnosed in nine of the cases (Fig. 3). Three animals had concurrent ipsilateral slab fractures, of the fourth tarsal bone in two cases (Fig. 5), and of the base of the second metatarsal bone in one case.

No accident had been observed in five of the cats, motor vehicle trauma was observed or suspected in five of the patients, one cat fell from a height, one dog had his leg caught in a fence and one had a fight with another dog. One or more additional injuries at a distant site of the skeleton were diagnosed in six cats, including mandibular fracture, traumatic disc herniation, coxofemoral luxation, pelvic fractures and tarsometatarsal luxation at the opposite limb. In this last case, the luxation also involved plantar instability and was treated with partial tarsal arthrodesis. Luxation of one or two phalangeal joints on the affected hind limb was present in two of the cats, and medial collateral ligament sprain at the talocrural joint of the affected tarsus was present in one cat (Table 1). Rupture of the joint capsule and short ligaments were confirmed during surgery at the expected site in all the patients. A single ComPact UniLock 2.0TM plate (thickness 1.0 mm) was applied across the affected joint in eight of the cats (Table 1). One screw only was inserted distal and proximal to the affected joint in seven of them. One cat with tarsometatarsal instability was repaired using three screws (Table 1). Two parallel ComPact UniLock 2.0TM plates (thickness 1.0 mm), each with one screw distal and proximal of the affected joint level, were applied in two cats (Table 1 and Fig. 4). A single 2-hole ComPact UniLock 2.4TM plate was used in one dog with proximal intertarsal instability, and two dogs with tarsometatarsal injuries had medial and lateral ComPact UniLock 2.0/2.4TM plates placed (Table 1 and Fig. 5). The small slab fractures noted in three of the animals were bridged with the implants. No intraoperative problems were encountered.

Postoperative radiographs revealed correct joint position and screw placement in all of the cases. A soft bandage was applied to protect the surgical wound for three to five days in six animals (Table 1). A splinted bandage was used in seven patients, for a time period ranging from three to six weeks. Concurrent injury to the tarsus or foot was the reason for additional external immobilization in four of those animals (Table 1).

Clinical outcome at one month to one year postoperatively was excellent in 11 animals, good in one cat and moderate in another cat (Table 1). Radiographs of 10 patients were available for follow-up evaluation (Table 1). Joint space narrowing was

evident in two of the cats (Table 1). The immobilized joints were fused four months postoperatively in one dog with tarsometatarsal instability (Table 1). Affected joint spaces appeared normal in the other patients. Screw breakage was encountered in one cat and one dog. A single plate with only two screws had been placed for proximal intertarsal instability in both of these cases (Table 1). Clinical examination of the cat revealed lameness and pain by joint flexion, and the loose plate was movable under the skin. Stress radiographs showed no significant joint instability and the implants were removed. In the dog, the broken screw did not appear to have any clinical relevance. Wound dehiscence over the implants was a complication in one dog with an open injury, which was treated by external coaptation (Table 1). Although all owners were encouraged to have the implants removed, only one cat and one dog were available for routine implant removal, at six and ten weeks postoperatively (Table 1). In the three cases where the implants were removed, fibrous tissue was present under the plate, and the affected joints were considered stable on palpation.

Discussion

Ruptures of the short dorsal intertarsal and tarsometatarsal ligaments are due to tarsal hyperextension injury (3). In talocalcaneal luxation, the talocalcaneal ligaments are disrupted as well as the talocentral ligaments, leading to separation between talus and calcaneus (7). These injuries are due to blunt trauma (7) and might occur secondary to hyperextension, or axial compression, allowing the base of the talus to slide along the central tarsal bone in a dorsal direction. Dorsal intertarsal and tarsometatarsal instabilities are considered to be uncommon in the canine (2, 3, 4, 18). Few cases have been reported in cats (10, 16). Although the incidence of plantar versus dorsal instabilities was not evaluated in this study, the present case numbers suggest that in cats, dorsal instabilities occur more often than plantar instabilities.

Concomitant injury to the short medial or lateral ligaments at the same joint level was common in the present cases (nine out of 13), as previously reported (14). Three patients had concurrent tarsal or metatarsal slab fractures. Neither lateral or medial instability, nor concurrent fractures had a negative effect on clinical outcome, suggesting that fixation stability was also sufficient in presence of such injuries. Injuries to distant sites of the skeleton were frequent in the cats and probably due to motor vehicle trauma. Six out of the ten cats had sustained one or more concurrent fractures or joint injuries at a distant site, indicating the need for a thorough clinical and orthopedic examination in these patients.

The dorsal side of the tarsus is under compression during weight bearing (3, 4, 14, 18). Fibrous healing of the short ligaments and joint capsule should therefore result in adequate joint stability. The intertarsal joints and tarsometatarsal joints are true synovial joints and small amounts of physiologic

movement have been described in the talocalcaneal and the proximal intertarsal joint, indicating that these joints have a functional role in ambulation (5, 7). Despite this, partial tarsal arthrodesis is often recommended in veterinary textbooks for dorsal intertarsal and tarsometatarsal ligament injuries (3, 14, 18). Numerous techniques for partial tarsal arthrodesis have been described (1, 2, 3, 6, 11, 12). Disadvantages of partial arthrodesis, regardless of the technique used, are invasiveness, long surgery duration, morbidity associated with bone grafting and the need for prolonged external immobilization of the tarsus until evidence of healing is present.

The small size of the intertarsal and tarsometatarsal ligaments in small animals renders primary repair difficult or impossible. An alternative is providing internal splinting of the affected joint, until fibrous healing of the short ligaments has restored joint stability (4, 8, 10). A dorsal miniplate in bridging function has been applied in clinical cases with dorsal intertarsal instability for this purpose (10, 16) and temporary cross pinning can be used for dorsal tarsometatarsal instabilities (4). In a recent study three greyhounds with dorsal intertarsal instability were treated successfully with a tension band repair using two screws and a figure-eight wire (8).

Prolonged joint immobilization leads to malnutrition and degenerative changes of the articular cartilage, periarticular fibrosis and intraarticular adhesion formation (3, 13, 15). These changes might eventually lead to fusion of the rigid or low-motion joints of the tarsus. Signs of impending arthrodesis occurred in three of the cases in the present study, identified as narrowed or fused joint spaces on the radiographs (Table 1). Although this occurred as early as six weeks postoperatively in one cat, no definitive conclusion could be drawn in the animals which were radiographed less than two months postoperatively, considering the time it usually takes to achieve fusion in arthrodesis. Implant removal four to six weeks postoperatively possibly could preserve joint integrity (Fig. 5c). Unfortunately, most of the owners refused a second surgery, because they considered the animals to be sound. In the three cases where the implants were removed, fibrous tissue was present under the plate and joint stability was considered to be good.

The use of an internal fixator system (ComPact UniLock 2.0/2.4™ System) for internal splinting of intertarsal and tarsometatarsal instabilities has several advantages over conventional plating (9). The locking mechanism between the plate and the screw heads allows placing the plate with a small distance to the bone, thus preserving local blood supply and encouraging fibrous healing of the short ligaments and joint capsule underneath the plate. Also due to the locking mechanisms, screw loosening is less likely than with conventional plating, and resistance to displacement is greater when only few screws are used (17). This reduces the need for surgical dissection and allows placement of short plates and screws, avoiding adjacent intertarsal joints. Drill bits with stops allow drilling holes of predetermined depth, avoiding

damage to adjacent joint surfaces. The self-tapping screws precisely engage into the bone, therefore improving the holding power.

Screw breakage occurred in two patients, both with instability at the proximal intertarsal joint, stabilized with only two screws (Table 1). The proximal intertarsal joint allows some degree of physiologic motion (5, 7). Continuous motion might have caused repetitive stress, metal fatigue and finally breakage of the screws. In the dog, clinical outcome was not negatively affected and the implants appeared still stable, due to interlocking of the remaining screw and plate. In the cat the plate was movable under the skin and could have caused pain. Also, the cat had suffered a tibiotarsal medial collateral ligament sprain on the affected tarsus, which might have contributed to the remaining lameness.

Additional external stabilization is recommended after partial arthrodesis for several weeks. Prolonged joint immobilization has deleterious effects on synovial joints (15), which might impede function of the tibiotarsal joint. None of the six animals without additional external stabilization in the present study suffered implant or fixation failure (Table 1), and the authors feel that external splinting is unnecessary with the described method, thus allowing early and complete function of the tibiotarsal joint. Complications associated with cast application after partial tarsal arthrodesis are common and include pressure sores and suture dehiscence (1). In the present study, suture dehiscence occurred in one of the seven animals, in which a splinted bandage was applied postoperatively.

Conclusion

Dorsal, dorsomedial and dorsolateral intertarsal and tarsometatarsal instabilities occurred more often in cats than in dogs in the present study. Internal splinting of these injuries appears to be a good alternative to partial tarsal arthrodesis, and the ComPact UniLock 2.0/2.4™ System allows selective stabilization of the small intertarsal and tarsometatarsal joints. The technique is easy and less invasive than partial tarsal arthrodesis. Although follow-up times were too short to evaluate the incidence of joint fusion, early implant removal would possibly avoid inadvertent arthrodesis. Further clinical experiences are necessary to evaluate the technique in large dogs.

Acknowledgments:

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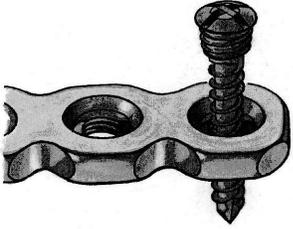
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	<p>Figure 1. ComPact UniLock 2.0/2.4™ System. The thread in the screw head engages the thread in the plate hole when the screw is tightened. This locks the screw in the plate, and the plate is not being pressed on the bone. The screws are self-tapping, shortening the duration of surgery and adding to the bone holding power.</p>
	<p>Figure 2. A ComPact UniLock 2.0™ plate was used to stabilize a dorsal distal intertarsal instability in a cat. The mediolateral postoperative radiograph is shown. Due to the locking mechanism between the screw heads and the plate, the contact between the plate and the bone can be reduced.</p>
	<p>Figure 3a+b. Hyperextension (3a) and varus (3b) stress radiographs of a cat with dorsolateral proximal intertarsal instability.</p>
	<p>Figure 4a+b. Mediolateral (4a) and dorsoplantar (4b) postoperative radiographs of the cat shown in Figure 3. Two ComPact UniLock 2.0™ plates were applied, one plate crossing the talocalcaneal joint and one plate placed between the talus and the fourth tarsal bone.</p>
	<p>Figure 5a+b+c. The dorsoplantar preoperative radiograph (5a) of a dorsal tarsometatarsal instability in a Border Terrier shows concurrent rupture of the short medial ligament and a slab fracture of the fourth tarsal bone. The postoperative dorsoplantar radiograph (5b) demonstrates positioning of a medial and lateral ComPact UniLock 2.0™ plate. The slab fracture was not directly stabilized, but bridged by the implants. Dorsoplantar radiographs of the same dog 11 months after the injury. The tarsometatarsal joint spaces are still open and clinical outcome was excellent. Implants had been removed 10 weeks postoperatively.</p>

The ComPact UniLock 2.0/2.4TM System^a and its Clinical Application in Small Animal Orthopedics

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Summary

This study describes the titanium ComPact UniLock 2.0/2.4TM locking plate system and reports its application in 9 selected clinical cases. The system was found useful for a variety of indications. Three categories of clinical applications are illustrated. They include: (a) long bone fractures, (b) cervical spinal fractures and instabilities and (c) joint instabilities and luxations. A brief introduction to the system has already been published (1).

Introduction

The introduction of locking bone plate/screw systems has generated certain advantages in fracture fixation over other plating methods. Conventional plates rely on firm compression of the plate to the bone and resulting friction forces. In contrast locking plate/screw systems function as internal fixators achieving stability by locking the screw to the plate. Locking of screws to the plate can be achieved by different methods (2,3). The locking mechanism of the UniLock system consists of threaded screw heads, which block in the corresponding threads of the plate (Fig. 1). Experimental studies have shown that internal fixators offer greater stability than standard reconstruction plates without locking screws, especially when only two screws are placed in each bone fragment (4-6). Another unique advantage of a locking plate/screw system is that the plate does not need to have intimate contact with the underlying bone. The adaptation of the plate is easier. As the screws are tightened, they interlock with the plate, thus stabilizing the segments without the need to compress the plate to the bone. This obviates the risk of altering the reduction of the fracture during the insertion of the screws. A diminished contact between plate and bone may also preserve periosteal blood supply. The extent of bone resorption under the plate is reduced and allows for placement of monocortical screws (2). Faster healing can be expected (7).

Materials and Methods

The ComPact UniLock system is available as a 2.0mm and a 2.4mm bone plate/screw system with a locking mechanism between the plate and the screw, designed originally for human maxillofacial surgery.

Titanium adaptation plates of 1.0 mm, 1.3 mm and 1.5 mm thickness are available for the ComPact 2.0TM UniLock system (Table 1, Fig. 2). Adaptation plates are either straight or angled or have an intermediate spacing section.

The thickness of the 1.3 and 1.5 mm plates is reduced in the intermediate spacing section area and reduces the contact to the underlying bone. The smallest plate consists of 4 screw holes with an intermediate spacing section, the largest of 21 straight and an angled section of 6 screw holes. All plates are cuttable to the desired length using special instrumentation. The design of the plates allows either for insertion of locking or non-locking corticalis 2.0 mm screws or a combination of both (Table 2). Non-locking 2.4 mm emergency screws and 2.0 mm self-drilling screws are also available. All screws are self-tapping and made of titanium alloy. Since the head of the screw has a cruciform recess, a special screwdriver with a corresponding cruciform tip (Stardrive[®]) is required.

Different straight or angled titanium reconstruction plates of 2.5 mm thickness are available for the ComPact 2.4TM UniLock system (Table 1, Fig. 2). The smallest plate consist of 14 and the largest of 24 straight and on each side an angled section of 6 screw holes. The oval cross section of the plate hole allows also for eccentric placement of non-locking screws with resulting compression of 0.6 mm per screw. Plates are cuttable using special instrumentation. Four different self-tapping titanium screws are provided (Table 2). Thread diameter of the locking screws is 2.4 mm and 3.0 mm. Non-locking corticalis screws of 2.4 mm and 2.7 mm emergency screws are also available.

Rigid fixation of fractures with the UniLock system is performed according to AO/ASIF techniques. Specific uses of exclusive UniLock instruments, depicted in Fig. 3, are described below. A simple plate cutter with deburring device is used to cut plates of the 2.0 mm system to the desired length. The plates are cut between the screw holes in contrast to the veterinary cuttable plates where the plate is cut in the screw hole (8). Plates of the 2.4 mm system are cut with the handheld SHORTCUTTM 2.4/Thorp instrument. Pointed flat-nosed pliers are used to contour the 2.0 mm system plates. As for a DC plate, the bending is performed between the screw holes. Special screws are inserted in the holes adjacent to areas where the plate is bent for contouring of a 2.4 mm reconstruction plate. These screws prevent deformations of the delicate threads in the plate and ensure a precise fit of the UniLock screws. Bending is performed with bending irons or a special plier. A soft template facilitating plate contouring to the underlying bone surface is also provided. Screw insertion technique varies according to the selected screw. Precise drilling perpendicular to the plate is important to insert and lock the screw to the plate. A special drill guide screwed into the plate hole centers the drill precisely and facilitates locking the screw to the plate. Non-locking corticalis screws are inserted using a standard drill guide to prevent the drill bit from bending and to protect the soft tissues

from injuries. They are used when perpendicular screw/plate placement is not warranted for anatomical reasons or if an interfragmentary lag screw is to be placed through the plate. Emergency screws can be used when the screw becomes loose during insertion.

The UniLock system is designed for maxillofacial human surgery. Indications include mandibular fractures and mandibular reconstruction after tumor removal (9). In veterinary surgery, the possible applications of the system are much wider given the different small bones and joints in cats and dogs. The authors have applied the system for different clinical situations to gain experience with the use of the system and delineate possible fields of indication. Three groups of clinical indications could be defined: a) long bone fractures b) cervical spinal fractures and instabilities and c) joint instabilities and luxations. Each group is documented with two to four selected cases.

Clinical Applications and Results

a) Long bone fractures

Case 1: A 4-month-old cat was presented with a spiral diaphyseal humeral fracture resulting from unknown trauma (Fig. 4A). The fracture was stabilized using a 2.0 mm position screw and a 2.0 UniLock plate (1.5mm) applied medially. Monocortical screws were placed in the area of the fracture and of the elbow joint to preserve blood supply and the articular surface. The cat was reevaluated 5 weeks postoperatively. A slight lameness was noted when walking and the cat slightly favored the contralateral leg when sitting. Normal range of motion and no pain was noted when manipulated. Radiographs revealed a healed humeral fracture in anatomical position (Fig. 4B). Implants were left in place and the owner reported return to full function 2 months after surgery.

Case 2: A 12-year-old Collie sustained multiple proximal metatarsal fractures with tarsometatarsal luxation after a horse stepped on his foot (Fig. 5A). The base of the 5th metatarsal bone was fixed with a tension band. A 2.0 UniLock plate (1.5mm) was used medially to stabilize the fracture and two screws were inserted in the central tarsal bone and in the second tarsal bone. No attempts were made to prepare the joint spaces for arthrodesis. A lateral splint was applied for four weeks. At the third postoperative day the dog started to use the leg. Small pressure ulceration 5 days postoperatively exposed 1.5 cm of the distal plate. A wet-dry bandage was applied and healthy granulation tissue covered the plate 14 days later. No lameness was apparent 5 weeks postoperatively and radiographs showed a completely healed fracture and evidence of partial intertarsal and tarsometatarsal arthrodesis in the vicinity of the screws (Fig. 5B). The owner refused to remove the plate because of the age of the dog and the good function of the limb.

Case 3: A 6-year-old Italian Whippet was presented with an acute lameness after playing. Radiographs revealed a metaphyseal oblique radius/ulna fracture (Fig. 6A). The radius was stabilized medially using a 2.0 UniLock plate (1.3mm). The third screw was accidentally placed in the fracture gap and the most distal screw was a long non-locking one because close joint proximity prohibited perpendicular insertion. The second and fourth proximal screws were monocortical screws. Additional external

support was provided using a splint for 4 weeks. The dog was lost to follow-up for 6 months but the owner reported return to full function after splint removal. Radiographs after 7 months showed a completely healed fracture in functional position and the dog was using the leg normally. The plate remained in a stable position despite the loosening of the third screw from proximal (Fig. 6B).

b) Cervical spinal fractures and instabilities

Case 4: A 4-year-old German Shepherd was presented after being hit by a car. Clinical examination revealed severe pain when manipulating the neck and tetraparesis. Computer tomography scan was performed, showing a minimally displaced oblique fracture through the cranial vertebral body of C2 (Fig. 7A). External coaptation was attempted during 5 days with a neck brace. The dog was able to ambulate but painful on slight manipulations of the neck. Surgical stabilization with two 2.0 UniLock plates (1.5mm) was performed. Two plates were applied transarticularly, ventrally to the body of C1 and C2, to reduce the fracture and to temporarily stabilize the atlantoaxial joint. The dog started to recover the third postoperative day and was sent home 5 days after surgery. Neurological examination revealed a slight proprioception deficit on all four legs after 6 months. Manipulation of the neck was pain free and rotational movement was slightly decreased. Radiographs showed a healed fracture of the vertebral body of C2 with minimal loss of reduction and a slight incongruent joint surface. Some additional arthrotic changes were noted with most of the screws either broken or dislocated (Fig. 7B).

Case 5: A 5-year-old Great Dane was referred for chronic neck pain and recent episode of nonambulatory tetraparesis. Myelography demonstrated massive extradural compression of the ventral spinal cord of the intervertebral space C6/C7. A ventral slot was performed and a large amount of disc material removed. Some instability was present thereafter; the intervertebral space C6/C7 was distracted and a cancellous bone graft placed in the slot. The distracted vertebrae were stabilized using two 2.4 UniLock reconstruction plates applied ventrally (Fig. 8A). The nonambulatory tetraparesis resolved the following days after the surgery. After two weeks the dog was sent home with ataxia. Clinical control 5 months after surgery revealed no neck pain but a mild ataxia and proprioception deficit on all four legs persisted. Radiographs showed stable implants (Fig. 8B).

c) Joint instabilities and luxations

Case 6: Luxation of the base of the talus was diagnosed in a 1-year-old cat after unknown trauma (Fig. 9A). The luxation was reduced and stabilized using a 2.0 UniLock plate (1.0mm) applied dorsally between the base of the talus and the central tarsal bone. The cat was sent home the next day and the owner instructed to keep it indoors for 1 month. No additional external support was applied other than a modified Robert-Jones bandage for 3 days. Clinical examination 1 month after surgery found a mild decreased flexion of the talocrural joint and a subtle lameness. Radiographs showed early fusion of the bridged intertarsal joint and stable implants (Fig. 9B). Two months after

surgery the plate has been removed and the cat returned to full function.

Case 7: A 3-year-old Siberian Husky suffered an acute lameness after playing with another dog. The referring veterinarian diagnosed a dorsolateral luxation of the 4th metatarsophalangeal joint two weeks after the onset of the lameness (Fig. 10A). The luxation was reduced and a 2.0 UniLock plate (1.5mm) used for temporary immobilization of the joint (Fig. 10B). A splint was applied for one week for additional support. The dog showed mild but consistent lameness until implant removal after 6 weeks. Thereafter return to full function was achieved with slight degrees of lameness after extended working periods.

Case 8: A cat of unknown age was presented with a comminuted talus fracture after a fall from the 6th floor. A tarsal panarthrodesis was performed using a 2.4 UniLock reconstruction plate applied dorsally and two cross pins. An additional pin served to fix the distal part of the fibula to the tibia and a cancellous bone graft was applied. (Fig. 11A). Two months after surgery radiographs revealed stable implants and almost complete fusion of the joints (Fig. 11B). A slight functional lameness was present consistent with tarsal panarthrodesis.

Case 9: A 2-year-old Papillon was presented after the fourth episode of a caudoventral hip luxation. The hip had been reduced and attempts at stabilization during three former surgeries included screws, relocation of the greater trochanter and pectineus relocation. Reluxation recurred soon after and the dog was referred to our institution (Fig. 12A). The luxation was reduced and a 2.0 UniLock plate (1.3mm) placed on the ventral acetabular rim to augment the transverse acetabular ligament and prevent reluxation (Fig. 12B). The dog won a show competition 7 months after the surgery, using the leg normally.

Discussion

a) Long bone fractures

The concept of internal fixation of long bone fractures has evolved in recent decades and is still developing. Precise reconstruction and absolute stability with the aim of direct bone healing were considered to be essential for success. Precise reduction usually requires an extensive surgical approach enhancing damage to the trauma induced compromised blood supply. Risk for delayed healing, infection and possibly refracture is increased. Stability was then achieved by the application of compression exerted by interfragmentary screws and compression plates. The emphasis then changed from mechanical to biological priorities (10). Biological internal fixation takes advantage of indirect bone healing and aims to functionally align the fragments. Exposure of the bone is avoided to reduce surgical trauma and to minimize iatrogenic additional vascular damage. Locking plate/screw systems as the UniLock System act as internal fixators. The contact between implant and bone is kept stable using screws which function like locked threaded bolts and prevent the plate pressing on the bone when the screws are tightened. The 1.3 and 1.5mm UniLock plates are undercut reducing the contact to the underlying bone. This results in less osteoporosity underneath the plate (11).

The fractures in cases 1 and 2 completely healed within 5 weeks. In case 1 a productive callus formation was consistent with the normal healing pattern of a 4-month-old cat. Radiographs of case 3 were only available after 7 months. The fracture had already remodeled with minimal callus formation. Screws had been accidentally placed in the fracture gap in cases 2 and 3. Since the screw locks to the plate regardless of bony purchase, they remained undetected during the surgery. However, no interference with fracture healing appeared although the screw in case 3 subsequently loosened. The short distal fragment in case 3 allowed for placement of only two screws and only one of the screws could be interlocked to the plate. The system allowed for placement of a long screw in the most distal metaphyseal cancellous area. DC plates ideally require engagement of 6 cortices per fragment. This was not possible in case 3. The fact that the fixation remained stable supports the theory that interlocked screws offer superior stability and that fewer screws must be inserted in shorter fragments (4-6).

b) Cervical spinal fractures and instabilities

Numerous techniques have been described for stabilizing cervical vertebral fractures and instabilities (12,13). Ventral internal fixation with pins or screws and bone cement is the stabilization method most widely used. A study reported that a plate applied to the vertebral body is about two times stronger regarding bending forces than vertebral body pins and bone cement but is more vulnerable to rotational forces (14). However, ventral vertebral body plating of the cervical spine is rarely used because adaptation to the underlying bone surface is difficult and the risk of damage to the spinal cord by use of bicortical screws.

Application of UniLock plates to the ventral cervical vertebra in cases 4 and 5 has unique advantages compared to conventional plates. The locking mechanism requires less precise contouring of the plate to the underlying cervical vertebra and the size of the system permits fixation with two small plates. The stabilizing effect of the second cortex is replaced by the locking mechanism, making use of monocortical screws possible (10,15). The predetermined depth of drilling with gauged drill bits controls the risk of iatrogenic damage to the spinal cord. Due to the presence of a thin cortex, long screws are necessary in order to achieve sufficient purchase in the cancellous bone and resulting increased stability (16). Two parallel plates were used in cases 4 and 5 to enhance rotational stability. Temporary stabilization of the atlantoaxial joint was attempted in case 4, allowing the fracture of C2 to heal. The great range of motion of the atlantoaxial joint and the resulting forces of a large size breed of dog make great demands on the implants. Resulted increasing activity of the dog subsequently led to implant failure. The time when the implant failed was unnoticed and apparently did not cause clinical signs. The implant provided adequate stability allowing the fracture to heal. Screws of 2.0 mm diameter are obviously too weak for permanent stabilization of the mobile atlantoaxial joint even for a locking screw/plate system. The 2.4 mm system used in case 5 proved to be adequate for fixation of instability of C6/C7. No implant

related complications were noted so far. Further cases are necessary to evaluate ventral vertebral plating in large dogs with the 2.4-mm system, which appears to have potential in the treatment of caudal cervical instabilities of wobbler dogs.

c) Joint instabilities and luxations

This category of indications includes luxations and subluxations of the various small distal limb joints and a caudoventral coxofemoral luxation. UniLock plates may provide temporary or permanent internal splinting of joints for the adaptation of carpal and tarsal subluxations and luxations of the digits. This allows healing of injured short ligaments for restoration of joint stability. The UniLock screws create only a small protrusion when locked to the plate. This allows their placement near tendineous structures (Cases 6-8).

Luxation of the base of the talus is a disabling injury. Classical treatments consist of placement of a position screw between the talus and calcaneus, followed by 4 weeks of external support with a splint (17), or placement of the same position screw in combination with a dorsomedial applied adaptation Mini-Plate (18). Case 6 demonstrates successful fixation of the talus and central tarsal bone with a short locking plate. Application of the plate on the dorsal surface puts the implant on the tension side of the injury. Mechanical stability following reduction therefore should be superior to single screw fixation and obviate the need for additional external support. Return to full function is facilitated.

Luxations of the metatarsophalangeal or interphalangeal joints are usually treated by suture repair of collateral ligaments and joint capsule imbrication (19). Existing fibroplasias complicate accurate suturing in cases of chronic luxations. Stable fixation of the joint is imperative if return to full function is to be achieved. Dorsolateral luxation of the 4th metatarsophalangeal joint was successfully stabilized using a 1.5-mm UniLock plate in case 7. The locking mechanism provided adequate stability for insertion of only one screw in each digit. Although permanent lameness was noted while the implants were in place, the dog returned to full function after removing the implants. Effects of prolonged joint immobilization are malnutrition and degenerative changes of the articular cartilage, periarticular fibrosis and intraarticular adhesion formation (20,21). Implant removal in cases 6 and 7 was performed after 8 and 6 weeks respectively to try to preserve full joint function.

Comminuted intraarticular fractures of the tarsal bones which can not be primarily repaired are best treated with partial arthrodesis or tarsal panarthrodesis. Surgical fusion of the talocrural joint is a challenge because of the magnitude and orientation of the forces of weight bearing and failure rates as high as 50 percent have been reported (22,23). A laterally applied plate necessitates resection of the distal fibula but is mechanically superior to a dorsally applied plate. Case 8 shows the possibility of tarsal panarthrodesis using a locking screw/plate system. The locking mechanism of an internal fixator should improve

stability (4-6) and possibly reduce implant failure in dorsally applied plates for tarsal panarthrodesis.

Caudoventral hip luxations can not be handled by closed reduction because of the risk of recurrent luxation in presence of an incompetent ventral transverse acetabular ligament (24). Two techniques have been reported for stabilizing these luxations. An autogenous corticocancellous bone graft can be implanted on the ventral acetabular region or the pectineus muscle can be used to stabilize the femoral head (24,25). The latter treatment already failed in case 9 and a 2.0 UniLock plate (1.3mm) was successfully used to stabilize the joint. The plate was found very useful to augment the transverse acetabular ligament in this case because of easiness to contour the plate and the locking mechanism facilitating plate adaptation to the underlying joint capsule and cartilage surface of the femoral head.

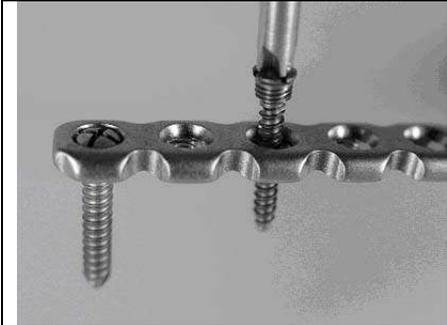
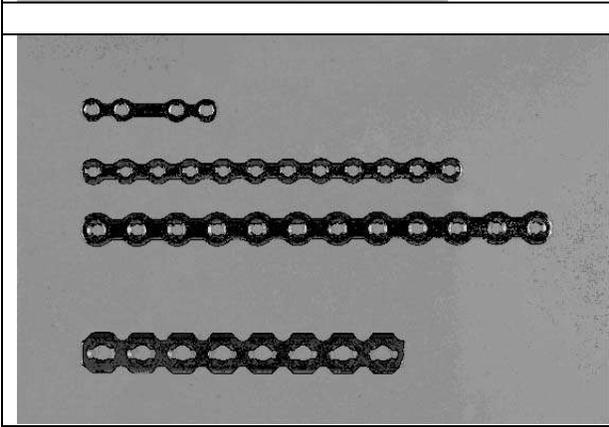
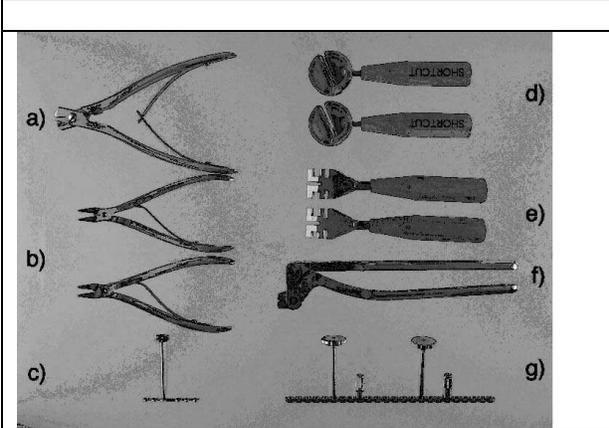
Conclusions

The UniLock system has proved useful in different applications in small animal surgery. The system allows stable internal fixation of long bone fractures in small dogs and cats or the fixation of small bones in larger dogs. Selected cervical spinal fractures and instabilities can be successfully stabilized using two plates and monocortical screws. UniLock plates may provide temporary or permanent internal splinting of joints allowing healing of injured ligaments and restoration of joint stability.

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Legends

	<p>Fig. 1 The threads in the screw hole of the plate and in the screw head comprise the locking mechanism in the UniLock system developed for human maxillofacial surgery.</p>
	<p>Fig. 2 UniLock system plates. From top: 1.0mm, 1.3mm and 1.5mm adaptation plates of the 2.0 mm system, 2.4mm reconstruction plate of the 2.4mm system.</p>
	<p>Fig. 3 Instruments for the UniLock 2.0 (a-c) and UniLock 2.4 (d-h) systems: a) plate cutter with deburring device, b) bending pliers, c) drill guide, d) SHORTCUT™ 2.4/Thorp, e) bending irons, f) bending plier with nose, g) long and short drill guides (2.4mm and 3.0mm).</p>

	<p>Fig. 4A Pre- and postoperative radiographs of a spiral diaphyseal humeral fracture in a 4-month-old cat, treated with an interfragmentary position screw and a medial 2.0 UniLock plate.</p>
	<p>Fig. 4B Postoperative radiographs after five weeks showing clinically good fracture healing. Note the reduced contact surface between the plate and the bone on the craniocaudal view preserving periosteal blood supply. Two monocortical screws were placed near the fracture and the joint areas.</p>
	<p>Fig. 5A Pre- and postoperative radiographs of a 12-year-old Collie. Proximal fractures of metatarsal bones two, three and five are noted. The 4th screw from proximal was accidentally placed in the fracture gap.</p>



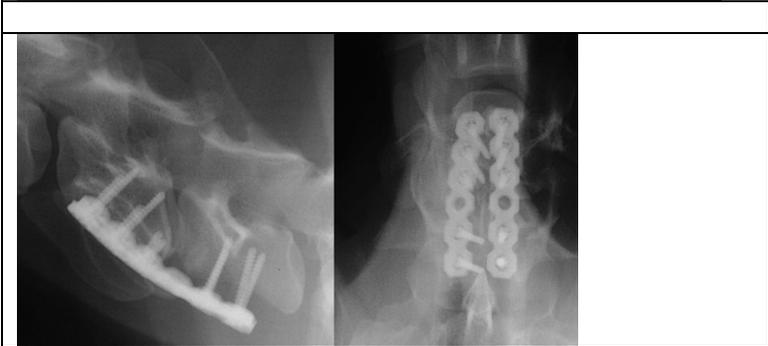
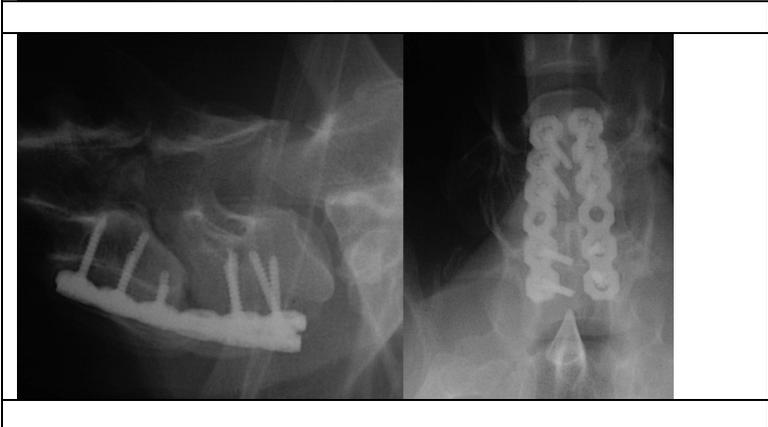
Fig. 5B Radiographs after 5 weeks showing clinically good fracture healing of metatarsal bones 2 and 3. Partial arthrodesis of the intertarsal and tarsometatarsal joints is evident in the vicinity of the screws. The locking mechanism of the plate prohibited pivoting of the 4th screw and subsequent interference with fracture healing.



Fig. 6A Pre- and postoperative radiographs of a 6-year-old Italian Whippet showing a metaphyseal oblique radius and ulna fracture. The plate on the radius was placed medially and two monocortical screws were used. The third screw was unfortunately placed in the fracture gap, preventing anatomical reduction.



Fig. 6B Radiographs after 7 months show clinically fracture healing. Loosening of the third screw from proximal is evident.

	<p>Fig. 7A CT reconstruction scan of the C2 vertebra of a 4-year-old German Shepherd and postoperative lateral view. A minimally displaced oblique fracture through the cranial vertebral body of C2 is visible (arrow). Local pain and neurologic deficit were present. Temporary atlantoaxial joint stabilization has been achieved with two ventrally applied plates using monocortical screws.</p>
	<p>Fig. 7B Radiographs after 6 months show a healed fracture in slight malunion and some arthrotic changes. Loosening or breakage of most of the screws is present. The dog recovered its neurologic function.</p>
	<p>Fig. 8A Lateral and ventrodorsal postoperative views of a 5-year-old Great Dane with C6-C7 disc protrusion and associated tetraparesis. Monocortical fixation with 2.4 UniLock plates was performed to stabilize the vertebrae after a ventral slot had been performed.</p>
	<p>Fig. 8B Radiographic appearance 5 months after surgery showing stable implants. The dog recovered most of its neurological functions.</p>

	<p>Fig. 9A Pre- and postoperative radiographs showing luxation of the base of the talus in a 1-year-old cat. A short plate was used for temporary stabilization of the joint.</p>
	<p>Fig. 9B Postoperative radiographs after 4 weeks showing stable implants. The implants were removed after 8 weeks and the cat regained a full function.</p>
	<p>Fig. 10A Preoperative radiograph of 3-year-old Siberian Husky showing a dorsolateral luxation of the 4th metatarsophalangeal joint.</p>
	<p>Fig. 10B Postoperative radiograph: The luxation was reduced and a plate used for temporary immobilization of the joint. The implants were removed after 6 weeks, and the dog returned to normal function.</p>

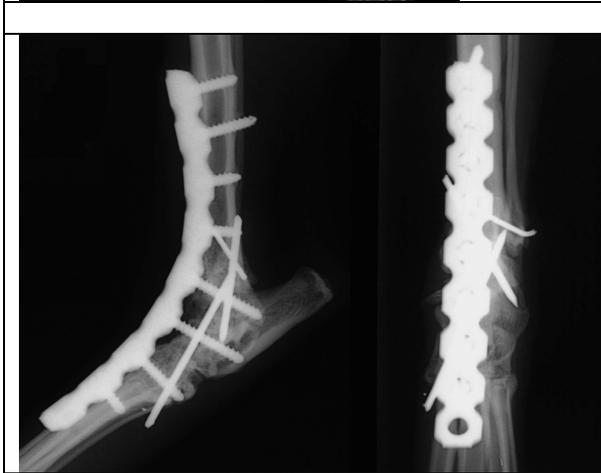
		<p>Fig. 11A Preoperative radiographs of a cat of unknown age with a comminuted talus fracture.</p>
		<p>Fig. 11B Postoperative radiograph after 2 months: Panarthrodesis was performed using a UniLock 2.4 plate applied dorsally and placement of three crossed pins for additional support. Progressive and almost complete fusion of the joints is noted.</p>
		<p>Fig. 12A Preoperative radiograph of a 2-year-old Papillon showing caudoventral coxofemoral luxation. The luxation has been formerly reduced and ventral stabilization attempted in three surgeries using screws, relocation of the greater trochanter and relocation of the pectineus muscle.</p>
		<p>Fig. 12B Postoperative radiographs. A 5-hole Unilock plate was placed on the ventral acetabular rim to augment ventral support and prevent relaxation.</p>

Table 1 UniLock system plates.

	Plate Type	Form	Plate Thickness (mm)	Plate Length (mm)	Number of Holes Available	Remarks	
2.0 System	Adaptation		1.0	99	20		
		straight	1.3	77	12		
			1.5	47, 95, 159	6, 12, 20		
		L-Plate	1.0		7	left + right	
		angled	1.5	189/81	21+6	left + right	
	Adaptation with spacing section			1.0	25, 40	4, 6	
		straight		1.3	43	6	
				1.5	53	6	
		angled		1.5		3+3, 4+4	
		crescent shaped		1.5		3+3	
2.4 System	Reconstruction	straight	2.5	112, 160, 192	14, 20, 24		
		angled	2.5	110/40 170/50	13+5 21+6	left +right	
		double-angled	2.5	33/162/33 41/178/41 49/194/49	4+20+4 5+22+5 6+24+6		

Table 2: UniLock system screws.

	Screw Type	Thread Diam. (mm)	Core Diam. (mm)	Head Diam. (mm)	Thread Pitch (mm)	Screw Length (mm)	Drill Bit threaded hole (mm)	Drill Bit glide hole (mm)	Head locking	Self-drilling
2.0 System	UniLock	2.0		2.95	0.75	5-18	1.5	2.0	Y	
	UniLock	2.0		2.95	0.75	5-8			Y	Y
	Corticalis	2.0		3.30	0.75	4-18	1.5	2.0		
	Emergency	2.4		3.31	1.0	6-12				
2.4 System	UniLock	2.4	1.7	4.0		8-22	1.8	2.4	Y	
	UniLock	3.0	2.4	4.0		8-22	2.4	3	Y	
	Corticalis	2.4	1.7	4.0		8-40	1.8	2.4		
	Emergency	2.7	1.9	4.0		8-18				

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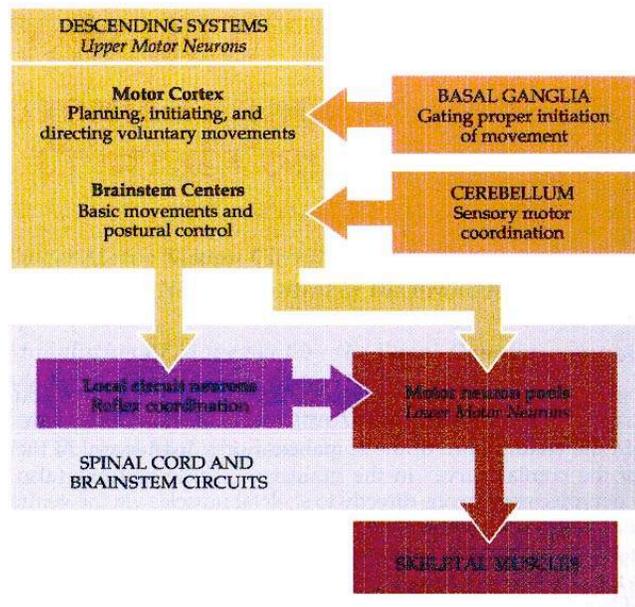
Introduction to neurophysiology

Thomas Riediger, Dr. med. vet.

Neurologic disorders are often accompanied by behavioral, autonomic, sensory or motor deficits. In many cases the type and the site of the lesion can be precisely localized by the neurologic examination. The knowledge about the fundamental neurocircuitries controlling the different physiological systems is a prerequisite for the interpretation of the neurologic observations. Focusing on motor function and sensation, the basic characteristics and the diagnostic relevance of these two very important complexes are summarized.

The concept of upper and lower motor neurons

The terms upper and lower motor neuron (UMN and LMN) are particularly important for the clinical classification of different motor deficits and the localization of the lesion. Lower motor neurons are located in the gray matter of the spinal cord and in brainstem motor nuclei and directly innervate the skeletal muscles. Ultimately, all contractions of the muscles whether voluntary or reflexive are produced by lower motor neurons representing the final common path for any motor function. The activity of LMN is controlled by local circuits (reflexes) on one hand and on the other hand by descending pathways from UMN, which are not directly connected with the muscles. Instead they synapse with local circuit neurons (interneurons) or in fewer instances directly with the LMN. Components of the UMN comprise nerve cell bodies in the cerebral cortex, basal ganglia and brain stem as well as their descending pathways in the brainstem and the spinal cord white matter. UMN are responsible for initiating voluntary movements and regulate the muscle tone used to support the body.



Functional organization of the motor system

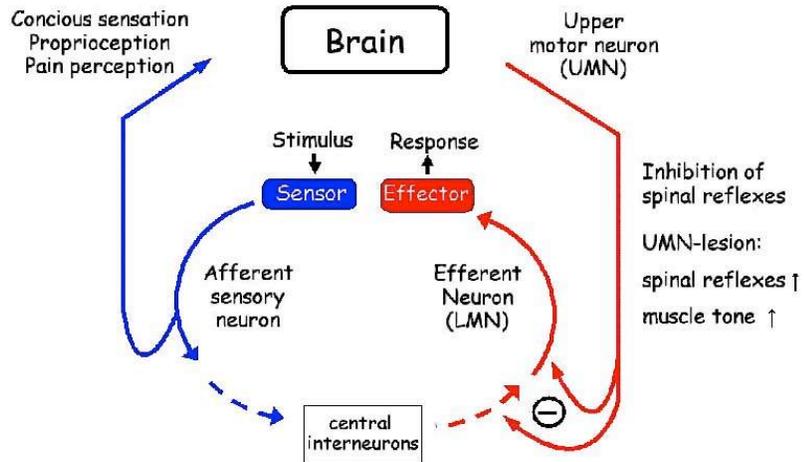
Spinal reflexes

Local circuitries in the spinal cord mediate a number of sensory motor reflex actions. A reflex is defined by a reflex arc consisting of an afferent sensory part, which directly or indirectly synapses with the LMN via local interneurons. The simplest of these reflexes is the stretch reflex, which provides a direct positive feedback to the muscle, which has been stretched. A lesion in any part of the reflex arc entails a loss or a decrease of the reflex. Since reflexes are confined to specific spinal cord segments their diagnostic value for the localization of an injury is high. Besides the hypo- or

areflexia, a damage to the LMN results in other so-called LMN signs. These include a decreased muscle tone, muscle atrophy, paralysis (weakness) or paresis (loss of motor function) in the muscles innervated by the damaged LMN pool.

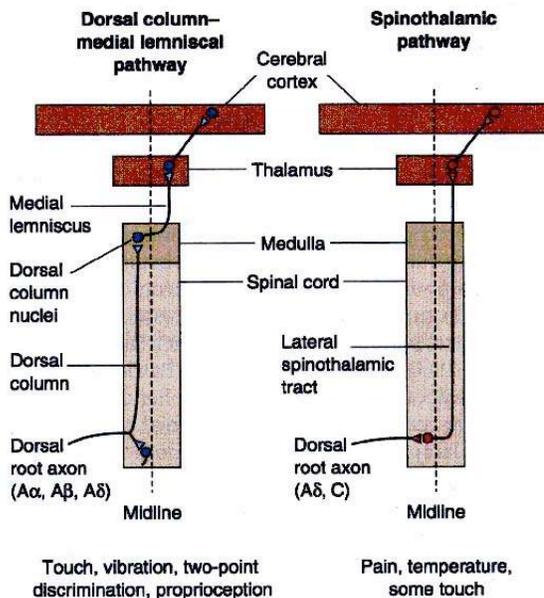
Supraspinal modulation of reflexes

Spinal reflexes are under the control of UMN. The overall effect of the UMN is an inhibitory effect on the spinal reflex and on the muscle tone. Therefore, a lesion of the UMN or their descending pathways disconnects the spinal reflex arc from its damping supraspinal influences and results in exaggerated reflexes as well as increased extensor muscle tone in all limbs caudal to the lesion.



Sensation

Cell bodies of sensory neurons reside in the dorsal root ganglia. A variety of different sensory signals are transmitted to the central nervous system via afferent nerves, including touch, temperature, pain and also signals from the joints, skin, muscles and tendons contributing to proprioception. Similar to the assessment of reflexes the assessment of sensation is very useful for the discrimination localization of different neurologic disorders. Sensory pathways responsible for proprioception, touch and vibration ascend ipsilaterally in the dorsal column and cross over in the brain stem before they



project to the thalamus and the cerebral cortex. Damage to these pathways disrupts the transmission of proprioceptive signals to the UMN and may lead to signs of ataxia, incoordination and loss of conscious proprioception caudal to the site of the lesion. Pathways transmitting noxious stimuli (deep pain) to the brain cross bilaterally in the spinal cord and ascend in the lateral spinothalamic tracts. Since these pathways are quite resistant to compressive injury, a loss of deep pain sensation is interpreted as a reliable indicator of severe spinal cord injury.

Localisation of neurologic disorders

Frank Steffen, Dr.med.vet., DECVN

The nervous system can roughly be divided in the central and peripheral nervous system. In a first approach it may be helpful to attribute the neurological deficits to one of these divisions before a more accurate diagnosis is done.

A generalized peripheral lesion can be distinguished from a central lesion by judgement of the quality of the spinal reflexes. Generalized hyporeflexia in a mentally normal animal is an indicator for a generalized LMN problem. Other symptoms indicate a centrally located lesion.

If the problem is located in the CNS, it has to be further specified to a spinal cord or a brain lesion. This question can be answered by looking at the cranial nerve function and the mental status. Cranial nerve deficits and/or behaviour or mental abnormalities indicate presence of an encephalopathy. Absence of these signs indicates a spinal cord lesion.

Detailed localisation

After the patient's problem has been attributed to one of the major divisions of the nervous system (peripheral nervous system, spinal cord or brain) a more detailed localisation is performed. Some rudimentary knowledge about anatomy and physiology of the divisions of the CNS is indispensable at this step. In the following section, clinically relevant features and main symptoms of the ten clinically relevant localisations are briefly summarized.

1. Peripheral nervous system

From a clinical point of view the PNS can be regarded as identical to the lower motor neuron system including the alpha-motor neuron in the ventral gray column of the spinal cord, the ventral and dorsal nerve roots, the peripheral nerve, the neuromuscular junction and the muscle. A complete lesion to one of the components results in flaccid paralysis of the affected limb, areflexia, atonia and anesthesia. Incomplete lesions occur as different degrees of paresis and weakness, decreased postural reactions, hyporeflexia and a decreased muscle volume and strength. Occasionally, an animal can have LMN weakness with normal reflexes (i.e. myopathy, myasthenia gravis). Monoparesis and Monoplegia is most often the result of a traumatic, neoplastic or a vascular lesion. A generalized lower motor neuron lesion is generally caused by metabolic-toxic, endocrine, inflammatory, degenerative or an inherited disease. In cats, ventroflexion of the neck is seen as a typical clinical feature in many disorders (i.e. hypokalemia, myasthenia gravis, polymyositis)

2. Spinal cord: C1-C5

A lesion to this area results in upper motor signs to the front and rear legs including different degrees of ataxia and spastic tetraparesis, proprioceptive deficits in all four limbs and normal to increased reflexes. The neck is often painful and carried low in compressive or inflammatory lesions. In severe lesions, hypoventilation may occur.

3. Spinal cord: C6-T2

A lesion to this cord segments produces LMN-signs in the front limbs and UMN-signs in the rear. The degree of gait abnormalities is broad and ranges from ataxia to tetraplegia with flaccid paralysis of the front limbs. Hyporeflexia in one or both front limbs is the most helpful clinical key to the localisation. The panniculus Reflex may be depressed uni- or bilaterally.

4. Spinal cord: T3-L3

A thoracolumbar lesion results in different degrees of ataxia and paraparesis/plegia of the rear limbs. The dysfunction is of the UMN-type. Urinary retention (spastic bladder) because of hypertonicity of the urinary sphincter is a common complication of this syndrome. The so called Schiff-Sherrington phenomenon (rigid extension of the front limbs and paraplegia of the hind limbs after sudden compression of the thoracolumbar spinal cord) is unique to the dog and not observed in other domestic animals. At the level of the lesion increased sensitivity is found, behind the level sensitivity is decreased.

5. Spinal cord: L4-S3(Cx)

A lesion to this area entails various degrees of involvement of the pelvic limbs, bladder, anal sphincter and tail. Clinical signs range from flaccid weakness to paralysis of pelvic limbs, perianal myotomes and tail. As the syndrome includes spinal cord segments and cauda equina nerves, slightly different lesion levels produce different clinical presentations. In compressive lesions, pain is usually elicited with manipulation of the lower back and tail. The anal sphincter may be flaccid and dilated with fecal incontinence. In complete lesions, the bladder is atonic with urine retention and overflow incontinence. Sensory function of the different dermatomes may be reduced or absent depending on the severity of the lesion.

Vestibular system

The peripheral component of the vestibular system consists of the inner ear receptor and the vestibular nerve. The central vestibular system include the vestibular nuclei in the brain stem and the flocculonodular lobe of the cerebellum. Differentiation between the two components is possible with the aid of the clinical symptoms in most cases.

6. Peripheral vestibular syndrome

A lesion to this part of the system causes a head tilt ipsilateral to the lesion, Nystagmus with a horizontal or rotatory direction (the quick phase of the nystagmus is away from the lesion), vestibular ataxia (falling/rolling towards the side of the lesion, hypotonia of the limb muscles ipsilateral to the lesion and hypertonicity away from the lesion and/or a tendency to drift towards the side of the lesion). Proprioceptive Deficits are typically not present in peripheral lesions. Cranial nerve deficits (Horner's Syndrom, Facial paralysis) frequently accompaign peripheral vestibular syndrome due to their proximity in the middle and inner ear.

Bilateral peripheral vestibular lesions cause no tilt but a characteristic swaying movement of the head and a decreased tone of extensor muscles resulting in a creeping gait. Vestibular eye movements are absent.

7. Central vestibular syndrome

A central vestibular disorder results in similar deficits as a peripheral lesion. However, the neurological presentation differs in some key-points. Signs of paresis and/or proprioceptive deficits in association with a head tilt indicate a central lesion. The direction of the nystagmus is similar to that seen in peripheral lesions, but a positional nystagmus or that is vertical in direction suggests presence of a central lesion. Multiple cranial nerve dysfunction (except sympathetic and facial nerve impairment) are also strong indicators of a centrally located lesion. Sympathetic dysfunction due a central lesion is rarely observed and, if present, other signs for central disease are obvious. Paradoxical vestibular disease is defined as a vestibular deficit (head tilt, nystagmus) opposite to the side of the lesion. It is usually caused by a lesion near the cerebellar peduncles and, thus, always centrally located.

8. Brainstem Syndrome

The syndrome is characterized by decreased mentation, obvious gait abnormalities (Tetraparesis, Tetraplegia, Hemiparesis) and multiple cranial nerve deficits (pons, medulla oblongata) including CN V, VI, VII, VIII, IX, X, XII. Respiratory function may be disturbed resulting in altered patterns of breathing.

If the lesion is located in the cranial brainstem (midbrain) abnormal postures such as opisthotonus (rigid extension of all limbs) may be observed. In unilateral lesions, the patient has a spastic hemiparesis on the opposite side.

In severe lesions, the animal may be stuporous or comatous. Oculomotor Nerve (CN III) deficits with normal vision may be present.

9. Cerebellar Syndrome

Cerebellar lesion result in a spastic, hypermetric gait in all four limbs and the body may sway to one side and the other (cerebellar ataxia). Hypermetria is usually more pronounced in the thoracic limbs. The stance is broad based and there is tremor of the head and body, especially notably when movement is initiated or during eating and drinking. Subtle, oscillatory or pendular eye movements may be observed. The menace response is decreased ipsilateral to the lesion without affecting vision. Proprioceptive tests may show an exaggerated response with normal initiation.

10. Cerebral Syndrome

A cerebral symmetric cerebral lesion causes various clinical signs in cats ranging from of apathy and depression to hyperexcitability, disorientation, aggression and seizures. There is only a minimal degree of ataxia in cortical lesions (i.e. pacing). But compulsive walking, restlessness and head pressing may occur. In unilateral lesions, the cat circles (usually to the side of the lesion) or exhibits pleurothotonus. Postural reactions are reduced in the contralateral limbs. Vision is impaired (contralateral to the lesion) but pupillary function is intact.

Prevention and revision of perioperative and postoperative complications with Zurich cementless canine hip prosthesis

Pierre M. Montavon, Prof. Dr. med. vet

Slobodan Tepic, Dr. Ing

Intraoperative and postoperative complications encountered with the application of *Zurich cementless* canine hip prosthesis have been identified in the course of two current clinical studies. One is a multicentric study involving 650 cases operated by 20 veterinary surgeons. The second study comprises 100 consecutive cases operated by one surgeon at the same clinic. Perioperative complications involved 4% of the cases and required immediate surgical revision. Postoperative complications one year after implantation involved 6,5% of the patients. Complications are avoidable and if occurring, successfully revisable. Explantation of implants performed in 1% of the operated cases were due to presence of infection.

The complications encountered and their incidences were: luxation of the prosthesis (3%), femoral fractures (1%), cup dislodgement or loosening (1%), acetabular fracture (0,5%), primary and after revision infection (1%). Late loosening of implants has been observed in isolated cases

Prevention and surgical revision of those complications are presented here.

Ventrocaudal luxation of the prosthesis occurred perioperatively, while taking mediolateral radiographs of the femur with a special positioning to evaluate the implantation of the prosthesis. Preventing the luxation was to eliminate wrong manipulation during the radiographical positioning of the patient. Operative revision consisted in either using a longer head and neck piece, in order to reduce the range of motion while tightening the periarticular structures, or removing part of the equatorial bevel of the polyethylene liner in the area of contact with the neck of the prosthesis, or changing the lateral opening and/or the retroversion angle of the cup while repositioning it. Similar operative measures were effectuated in cases where a spontaneous luxation had occurred, usually during the initial postoperative weeks.

Postoperative femoral fractures happened days postoperatively, mainly in older dogs with thin femoral cortices and muscular hypotrophy of the thigh. German Shepherds were overrepresented in this category. A simultaneous minimal trauma was eventually reported. An oblique fracture line would typically run from one distal hole toward distal. Preventive measures included the avoidance of excessive reaming or the endosteal cavity in any patient. A shorter stem was used in risk patients, to reduce the bending moments and to anchor the stem in the softer metaphyseal bone area. Attempts were made to tighten a cerclage wire just below the most distal screw of the prosthesis in those patients. A cerclage wire also was placed around the proximal femur in patients where a crack was heard or a fissure could be seen during the preparation of the endosteal area or the insertion of the stem, in order to avoid the development of complete fractures.

Cerclage wires were kept away from the screws used for fixation of the stem. In cases of displaced fracture of the femur, a long plate was used on the lateral aspect, anchored in the trochanteric and in the distal area of the femur.

Cup dislodgement can occur when dorsal or ventral bony coverage of the cup are insufficient. Lack of dorsal bone coverage is present in cases of severe coxarthrosis with coxa magna and plana and flattened acetabulum. Implantation of a larger size cup worsens the situation and should be avoided. In these cases a rotation toward ventral produces the dislodgement of the cup. Measures of prevention are effective. They consist in placing two 4.0 mm titanium cancellous bone screws, tangentially to the ventral equator of the cup, at 4 and 8 o'clock. The screws are used in a self-tapping manner and after tightening, their heads come in contact with the shell of the cup. Reconstruction of the dorsal acetabulum with a piece of the femoral head represents another alternative, but is more time consuming. It has been described in the literature.

Careless reaming of the ventral area during preparation of the acetabular cavity or in cases previously operated with a triple pelvic osteotomy and excessive correction, lack of ventral bone coverage may produce dislodgement of the cup with rotation toward dorsal. Similar measures of prevention are taken, but now placing the tangential screws at 2 and 10 o'clock.

A good press-fit of the cup achieved during its implantation is the best measure to prevent cup dislodgement or later cup loosening with lack of osseointegration. This can be achieved by adequate reaming during the preparation of the acetabulum and giving the retroversion angle to the cup, imposed by the anatomy in presence. The design of the cup requires cranial and caudal bony contact with its equator. This dictates the retroversion positioning of the cup, which can be evaluated intraoperatively and will require slightly superior (by 10 degree) anteversion of the stem during its implantation, in order to prevent postoperative luxation of the prosthesis. The range of motion of the prosthesis is then superior to the physiological one of a normal hip joint.

Acetabular fracture is associated with too dorsal positioning of the cup or with its oversizing. Both situations feature a loss of bone stock toward dorsal or medial, resulting in the weakening and eventual fracture in the acetabular area. Prevention of this event resides in placing the cup in the vicinity of the ventral acetabular transverse ligament and preserving the medial acetabular bony support. Lack of medial acetabular bony support can lead also to progressive migration of the cup toward medial, requiring a later replacement with a larger size cup. Fresh fracture or fracture occurring during the surgery may be successfully repaired with a bone plate placed on the dorsal acetabulum and acting as a tension plate, reestablishing the press-fit of the cup.

Infection of the prosthesis is a disastrous event leading to the temporary or definitive removal of the prosthesis. Evaluation of the patient and aseptic surgical techniques are uppermost important measures for preventing infection. The rate of infection (1%) is low for primary intervention but high (25%) in revision procedures. Treatment consists in implant removal, long-term administration of adequate antibiotics, and eventual placement of drains for local antiseptic perioperative treatment. Reimplantation of implants several months later can be considered if the condition of the bony structures allows their fixation.

Late loosening of implants has been observed. Its low incidence rate still has to be determined on a large number of clinical cases. It was caused by the contact between the screw placed at the pole of the cup backing out and the femoral head and neck piece. The fretting between the two surfaces produces particles of titanium. Those can have an abrasive effect on the polyethylene liner enhancing the possibility of particular disease. Both surfaces of osseointegration of the prosthesis, that is the cup and the screw fixation of the stem can be affected. Prevention of the problem is avoiding the use

of the screw for the fixation of the cup, unnecessary if a good press-fit is obtained. Polyethylene caps have been recently developed, to cover the head of the screw, when fixation of the cup is needed. Surgical treatment resides in replacement of the implants, using a larger size cup to obtain press-fit and restoring of screw fixation of the stem, placing it with a slightly different anteversion and axial level.

Literature references available upon request to the authors

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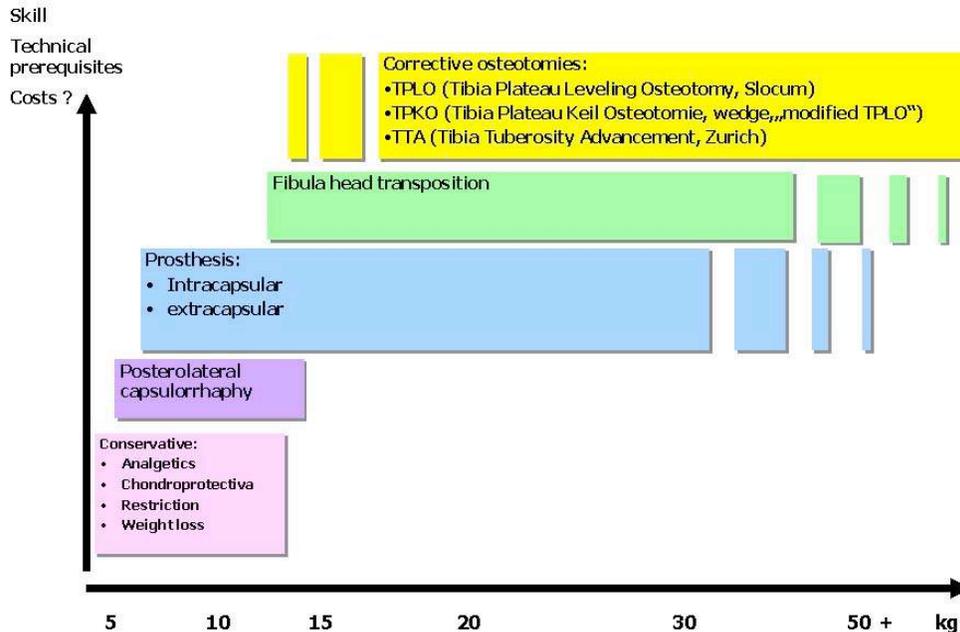
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Cranial cruciate ligament rupture: pathogenesis, diagnosis, overview methods

Daniel Koch, Dr. med. Vet. ECVS

Barclay Slocum's approach to stifle biomechanics by introducing muscle forces (1993) has led to a new understanding of the pathogenesis and treatment of cranial cruciate ligament rupture. It must be outlined, that a complete rupture is always preceded by partial tearing of the cranial cruciate ligament. This is mostly confirmed in the anamnesis by intermittent lameness periods, by signs of osteoarthritis, even in so-called acute ruptures, and by macroscopic and microscopic examination of the excised ligaments, which always show degeneration (Geyer, 1966). The force, acting on the ligament, is the cranial tibial thrust. Its magnitude is dependent on body weight and on the geometry of the proximal tibia and the distal femur. Only corrective osteotomies can reduce this force effectively.

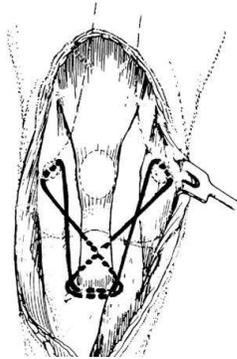
A rupture of the cranial cruciate ligament is diagnosed by the drawer sign. The tibia compression test is an alternative for diagnosis. Arthroscopy, MRI or arthrograms are not necessary for diagnosis, but may help detecting meniscal lesions and partial tears. Radiography is made for exclusion of other diseases as OCD, rupture of the long digital extensor, or bone tumor, for perioperative planning and in cases of partial tearing, where the drawer sign is not elicited.



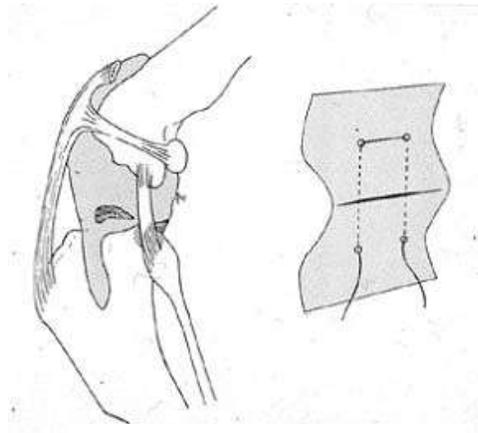
Treatment of cranial cruciate ligament rupture is based onto the body weight. Dogs (and cats) less than 5 kg are treated by NSAID or by posterolateral capsulorrhaphy. Intracapsular or extracapsular (de Angelis or Flo's procedure, fibula head transposition) techniques are recommend up to 20 kg body weight. It must be recalled, that the prosthesis then undergoes the same forces, which caused rupture of the cranial cruciate ligament. Definitive treatment for large and giant breed dogs is performed either by Slocum's tibia plateau leveling osteotomy (TPLO), the tibia wedge osteotomy (TWO) or by the tibia tuberosity advancement (TTA). All techniques reduce the cranial tibial thrust by

either rotating the tibia plateau or by changing the force direction of the quadriceps muscle. The TTA is originated from Zurich university. Three years experience show a rapid recovery and reliable healing. The intervention is straight forward.

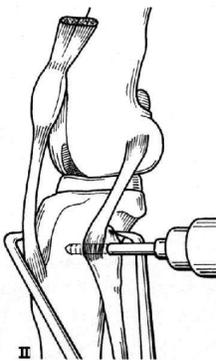
All surgical interventions are accompanied by NSAIDs for a rapid recovery. Physical therapy is indicated, where the dogs do not use the their limb after 7 days. Full recovery after TTA is expected after 2-3 months.



Flo's extracapsular technique



Posterolateral capsulorrhaphy



Fibula head transposition



Tibia tuberosity advancement

Tibial tuberosity advancement (TTA) for the treatment of cranial cruciate disease in dogs: evidences, technique and initial clinical results.

Pierre M. Montavon, Prof. Dr. med. vet.

Daniel M. Damur, Dr. med. vet. ECVS

Slobodan Tepic, Dr. Ing

Biomechanical considerations have influenced the treatment of cranial cruciate disease in dogs. Actual techniques tend to neutralize the tibiofemoral shear forces, therefore compensating for the deficit of the cruciate ligament. Biomechanic studies show the angle between the tibial plateau and the patellar ligament being responsible for the production of tibiofemoral shear forces, in both the human and canine species. They are directed toward cranial as the stifle is extended. It is possible to influence the shear forces by changing the geometry of the tibia, that is, by leveling the tibial plateau or by advancing the tibial tuberosity. One *in vitro* study demonstrated the replacement of the function of transected cranial cruciate ligament by advancing the tibial tuberosity in canine stifles.

The clinical application of the tibial tuberosity advancement requires preoperative planning made on mediolateral radiographs of the extended stifle, avoiding the cranial subluxation of the tibia in cases with ruptured cranial cruciate ligament. The patellar ligament is represented by its cranial border and the orientation of the tibial plateau by a line passing through both tibial origins of the cranial and caudal cruciate ligaments. The distance of cranial advancement necessary to bring the patellar ligament perpendicularly to the tibial plateau is figured out. This translation has to be planned around the patella as the center, in order to maintain its original position in the femoral sulcus. Existing template facilitates the planning and help in determining the size of the plate necessary to stabilize the osteotomized tibial tuberosity.

Arthroscopy or medial arthrotomy are performed to treat eventual meniscal lesions in presence of complete rupture of the cranial cruciate ligament.

Medial approach to the proximal tibia is performed from the cranial aspect of the medial meniscus to the saphenous vein distally. The pes anserinus is incised and carefully elevated, leaving intact the medial collateral ligament and the patellar ligament insertion with its bursa.

The desired number of holes for placement of the plate with its prongs is drilled with a special drill guide and a 2.0 mm drill bit.

The holes are placed just behind the cortex of the margo cranialis, the first one being placed at the level of the tibial tuberosity, just medial to the tibial insertion of the patellar ligament. Transverse osteotomy of the tibial tuberosity is then performed, starting at the midpoint between the margo cranialis and its junction with the tibial body, but above the preplanned screw fixation of the plate used for fixation of the osteotomy, to avoid risk of tibial fracture later on. The osteotomy is proximally incomplete and will lay cranial to the tuber of Gerdy when completed, to preserve the tendon of the long digital extensor muscle.

All implants to be used are made of pure titanium. They consist of a 3 – 8 holes plate with according prongs, to accommodate both the right and left tibia. Spacing cages of 3 – 12 mm with of different lengths to be inserted in the distracted osteotomy in order to advance the tibial tuberosity, giving its new position to the patellar ligament, are able to counteract the high forces in presence.

The plate is contoured if necessary, to adjust to the surface of the proximal tibia and then mounted together with the prongs. After their insertion into the predrilled holes, the osteotomy is completed and the tibial tuberosity translated toward cranial and proximal. A cage of desired length and width is inserted to maintain the space and the construction is secured with pin-pointed forceps. Plate and cage are secured with screws. The patellar mechanism is controlled for alignment and stability. The defect created at the osteotomy site can be filled with cancellous bone graft. Transecting the tibial tendon allows to cover the implants during the wound closure. Soft tissue structures such as the saphenous vein and nerve should be left intact. The wound is covered but the leg is not bandaged.

The developed implants are reliable for maintaining the advancement of the patellar ligament until healing of the osteotomy, which occurs 6 to 8 weeks postoperatively. Clinical results are satisfactory, with early return to function of the limb. Force plate gait analysis performed 6 months postoperatively demonstrates nearly normal to normal recovery of function. Radiographs taken at the same time document little or no progression of arthrosis of the stifle.

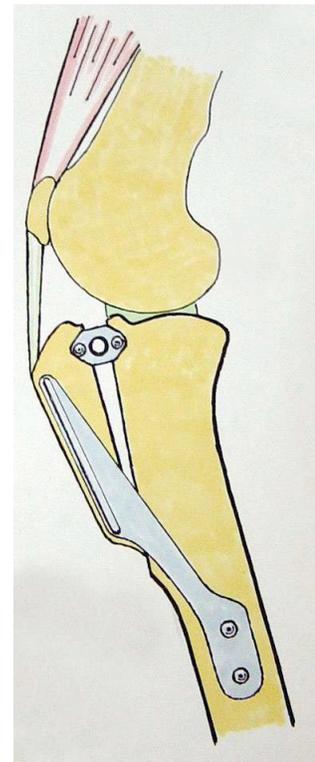
Clinical study of 200 cases operated by 15 different surgeons, including their learning curves, produced complications in 7 cases, mainly secondary to surgical misjudgment. In four cases the prongs of the plate were placed too caudally, ripping through the thin and soft bone. One case, where the prongs were placed too cranially, sustained an undisplaced fracture of the tibial tuberosity. In two cases, the osteotomy of the tibial tuberosity was started too distally, below the plate fixation and fractured the tibia. All complications could be treated or revised successfully, and healed without consequences for the patients. Latest series of 40 patients operated at our institution showed no surgical complication. No additional postoperative meniscal damages have been observed at this date.

The lesser invasive technique reduces operative time and perioperative morbidity. Respecting the normal range of motion of the stifle joint preserves integrity of undamaged menisci, without losing their intraarticular caudal support. Maintaining the original position of the patella within the sulcus and decreasing the retropatellar pressure by advancing the tibial tuberosity should help the chondromalacia present in all chronic cases of cruciate disease as evidenced during arthroscopy. The original conformation of the tibia is respected during the surgery. The lack of need for full leg bandage postoperatively should alleviate possible complications described elsewhere. These advantages improve the short- and middle-term results of the surgical treatment for the canine cranial cruciate disease.

The technique giving good, evidenced results is recommended for clinical application.

Literature references available upon request to the authors

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Oncosurgery

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Biopsy

Accurate interpretation of a properly acquired biopsy specimen is probably the most important step in cancer management. *Pathology is everything!* Not only will the biopsy provide the means to establish the diagnosis but also it allows prediction of biologic behaviour. This provides a basis for therapeutic alternatives such as the type and extent of treatment. Basically all masses should be histologically evaluated before or after removal. *If it's worth taking off it's worth looking at!* Unfortunately the biopsy is often performed too perfunctorily (or not at all!) which almost invariably leads to serious problems in patient management. The clinician must keep the three basic principles of oncology ("*biopsy, biopsy, and biopsy*") in focus but must not be so single minded as to perform a biopsy in a fashion that jeopardizes the patient's prognosis or quality of life or that increases the risks of the definitive procedure. For example, if a lesion on an extremity is biopsied through a transverse skin incision as opposed to a longitudinal one, the tumor may not be able to be removed with a limb preserving surgery because many tissue compartments have been contaminated by the biopsy. Remember, the entire biopsy tract must be removed *en masse* with the tumor with any definitive surgery. In this example this may only be possible by otherwise unnecessary limb amputation. The extent of problems from biopsy are not known in veterinary medicine, however, the Musculoskeletal Tumor Society published a report from information on 329 people with newly diagnosed soft tissue and bone malignancies. There were major errors in the diagnosis in 18.2%, non-representative or technically poor biopsies in 10.3%, problems in the skin, soft tissue or bone of the biopsy wound in 17.3%, and the optimum treatment had to be altered as a result of problems related to the biopsy in 18.2%. An unnecessary amputation was performed as a result of problems related to biopsy in 4.5% and the prognosis and outcome was considered to be adversely affected in 8.5%. This does not mean biopsy should be avoided; the recommendation based on these data is that the biopsy should be planned as carefully as definitive surgery. Biopsy is not known to increase the risk of systemic spread of cancer (metastasis), however tumor cells can spread within the biopsy surgical field or into body cavities increasing the risk of local tumor spread or tumor implantation.

Many variations in technique and equipment for biopsy procedures are described in the veterinary literature, but the common goal is to procure enough neoplastic tissue to establish an accurate diagnosis. Many biopsy techniques could be used on any given mass. Which procedure to use will be determined by specific goals for the case, site of the mass, equipment available, general status of the patient and personal preference and experience.

Preoperative and postoperative biopsy

When should an accurate tissue diagnosis be attained before treatment? This question can be answered by first answering these questions:

1. Would the result of the biopsy alter the type of treatment (surgery vs. radiation vs. chemotherapy, etc) or the extent of treatment (conservative vs. aggressive resection)? Certain cancers (e.g. soft tissue sarcomas, oral fibrosarcomas or mast cell tumors) have high local recurrence rates and therefore require removal with wider margins than benign lesions.

Several studies in animals and people have shown a positive correlation between permanent local disease control (preferably after first surgery) and survival. In other words, do the resection correctly the first time. A biopsy is particularly important if the surgery is in a difficult location for reconstruction (e.g. distal extremity, tail or head and neck) or if the proposed procedure carries considerable morbidity (e.g. maxillectomy or amputation). Virtually all externally accessible masses, beyond benign skin tumors, should have a tissue biopsy prior to therapeutic operative intervention.

On the other hand, if knowledge of tumor type would not change the treatment (lung lobectomy for solitary lung mass or splenectomy for splenic mass) or if the biopsy is as difficult or dangerous as the curative treatment (brain biopsy) then the biopsy information should be attained after the surgical removal.

2. Would the result of the biopsy (and therefore the knowledge of the prognosis) alter the owner's willingness to treat their pet? For example, some owners would be willing to do a mandibulectomy for an acanthomatous epulis (benign oral tumor) with an excellent prognosis but not for a melanoma with a poor prognosis.

General guidelines for tissue procurement and fixation

1. The proper performance of an incisional or needle biopsy does not negatively influence survival, even though a short-lived increase in cancer cells can be measured in draining vessels and lymphatics. The advantages of an accurate diagnosis far outweigh the theoretical disadvantage of enhancing tumor metastasis. On the other hand, cancer cells may be allowed to contaminate the tissues surrounding the mass, making resection more difficult. Careful haemostasis and obliteration of dead space will minimize local contamination of the biopsy site. Furthermore, the biopsy site should be planned so that it may be subsequently removed along with the entire mass. In particular, care should be taken not to "spill" cancer cells within the thoracic or abdominal cavities during a biopsy where they may seed pleural or peritoneal surfaces.
2. The junction of normal and abnormal tissue is frequently the best area for the pathologist to see differences in tissue as well as invasiveness. Do not perform biopsies in areas of ulceration or inflammation.
3. The larger the sample, the more likely it is to be diagnostic. Tumors are not homogeneous and usually contain areas of necrosis, inflammation and reactive tissue. Several samples from one mass are more likely to yield an accurate diagnosis than a single sample.
4. Biopsies should not be obtained with electrocautery, as it tends to deform the cellular architecture. Electrocautery is better utilized for haemostasis after blade removal of a diagnostic specimen or not at all.
5. Care should be taken not to unduly deform the specimen with forceps, suction, or other handling methods prior to fixation.
6. If evaluation of margins of excision is desired, it is best if the surgeon marks the specimen (fine suture on questionable edges or immersion of the specimen in India ink or "painting" questionable margins with India ink or special marking dyes) or submits margins in a separate container.

7. Proper fixation is vital. Tissue is generally fixed in 10% buffered neutral formalin with one part tissue to 10 parts fixative.
8. Tissue should not be thicker than one centimeter or it will not fix deeply. Large masses can be cut into appropriate sized pieces and representative sections submitted or sliced like a loaf of bread, leaving one edge intact, to allow fixation. After fixation (2-3 days), tissue can be mailed with a 1:1 ratio of tissue to formalin.
9. **A detailed history should accompany all biopsy requests!!** Interpretation of surgical biopsies is a combination of art and science. Without all the vital diagnostic information (signalment, history of recurrences, invasion in bone, rate of growth, etc), the pathologist will be significantly compromised in his or her ability to deliver accurate and clinically useful information.
10. A veterinary trained pathologist is preferred over a pathologist trained in human diseases. Although many cancers are histologically similar across species lines, enough differences exist to result in interpretive mistakes.

Biopsy methods

The more commonly used methods of tissue procurement are needle punch biopsy, incisional biopsy and excisional biopsy.

Needle Punch Biopsy

This method utilizes various types of needle core instruments (Franklin modified Vim-Silverman or Tru-cut, etc) to obtain tissue. The most common instrument used in our hospital is the Tru-cut needle. Students practice the use of the instrument on apples prior to biopsy of an actual tumor. *If you cannot biopsy an apple, you won't have much luck on a tumor!!* These instruments are generally 14 gauge in diameter and procure a piece of tissue that is about the size of the lead in a lead pencil and 1 to 1.5 cm long. In spite of this small sample size, the pathologist can usually visualize the structural relationship of the tissue and tumor cells. Virtually any accessible mass can be sampled by this method. It may be used for externally located lesions or for deeply seated lesions (kidney, liver, prostate, etc) via closed methods or at the time of open surgery.

The most common usage of the needle punch biopsy is for externally palpable masses. Except for highly inflamed and necrotic cancers (especially in the oral cavity) where incisional biopsy is preferred, most biopsies can be done on an outpatient basis with local anaesthesia and only rarely sedation. The area to be biopsied is clipped and cleaned. The skin or overlying tissue is prepared as for minor surgery. If the overlying tissue (usually skin and muscle) is intact, it is blocked with local anaesthetic in the region that the biopsy needle will penetrate. Tumor tissue is very poorly innervated and generally does not require local anaesthesia.

The mass is fixed in place with one hand or by an assistant. A small 1 to 3 mm stab incision is made in the overlying skin with a scalpel blade to allow insertion of the biopsy instrument. Through the same skin hole, several needle cores are removed from different sites to get a "cross section" of tissue types within the mass. The tissue is then gently removed from the instrument with a scalpel blade or hypodermic needle and placed in formalin. Samples may be gently rolled on a glass slide for cytology preparations before fixation. Sutures are generally not required in the skin hole. Needle

biopsy tracts are probably a minimal risk for tumor seeding but if possible are removed intact with the tumor at subsequent resection.

The Tru-cut needle is "disposable" with plastic casings and therefore cannot be steam sterilized. It may, however, be gas (ethylene oxide) sterilized and used repeatedly until it becomes dull.

Needle core biopsies are fast, safe, easy, and cheap and usually can be performed as outpatient procedures. They are generally more accurate than cytology but not as accurate as incisional or excisional biopsy.

Incisional Biopsy

Incisional biopsy is utilized when neither cytology nor needle core biopsy has yielded diagnostic material. Additionally, it is preferred for ulcerated and necrotic lesions since more tissue can be obtained. Under sterile conditions, a wedge of viable tumor tissue is removed from the mass. Ideally, a composite biopsy of normal and abnormal tissue is obtained from a location that will not compromise subsequent curative resection. Care should be taken not to widely open uninvolved tissue planes that could become contaminated with released tumor cells. Small incisions through muscle bellies are preferred to contaminating intramuscular compartments. The incisional biopsy tract is always removed in continuity with the tumor at subsequent resection.

Excisional Biopsy

This method is utilized when the treatment would not be altered by knowledge of tumor type (e.g. "benign" skin tumors, solitary lung mass, splenic mass, etc). It is more frequently performed than indicated but when used on properly selected cases, it can be both diagnostic and therapeutic as well as being cost effective.

Interpretation of results

The pathologist's job is to determine: 1) tumor vs. no tumor, 2) benign vs. malignant, 3) histological type, 4) grade (if applicable), and 5) margins (if excisional). Making an accurate diagnosis is not as simple as putting a piece of tissue in formalin and waiting for results. Many pitfalls can take place to render the end result inaccurate. Potential errors can take place at any level of diagnosis and it is up to the clinician in charge of the case to interpret the full meaning of the biopsy result. If the biopsy result does not correlate with the clinical scenario, several options are possible:

1. Call the pathologist and express your concern over the biopsy result. This exchange of information should be helpful for both parties and not looked upon as an affront to the pathologist's authority or expertise. It may lead to:
 - a. Re-sectioning of available tissue or paraffin blocks
 - b. Special stains for certain possible tumor types (e.g. toluidine blue for mast cells)
 - c. A second opinion by another pathologist.
2. If the tumor is still present in the patient, and particularly if widely varied options exist for therapy, a second (or third) biopsy should be performed.

A carefully performed, submitted and interpreted biopsy may be the most important step in management and subsequent prognosis of the patient with cancer. All too often tumors are not

submitted for histological evaluation after removal because "the owner didn't want to pay for it". Biopsies should not be an elective owner decision. *Biopsy is as fundamental to proper case management as closing the skin after ovariectomy.* The charge for submission and interpretation of the biopsy should be included in the surgery fee if need be but the biopsy must be done. *Because of increasing medico legal concerns, it is not medical curiosity alone that mandates knowledge of tumor type.*

Tumor staging

Cancer is the only curable chronic disease. Surgeons can cure cancer by finding a patient without metastatic disease, correctly identifying the cancer tissue and cutting completely around it without leaving or spilling any cancer cells in the body. Besides a degree of luck and good judgment for this event to transpire, the patient must be adequately *STAGED*. Staging is the technique of breaking tumors up into categories. The cancer therapist must know, therefore, to which "category" the patient's tumor belongs. Staging is a way of separating "early cancer" from "late cancer" or "advanced cancer". In this sense, a time related progression of the disease is described. The implication is that survival rates are higher for patients with localized cancer compared to those with distant spread of disease. This is important information for deciding the proper surgical dose, or whether a cure is possible and may influence a pet owner's willingness to treat. Staging must be done in a systematic, reproducible way. A detailed description of the World Health Organization T N M Classification of Tumors in Domestic Animals is beyond the scope of this discussion. Rather, I want to address staging in the context of "surgical oncology thinking". Readers are directed to two references in particular for more detailed information about staging:

1. UICC TNM Classification of Malignant Tumours, Ed., M. Harmer, 3rd ed., Geneva, 1978.
2. Owen LN. World Health Organization T N M Classification of Tumors in Domestic Animals, In Clinical Veterinary Oncology, Withrow SJ and MacEwen EG Eds., JB Lippincott Co., Philadelphia, 1989, pp 448-189.

The objectives of a tumor staging system

1. To help plan appropriate treatment
2. As a prognostic tool
3. To assist in evaluation of treatment results
4. To standardize information to enable comparison of outcome from different trials at different institutions
5. To contribute to the continued investigation of animal cancer
6. To help establish comparative models for human cancer

The TNM system has been proposed as a way to meet these objectives.

The TNM system

- T - represents an assessment of the extent of the primary tumor.
- N - represents an assessment of the involvement of the regional lymph nodes
- M - is an indicator of whether metastatic disease is detectable

The extent of malignant disease is then represented by adding numbers e.g. T1, T2...N0, N1...M0, M1...etc. This can be made even more sophisticated by adding a lower case letter to the T classification to represent the presence or absence of fixation to surrounding tissue, or ciphers (- or +) to the N classification to denote the absence or presence of histological confirmation of tumor extension to an enlarged lymph node. There are even provisions for histological grade or histological extension e.g. high grade malignancy is a G3 and tumor confined to the mucosa is P1. There are, for

certain sites, additional pathological categories such as for lymphatic invasion in bladder cancer, L0-L3, or for tumors of the kidney, invasion into lymphatics; V0-V2.

Stage grouping

The TNM classification provides a means for precise recording of the apparent extent of disease. For identifying statistically meaningful differences in survival probabilities cases are generally divided into clinical groups (Table 1). In a tumor with four possible degrees of T, four degrees of N and two degrees of M, the number of groups, extending from T1 N0 M0 at one end of the scale to T4 N3 M1 at the other, is 32. To record individual cases in these groups is simple; to reproduce tables containing that number is impractical except for very large series.

Table 1 An example of stage grouping.

TNM Groups		Clinical Stage	No Groups per Stage
T1 N0 M0	T2 N0 M0	I	2
T1 N1 M0	T2 N1 M0	II	2
T1 N2, 3 M0	T2 N2, 3 M0	III	12
T3 N0, 1,2,3 M0	T4 N0, 1,2,3 M0		
Any TN symbols + M1		IV	16

This all may seem complicated. There is method to this madness however and the TNM classification is a serious attempt to standardize classification of animal tumors. Unfortunately the tumor staging in the current system is not always applicable to the clinician because it may not truly reflect a meaningful prognostic guide in every tumor type or location. We still need a modification of this system, which has largely been an adaptation from a human tumor classification system, so that tumor classification correlates with survival probability. Even given these shortcomings it is vital that the clinical oncologist know about tumor staging and the tools available to perform this task.

The primary tumor

The histological type and (in many instances) the histological grade of tumor are of major importance to selecting the proper surgical technique. Virtually all external masses should have a minimum of cytological evidence of benign versus malignant disease. Preferably, a biopsy should be performed and evaluated BEFORE the definitive surgical treatment. The principles of biopsy are presented elsewhere in this seminar series but since *Pathology is everything - all our efforts, expertise, judgment and evaluations hinge on obtaining a correct histological diagnosis*; it is warranted to stress the importance of biopsy. **IT IS IMPERATIVE THAT YOU KNOW WHAT YOU ARE TREATING!**

You also need to know where the tumor is or rather the anatomical extent of the local tumor. This is the **T** classification. Tools for assessing this include: physical examination, standard radiographic techniques, ultrasonography, contrast studies (angiography, cystography, gastrography, pneumoventriculography, myelography etc.), endoscopy, tomography, computed tomography (CT), magnetic resonance imaging (MRI), nuclear scintigraphy, single photon emission computed tomograph (SPECT), thermograph and on and on. Some of the more sophisticated tests are very useful in certain anatomical sites and for various tumors but in other situations are at the very least

"over kill" and lend nothing to making a decision for appropriate treatment. Examples of some of these situations will be discussed.

The regional lymph node

Assessment of the involvement of the regional lymph node is the **N** part of the staging formula. A great deal of controversy surrounds the surgical management of regional lymph nodes draining the primary tumor site. As a general rule, epithelial cancers are more likely to metastasize to lymph nodes than are mesenchymal cancers. However, any enlarged regional lymph node requires investigation. Lymphadenomegaly may be from metastasis of cancer (firm, irregular and sometimes fixed to surrounding tissue) or from hyperplasia and reactivity to various tumor factors, infection, or inflammation. The former cause is a poor prognostic sign and the latter may be a beneficial host response. Enlarged lymph nodes as a result of cancer metastasis and invasion are generally uniformly effaced by tumor cells and can often be diagnosed by fine needle aspiration. Positive lymph nodes usually are a sign of impending systemic metastasis. Lymph nodes should be removed under two general circumstances:

1. If the lymph node is positive for cancer and not fixed to surrounding normal tissues, it may be possible to remove the node with some therapeutic intent. Frequently however, many lymph nodes drain a primary tumor site (e.g. oral cavity) and lymphadenectomy is incomplete (e.g. neck dissection). Although it is usually not practical, removal of the primary tumor, intervening lymphatic ducts and draining lymph node has been recommended (*en bloc* resection). *En bloc* resection may be possible for a malignant toe tumor with metastasis to the popliteal lymph node, but is usually only accomplished with amputation. Few other anatomic sites are routinely amenable to this therapy.
2. Normal appearing lymph nodes which are known to drain a primary tumor site should be randomly sampled (biopsy or cytology) to gain further staging information. This is particularly important if adjunctive treatment decisions (irradiation or chemotherapy) would be predicated on confirmation of residual cancer. Intrathoracic or intraabdominal lymph nodes are perhaps most crucial since they are not readily accessible to follow-up examination.

Lymph nodes are not removed under two general circumstances:

1. Lymph nodes in critical areas (retropharyngeal, hilar, mesenteric) which have eroded through the capsule and become adherent (fixed) to surrounding tissues cannot be curatively removed without serious harm to the patient. They are best biopsied and left alone or treated with other modalities. The occasional exception is metastasis of limb and foot tumors to prescapular and popliteal lymph nodes, which can be removed with amputation (radical *en bloc* resection).
2. Prophylactic removal of "normal" draining lymph nodes or chains of lymph nodes (as opposed to sampling for stage) is of no benefit and may be harmful. Regional lymph nodes may in fact be the initiator of favorable local and systemic immune responses and elective removal has been associated with poor survival in certain human cancers.

Metastasis

In veterinary practice the assessment of the **M** classification is the evaluation of good quality, properly positioned thoracic radiographs. In some cases abdominal radiography may be important,

such as for mast cell tumors. Thoracic radiographs should be taken with the animal conscious. Anesthetized animals very rapidly develop atelectasis in the lung lobes of the dependant hemi thorax. This makes identification of soft tissue dense lung metastasis inaccurate. It is advisable to take both lateral views to make a complete evaluation of the pulmonary tissue. Tumors in the uppermost lung fields will be outlined by stark contrast to the air filled lung whereas the dependant lung has more blood perfusion and there is a soft tissue to fluid density contrast making identification of lung nodules difficult. Nodules may even "disappear" on contralateral views. It is important to perform this part of the staging process as accurately as possible because in most cases, metastatic disease has a serious negative impact on survival. Even with the best technique, small lung nodules (less than .75 to 1 cm in diameter) may be missed with plain radiography. Fluoroscopy and lung CT may help improve the sensitivity. Nuclear scintigraphy is not uniformly a good tool for identifying metastatic disease in soft tissue but with the appropriate radiopharmaceutical it is an extremely sensitive study for identifying bone metastasis. Unfortunately nuclear bone scans are not selective and many disorders of bone may mimic bone metastasis (tooth abscess, arthritis, healing fractures etc.).

What do you do with the **M1** case? This is an appropriate time to talk about palliation. Palliative surgery is an attempt to improve the quality of the patient's life (pain relief or improved function) but not necessarily the length of the patient's life. This type of surgery requires very careful consideration of the expected morbidity of the procedure versus the expected gain to the patient and the client. In essence, it comes down to a decision of when to give up. One of the most difficult decisions in surgical oncology is the decision not to operate. Treatment of any kind should never be worse than no treatment.

Certain situations do exist, however, where palliative surgery may be beneficial. If an infected and draining mammary tumor in a patient with asymptomatic lung metastasis is the limiting factor in the patient's life, mastectomy may still be a logical procedure. Splenectomy for haemangiosarcoma is commonly performed but probably has little impact on survival and can be considered palliative, since it will stop the threat of immediate haemorrhage.

Conclusion

Surgery will be the mainstay of cancer treatment in veterinary medicine for many years to come. It is also clear that just because a surgical procedure is possible is not the best reason to do it. Although rhinotomy and curettage of the canine nasal cavity can be performed, it does not improve survival over untreated patients. Likewise, simple versus radical mastectomy in the dog does not influence survival but it may in the cat. *More surgery is not always better surgery.* Long term follow-up of well staged and graded tumors with defined surgical technique is necessary to demonstrate the true value of any operation. A great deal of progress in surgical technique and surgical thinking needs to take place before the role of surgery in cancer management can be optimized. A better understanding of expected tumor biology and more precise staging methods (angiograms, CT scans, etc) will hopefully facilitate more precise surgical operations to be performed. In spite of these anticipated advances in technology and understanding of biology, the most difficult aspect to learn is surgical judgment.

Surgical oncology

Introduction

I have had the privilege to be trained by and work with one of the foremost veterinary cancer surgeons of our time, Stephen J. Withrow (SJW). Much of what follows I have gleaned from his example. Steve recognizes that to be a winner in the fight against cancer it is not enough to be a technically excellent surgeon, although this helps. He says that what separates a surgical oncologist from other surgeons is awareness and proficiency of some unique cancer operations and most importantly, solid grasp of tumor biology and a close interaction with other cancer specialties (chemotherapy, radiation therapy, surgical pathology, diagnostic imaging, immunotherapy, etc). An oncology surgeon must be able to apply *SURGICAL ONCOLOGY THINKING*. To impart this concept, I tell my students, residents and fellows what Steve told me years ago, and that is to inwardly ask these questions before attempting a surgical treatment for cancer:

1. What am I treating? Does the biopsy fit the clinical situation? For instance a fibroma in the oral cavity does not erode bone, so if this is occurring then maybe it is something else such as a fibrosarcoma.
2. What is the known biology of this cancer? Is it highly invasive, what is the metastatic potential, does histological grade predict outcome, are there any other prognostically significant variables, etc.?
3. Is a cure possible? If so, aggressive interventions are justified based on a projected long-term survival.
4. What is the proper surgical dose? Just as chemotherapy and radiation are described by dose, surgical procedures can be described by dose: intralesional, marginal, wide or radical. Each of these "surgical doses" has an appropriate time and place. (Table 2)
5. What are my alternatives to surgery? A careful multidisciplinary approach to the individual patient is best planned from the outset, rather than after a poorly performed or timed surgery.

"THE GOOD CANCER SURGEON MUST BE A THINKING BIOLOGIST, NOT A SLASHING TECHNOLOGIST" - SJW.

Complete surgical removal of localized cancer cures more patients (human and animals) than any other form of treatment. To attain this ideal goal, surgeons must have a thorough understanding of anatomy, physiology, resection and reconstruction options for all organs, expected tumor behaviour and the various alternatives or adjunctive treatments. Surgical oncologists should not only be good technicians (cancer carpenters) but dedicated tumor biologists. Surgery will play a role at one point or another in the management of most cancer patients. This surgery may include any of the following: diagnosis (biopsy), resection for cure, palliation of symptoms, debulking and a wide variety of ancillary procedures to enhance and compliment other forms of treatment.

Most patients with cancer are "old". Old is a relative term. It is much more important to know the physiologic age of the patient than its chronologic age. An "old" dog or cat with normal measurable organ function should not be denied treatment simply on the basis of age. I am aware of no cancer where increasing age worsens tumor related prognosis. In fact the opposite is sometimes true; in some instances young animals have a worse prognosis than older animals with the same histological tumor type. "Old" animals will tolerate aggressive surgical intervention as well or as poorly as "young" patients.

Surgery for diagnosis

Biopsy principles will be covered in the next section, however it bears emphasizing that properly timed, performed and interpreted biopsies are one of the most crucial steps in the management of the cancer patient. Not only does the surgeon need to procure adequate tissue to establish a diagnosis but also the biopsy must not compromise subsequent surgical resection.

Surgery for cure

Before a surgeon can be in a position to provide the optimal operation for the patient with cancer, he or she should be able to answer the following questions:

1. What are the type, stage, and grade (if this has bearing on outcome) of cancer to be treated?
2. What are the expected local and systemic effects of this tumor type and stage?
3. Is a cure possible?
4. Is an operation indicated at all?
5. What are the options for alternative treatment?

A recurring theme in surgical management of cancer is that the first surgery has the best chance of cure. Several mechanisms for this improvement in survival have been advanced. Untreated tumors have had less chronologic time to metastasize than recurrent cancer. Untreated tumors have near normal anatomy, which will facilitate operative maneuvers. Recurrent disease may have had seeding of previously noninvolved tissue planes requiring wider resection than would have been required on the initial tumor. An ill-defined negative aspect of recurrent cancer is reported to be related to changes in vascularity and local immune responses. Regardless of the mechanism, curative intent surgery is best performed at the first operation.

The actual surgical technique will obviously vary with the site, size and stage of the tumor. Some general statements that need to be emphasized with cancer surgery are:

1. All incisional biopsy tracts should be excised in continuity with the primary tumor, since tumor cells are capable of growth in these wounds. Fine needle aspiration cytology tracts are of little concern while punch biopsy tracts are of intermediate concern. With this in mind, all biopsies should be positioned in such a manner that they can be removed at surgery.
2. Early vascular ligation (especially venous) should be attempted to diminish release of large tumor emboli into the systemic circulation. This is probably only clinically meaningful for those tumors with a well-defined arterial and venous supply such as splenic tumors, retained testicles and lung tumors. Small numbers of cancer cells are constantly being released into the venous circulation

by most tumors. Larger, macroscopic cell aggregates may be more dangerous, however, and these may be prevented from vascular escape with early venous ligation.

3. Local control of malignant cancer requires that an adequate margin of normal tissue be removed around the tumor. Resection can and should be classified in more detail than radical vs. conservative. Tumors with high probability of local recurrence (soft tissue sarcoma, malignant mast cell tumors, feline mammary adenocarcinoma, etc) should have 2 to 3 cm margins removed 3-dimensionally. Tumors are not flat and wide removal in one plane does not ensure complete excision. Fixation of malignant cancer to adjacent structures mandates removal of the adherent area in continuity with the tumor. This is commonly seen with oral cancer that is firmly adherent to the underlying mandible or maxilla. *Invasive cancer should not be peeled out, shelled out, enucleated, curetted or whittled on if a cure is expected.* Some malignant cancers are surrounded by a pseudocapsule. This capsule is composed of compressed and viable tumor cells, not healthy reactive host cells. The pseudocapsule is therefore not a plane for dissection if cure is the goal. If a malignant tumor is opened at the time of resection, that procedure is reduced to no better than a large biopsy. A level of dissection that is one tissue plane away from the mass should be strived for. Invasion of cancer into the medullary cavity of a bone requires subtotal or total bone resection and not curettage. Surgery may be measured in terms of *dose*, much like chemotherapy and radiation therapy (Table 2).

4. Tumors should be handled gently to avoid risk of breaking off tumor cells into the operative wound where they may grow. Copious lavage of all cancer wound beds will help mechanically remove small numbers of exfoliated tumor cells but should not replace gentle tissue handling.

Table 2 Classification of wound margins.

TYPE OF SURGERY	PLANE OF DISSECTION	RESULT
Intracapsular	Tumor removed in pieces or curetted: "debulking"	Macroscopic disease left behind
Marginal	Removal just outside or on the pseudocapsule	Usually leaves microscopic disease
Wide	Tumor and capsule not entered, cuff of normal tissue surrounds the specimen	Possible skip lesions
Radical	Entire compartment or structure removed (E.g. amputation)	No local residual cancer

The aggressiveness of resection should only rarely be tempered by fears of wound closure. It is better to leave a wound partially open with no cancer than closed with residual cancer.

Lymph node removal

A great deal of controversy surrounds the surgical management of regional lymph nodes draining the primary tumor site. As a general rule, epithelial cancers are more likely to metastasize to lymph nodes than are mesenchymal cancers. However, any enlarged regional lymph node requires investigation. Lymphadenomegaly may be from metastasis of cancer (firm, irregular and sometimes fixed to surrounding tissue) or from hyperplasia and reactivity to various tumor factors, infection, or

inflammation. The former cause is a poor prognostic sign and the latter may be a beneficial host response. Enlarged lymph nodes as a result of cancer metastasis and invasion are generally uniformly effaced by tumor cells and can often be diagnosed by fine needle aspiration. Positive lymph nodes usually are a sign of impending systemic metastasis. Lymph nodes should be removed under two general circumstances:

1. If the lymph node is positive for cancer and not fixed to surrounding normal tissues, it may be possible to remove the node with some therapeutic intent. Frequently however, many lymph nodes drain a primary tumor site (e.g. oral cavity) and lymphadenectomy is incomplete (e.g. neck dissection). Although it is usually not practical, removal of the primary tumor, intervening lymphatic ducts and draining lymph node has been recommended (*en bloc* resection). *En bloc* resection may be possible for a malignant toe tumor with metastasis to the popliteal lymph node, but is usually only accomplished with amputation. Few other anatomic sites are routinely amenable to this therapy.

2. Normal appearing lymph nodes which are known to drain a primary tumor site should be randomly sampled (biopsy or cytology) to gain further staging information. This is particularly important if adjunctive treatment decisions (irradiation or chemotherapy) would be predicated on confirmation of residual cancer. Intrathoracic or intraabdominal lymph nodes are perhaps most crucial since they are not readily accessible to follow-up examination.

Lymph nodes are not removed under two general circumstances:

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Palliative surgery

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Certain situations do exist, however, where palliative surgery may be beneficial. If an infected and draining mammary tumor in a patient with asymptomatic lung metastasis is the limiting factor in the patient's life, mastectomy may still be a logical procedure. Splenectomy for haemangiosarcoma is commonly performed but probably has little impact on survival and can be considered palliative, since it will stop the threat of immediate haemorrhage.

Debulking surgery

Incomplete removal of a tumor (planned or unplanned) is referred to as debulking or cytoreductive surgery. It is commonly performed but rarely indicated. Its theoretical indication is to enhance the efficacy of other treatment modalities. Debulking is a practical consideration prior to cryosurgery to decrease the amount of tissue to freeze and the time it will take. It may also help the treatment planning and dosimetry with certain forms of irradiation but the improved cancer control achieved is more a result of geometric considerations than removal of a few logs of tumor cells. Removing 99.9% of a one-centimeter tumor (1×10^8 cells) still leaves a million cancer cells behind. Immunotherapy and chemotherapy could theoretically be helped by tumor volume reduction. If deep-seated tumors are debulked with the anticipation of postoperative radiation therapy, the margins of known tumor or the operative field should be marked with radiopaque metal clips to allow proper treatment planning from radiographs.

Surgery and chemotherapy

The combined use of chemotherapy and surgery is becoming more commonplace in veterinary oncology. Many chemotherapy agents will impede wound healing to some extent. In spite of this risk, few clinically relevant problems occur when surgery is performed on a patient receiving chemotherapy. General recommendations are to wait 7 to 10 days after surgery to begin chemotherapy, especially for high-risk procedures. The use of intraoperative or perioperative chemotherapy is receiving increased attention and could have greater implications to wound healing.

Surgery and radiation

Theoretical advantages can be advanced for both pre- and postoperative radiation. Either way, some impairment of wound healing potential will exist. Radiation damage to normal tissues (stem cells, blood vessels and lymphatics) is more permanent than chemotherapy damage. As radiation dose and field size increase, the potential complications (with or without surgery) increase. If radiation therapy is given preoperatively, surgery can be performed after acute radiation reactions have resolved. Postoperative radiation is recommended to start immediately postoperative or after a two to three week delay. In spite of the theoretical problems, surgery can be safely performed on irradiated tissues. Complications may occur but are not prohibitive.

Prevention of cancer

Certain common cancers in dogs and cats can be prevented. It is well known that early (< 1 yr) oophorectomy will reduce the risk of mammary cancer in the dog (and to a lesser degree, the cat), by 200-fold over intact bitches. Castration of the male dog will help prevent perianal adenomas, prostatic adenocarcinoma and obviously testicular cancer. Elective removal of cryptorchid testes is another example of preventative surgery.

Miscellaneous oncologic surgery

With greater use of regional intraarterial chemotherapy, surgeons may be called upon to place long-term vascular access catheters.

Surgeons and radiotherapists may work together for the operative exposure of nonresectable cancer so that large doses of irradiation may be delivered to the tumor or tumor bed after exclusion of radiosensitive structures (intraoperative radiation therapy).

Discussion

It is clear that surgery will be the mainstay of cancer treatment in veterinary medicine for many years to come. It is also clear that just because a surgical procedure is possible is not the best reason to do it. Although rhinotomy and curettage of the canine nasal cavity can be performed, it does not improve survival over untreated patients. Likewise, simple versus radical mastectomy in the dog does not influence survival but it may in the cat. *More surgery is not always better surgery.* Long term follow-up of well staged and graded tumors with defined surgical technique is necessary to demonstrate the true value of any operation. A great deal of progress in surgical technique and surgical thinking needs to take place before the role of surgery in cancer management can be optimized. A better understanding of expected tumor biology and more precise staging methods (angiograms, CT scans, etc) will hopefully facilitate more precise surgical operations to be performed. In spite of these anticipated advances in technology and biology, the most difficult aspect to learn is surgical judgment.

Chemotherapy

Great advances have been made recently in the clinical use of chemotherapy in veterinary oncology. This is particularly true in the management of canine and feline lymphoma and in certain adjuvant settings for solid tumors. Many drugs in common use have become "off patent" and available under generic labels making them more affordable. This has resulted in part to a more wide spread use of chemotherapeutic agents. These cancer killing drugs are no longer just the tools of the research scientist or the veterinarian in academic referral practice. Chemotherapy can be effectively used in private veterinary referral and general practice. A mystique still shrouds this area of internal medicine however. There is also opportunity for misuse of chemotherapeutic agents or reliance on drugs to perform tasks outside their limitations. Chemotherapy does not represent the "silver bullet" of cancer medicine and to over rely on drugs to perform tasks more appropriately and effectively completed by other means such as surgery or radiation therapy is a travesty.

Ways chemotherapy is generally used.

1. In systemic disease such as lymphoma.
2. As adjunct to local methods of treatment (adjuvant).
3. As the first treatment for patients with localized cancer (neoadjuvant).
4. By direct instillation into sanctuaries (intra thecal) or by site directed perfusion of specific regions of the body (hepatic artery infusion, intracavitary or intra operative such as OPLA or Atrigel)
5. In desperation!

Big is bad

For solid cancers the following generality usually applies. Potential curability by drugs is inversely proportional to the tumor burden of the patient.

Appropriate situations for employing chemotherapy will be discussed in the lecture but for useful take home guides the following hand outs are provided. These are outlines for the use of common chemotherapeutic agents along with pet owner information sheets. Client education is an extremely important part of chemotherapeutics and I have found owner information sheets help owners notify you of early signs of impending toxicity so serious complications can be avoided.

Cisplatin Administration Technique

Dosage and Frequency: The dosage for cisplatin in dogs is 70 mg/m² given intravenously every three weeks for up to 6 treatments (see meter squared conversion table on back page).

Note: This dosage is not safe for use in cats. A safe dosage has not been determined in cats.

Potential Side Effects of Cisplatin:

1. Kidney damage. This is the reason for the diuresis protocol outlined below.
2. Nausea, vomiting and/or loss of appetite. Nausea and vomiting often occur during drug administration, however, it is rarely persistent. Chlorpromazine (0.03 mg/kg) or butorphanol (0.2 mg/kg) give subcutaneously may help alleviate this.

3. Bone marrow suppression. White blood cell counts drop to the lowest points on days 6 and 15 post treatment (bimodal nadir). We do not routinely test for these changes unless symptoms occur.
4. Deafness. This is a problem in human patients but is difficult to evaluate in dogs. we have not recognized this problem in animals.
5. Hair loss. This is not common, however, shaved areas will be slow to regrow.
6. Peripheral neuropathy. This is rare in animals but has been observed in people.

*Due to these potential side effects, the following diagnostic tests should be performed **prior** to each drug administration:*

1. Complete blood count (CBC) and platelet count. A neutrophil count of less than 2500 or a platelet count of less than 75,000 generally necessitates drug delay or withdrawal. In these patients, CBCs should be performed weekly until the neutrophil and platelet counts exceed 2500 and 75,000 respectively, at which time the drug can be readministered.
2. Blood urea nitrogen (BUN), serum creatinine, and urine specific gravity. The presence of underlying renal disease greatly increases the likelihood of cisplatin induced kidney damage and would necessitate alternate treatment plans. The BUN and creatinine should be normal, and urine specific gravity should ideally exceed 1.035 without an abnormal sediment (casts/protein).

Short term (4 hour and 20 minute) saline diuresis protocol for the administration of cisplatin:

1. Following placement of an indwelling intravenous catheter, normal saline (0.9% NaCl) solution is administered intravenously for 3 hours at 25 ml/kg/hour. This may require an infusion pump to deliver fluids at a high enough rate.
2. At the end of the third hour, the cisplatin (70 mg/m²) is diluted in 6 ml/kg of normal saline (0.9% NaCl) and administered intravenously over 20 minutes.
3. After cisplatin injection, saline diuresis is continued at 25 ml/kg/hr for one more hour.

Note: Dogs should be placed on racks during cisplatin administration and subsequent diuresis. Urine should be treated as if contaminated with cisplatin: i.e. hospital staff should wear latex gloves when handling or cleaning up urine. Dogs should be washed (bathed or hosed off) and allowed to void their bladders prior to discharge.

Adriamycin^R (doxorubicin) - Administration Techniques

Adriamycin is one of the most effective chemotherapeutic agents used in human and veterinary medicine. The drug has a relatively broad spectrum of activity and some potential toxicities. Careful monitoring of each patient treated with this drug is essential to limit adverse effects.

Since extravasation is a serious side effect of Adriamycin, an indwelling plastic or teflon catheter (i.e., Sovereign or Gelco) should be used. Butterfly and similar type catheters have proven unsatisfactory for the administration of Adriamycin. Special attention should be paid to aseptic technique prior to IV catheterization of immunosuppressed patients. The goal of catheterization is a clean "first stick" venipuncture; do not use a vein that has had a recent venipuncture or catheter. Since Adriamycin

reacts with heparin and corticosteroids to form a precipitate, 0.9% NaCl should be used for catheter flushes.

The Adriamycin should be administered in a minimum of 0.5-1ml/kg of 0.9% NaCl over 30-45 minute period. We routinely put the appropriate dose in 250ml of 0.9% NaCl for administration of this drug to dogs of all sizes. The drug is then allowed to drip in by slow gravity-feed. Occasional administration reactions in the dog include head shaking (i.e., ringing in the ears) urticaria, acute severe anaphylaxis, and nausea and vomiting. Anaphylaxis is managed by administration of corticosteroids, antihistamines, and fluid therapy; the other reactions can usually be managed by decreasing the rate of drug administration. The chance of anaphylaxis increases slightly with subsequent administrations but is still under 10%. If anaphylaxis occurs, it will be during or shortly after the administration of the drug. The catheter should be thoroughly flushed with 20ml 0.9% NaCl prior to removal to prevent drawing residual Adriamycin through the subcutaneous tissue at the catheter site.

The recommended dosage of Adriamycin for dogs is 30 mg/m² at three week intervals or to a total cumulative dose of 150-180 mg/m². To calculate a patient's m² volume, see the accompanying chart. In small dogs or cats, a dosage of 1 mg/kg may be safer.

Additional potential side effects of Adriamycin include diarrhea, hair loss, bone marrow suppression, and cardiac toxicity. Hair loss associated with Adriamycin is somewhat breed-dependent. Dogs with continually growing hair coats seem to be the most severely affected. Hair growth will resume once the drug is discontinued, but it may be thinner, finer, and a different color. Shaved hair will regrow slowly until the drug is withdrawn. Cats will often lose their whiskers. Gastrointestinal upset can occur in varying degrees with the most severe symptoms usually seen in the smaller patients. Problems begin 1-5 days post-administration and usually last 24-48 hours. In most cases the side effects are self limiting and can be managed by dietary adjustments. Owners should be instructed to contact the clinic if the signs are severe or protracted. Myelosuppression following Adriamycin administration is common. The greatest depression in neutrophil counts is seen at about seven to ten days post treatment. Most animals will have bone marrow recovery by the time they represent at three weeks, but a CBC should be done to rule out severe myelosuppression. A neutrophil count of less than 3 X 10⁹ cells/L necessitates a delay in therapy. In these patients, CBCs should be performed weekly until the neutrophil count again exceeds 3 X 10² cells/L and drug therapy can be resumed.

Trimethoprim sulfa should be given to animals whose neutrophil count is less than 1.5 X 10² cells/L or in any animal with signs of sepsis, fever, or local infection. Cardiomyopathy is a late occurring side effect of Adriamycin. At a total cumulative dose of 240 mg/m² about 10-20% of dogs will develop cardiotoxicity. Although very rare, cardiomyopathy can occur even with the first dose. Pre-existing cardiac disease has not seemed to significantly increase the chances of cardiac toxicity. At the recommended dose, the risk of cardiac side effects does not outweigh the potential therapeutic advantages.

We recommend waiting 2 months after your animal receives chemotherapy to resume vaccinations.

CYTOXAN, ONCOVIN, PREDNISONE (COP)

Several protocols incorporating cyclophosphamide (Cytoxan®, Cycloblastine®), vincristine (Oncovin®) and prednisone have been published. The following references should be consulted

before any animals are treated with cyclophosphamide, vincristine and prednisone to gain further, more detailed understanding about potential benefits and toxicities. Several other protocols exist and are described in a variety of references.

For convenience, the following dosages and schedules of administration are noted:

Canine Lymphoma

C: cyclophosphamide (50 mg tablets): 50 mg/m² orally on days 1, 2, 3 and 4 every third week or, 200-250 mg/m² given orally once every third week.

NOTE: The dosage of cyclophosphamide should be rounded down to the nearest whole tablet. If excessive myelosuppression occurs (neutrophils < 1.5 X 10²/L) the subsequent dose of cyclophosphamide is reduced by 25%. You may want to contact a pharmacist if you have difficulty formulating the correct dose for your specific patient.

O: vincristine (1 mg/ml), 0.75 mg/m² IV weekly for 4 weeks, then once every third week.

P: prednisone - 1 mg/kg orally daily for 4 weeks then every other day.

*Treatment continues for one year as for weeks 7-16.

Feline Lymphoma

Cyclophosphamide and vincristine are administered as in canine protocol.

P: prednisone - 2 mg/kg orally daily for one year after which time the dose is tapered.

Potential side effects

Cyclophosphamide

- Alopecia in certain breeds (eg: poodles, old English Sheepdog, Afghan hounds)
- Nausea, vomiting, diarrhea, anorexia
- Lethargy
- Neutropaenia, thrombocytopaenia - nadir (lowest counts) 5-7 days
- Sterile haemorrhage cystitis - drug should be discontinued if this occurs.

Chlorambucil is substituted for cyclophosphamide if sterile haemorrhage cystitis is diagnosed.

Vincristine

- Perivascular extravasation results in severe tissue necrosis (be careful)
- Peripheral neuropathies
- Constipation
- Alopecia
- Nausea, vomiting

Prednisone

- Polyuria, polydipsia
- Polyphagia
- Panting

- Elevated serum alkaline phosphatase
- Hepatomegaly
- Iatrogenic hyperadrenocorticism

We recommend waiting 2 months after your animal receives chemotherapy to resume vaccinations.

Guidelines for the Safe Handling of Cytotoxic Drugs

The use of cytotoxic drugs to treat neoplastic, immune mediated and other conditions has become quite commonplace in Veterinary practice over the last decade. Marked benefits to most animals are realized when these drugs are used. Up until now, there has been no regulatory control over the preparation, transport, administration or disposal of these cytotoxic agents. This is of concern since cytotoxic drugs are toxic in their own right and can be carcinogenic, teratogenic, mutagenic and cytotoxic. These risks of toxicity are largely born by the patient receiving cytotoxic drugs. There are, however, also risks to those handling the drugs and waste products. Most institutions using cytotoxic drugs established their own guidelines to protect people handling these dangerous drugs.

On September 1st 1997, the Queensland Department of Health declared cytotoxic drugs hazardous chemicals. Hazardous chemicals fall under the jurisdiction of the Department of Workplace Health and Safety. It therefore became necessary to write guidelines for the safe handling of cytotoxic drugs.

The Department of Workplace Health and Safety launched a document on Friday November 14th 1997 and it is imperative that all veterinarians using cytotoxic drugs be fully aware of these guidelines.

I will outline and precis this document here but urge you all to either obtain a copy¹ or review the actual document, which can soon be found on the Internet.²

1. Preparation of Cytotoxic drugs.

Unless a biological safety cabinet complying with Australian Standards (AS 2567) is used, cytotoxic drugs should be purchased from facilities properly equipped to dispense these drugs. For most of us, this will mean buying pre-prepared injectable agents from companies such as Cytomix³

One of the areas of great risk for exposure is in aerosolisation of parent, raw, undiluted drugs. This risk is very high if drugs are withdrawn from multi-use vials without following precautions described in the guidelines.

2. Administration.

Many of the chemotherapeutic agents used are extremely irritating to tissues. As well as taking great care to prevent toxicity to the patient, care must be taken to prevent absorption, ingestion, eye contact and aerosolisation causing risk to operators. The Guidelines describe appropriate workplace safety and personal protection equipment (PPE). At least an impervious gown, latex gloves (double),

¹ Queensland Government Department of Training and Industrial Relations; Workplace Health and Safety – Guide for Handling of Cytotoxic (Antineoplastic) Drugs and Related Waste.

² <http://www.dtir.qld.gov.au/hs/hs.htm>

³ Cytomix: 1/169 Beavers Road, Northcote Vic 3070. Phone: 1800 636672, Facsimile 1800 624887

protective eyewear and mask (not a surgical mask) should be worn by the person administering injectable cytotoxic agents.

3. Waste disposal.

All cytotoxic waste (including used PPE, syringes, needles, fluid lines etc) must be disposed of in appropriate, designated cytotoxic waste disposal receptacles.

Waste management companies such as Ace Waste provide services to ensure proper pick-up and incineration of cytotoxic waste.

4. Accidental Spills

The guidelines provide information on management of accidental cytotoxic drug spills. Spill kits must be provided in areas of preparation of cytotoxic drugs. These kits are commercially available or can be assembled as homemade kits. Spills must be documented and action taken must be recorded.

5. Handling of Waste from animals receiving Cytotoxic drugs.

The guidelines contain information on proper handling of excreta and body fluids from animals receiving cytotoxic drugs. This information must also extend to owners of pets for home care. Urine can contain high concentrations of certain cytotoxic drugs and breakdown products. Similarly, faeces can be contaminated. Personnel must be protected from exposure to contaminated waste. It is important that kennel staff do not cause aerosolisation of substances from excreta. All animals receiving cytotoxic drugs must be identified with cage labels.

6. Information for owners and personnel

Most of us administering chemotherapy already provide owners with written information about the drugs used. We are, in fact obliged to provide written information to clients and personnel about the potential hazards and how to minimize the risks. We are also obliged to provide training for staff involved with cytotoxic agents.

In addition, MSDS information must be kept and be readily available to employees for all hazardous chemicals used in your clinic. A risk assessment should be completed for each drug. Based on the risk assessment, action should be taken to ensure compliance with the guidelines, or discontinue the use of the hazardous chemicals in the workplace.

The implication of these guidelines is significant. Each of us must consider our current practice of handling cytotoxic drugs, perform a risk assessment and consider ways to fully conform to the guidelines. We owe this to our staff our clients and ourselves.

We should not look at this document as a hindrance to our normal clinical practice but as an opportunity to improve the way we do things. At the University of Queensland, all the necessary steps have been taken to comply with the guidelines for the safe handling of cytotoxic drugs in small animals. We are modifying handling practices to ensure a safe workplace.

I urge you all to take a responsible look at chemotherapy handling protocols in light of this new and important document.

Canine mast cell tumor

Mast cell tumor (MCT) represents the most common malignant cutaneous tumor in the dog. There is a large degree of variation in the histologic appearance and biologic behavior of canine MCT, ranging from histologically and behaviorally benign to histologically and behaviorally malignant.

MCT of low or intermediate histologic grade (Patnaik Grade I or II) comprise 60 to 79% of all cutaneous MCT in the dog. These tumors exhibit quite aggressive local tissue invasion, necessitating **aggressive surgery with wide (at least 3 cm) margins**. However, their metastatic rate is relatively low (less than 10%). High-grade or undifferentiated MCT (Patnaik Grade III), in addition to being very locally infiltrative, have a considerably higher metastatic rate. Thus, aggressive surgery or other local therapies, while still necessary, are considered insufficient for optimum control. The presence of these highly metastatic undifferentiated tumors, and the necessity for major reconstructive or disfiguring surgery (e.g. amputation, body wall resection) in order to achieve histologically "clean" margins, have prompted the search for other effective treatment modalities.

Prior studies have identified several prognostic factors associated with MCT: 1) Histologic grade is one of the strongest prognostic indicators; dogs with grade III tumors typically die of their disease rapidly despite appropriate local therapy. **Median survival of dogs with grade III MCT after surgery alone is thought to be in the 3-6 month range;** 2) Clinical stage - Dogs with metastasis to regional lymph nodes or other structures at presentation having a less favorable long-term prognosis; 3) Location - Tumors in the preputial, perianal, oral, subungual and other mucocutaneous sites typically have worse prognoses; 4) Recurrence following initial surgical excision is felt by some to be a negative prognostic indicator; 5) The presence of systemic signs (anorexia, vomiting, hematemesis, melena) is a strong negative prognostic indicator.

In addition to aggressive local surgery, several other local therapeutic modalities have been investigated for the adjuvant treatment of canine MCT. **Radiotherapy (RT)** has proven to be a very effective local treatment modality when combined with "marginal" surgical excision. **2-year control rates of 85 to 90%** can be expected when incompletely excised low- or intermediate-grade MCT are treated with RT. Radiotherapy to bulky tumors is consistently less effective than RT to microscopic disease, with a one-year control rate of approximately 50%. Alternative local therapies that have been reported include hyperthermia with RT, interstitial RT, photodynamic therapy, intralesional corticosteroids, cryotherapy, and intralesional deionized water injection. None are as thoroughly investigated, clinically effective, or practical for achieving long-term local control as are appropriately aggressive surgery and/or RT.

Animals with undifferentiated MCT, MCT that have metastasized, or tumors in a historically unfavorable location (see above) may benefit from the addition of some form of systemic therapy to appropriate local therapy. In addition, aggressive surgery or RT may be declined by some owners for various reasons. Recently, several studies have been published investigating various systemic therapies for canine MCT, the results of which are summarized in **Table 4**.

Table 4: Response to Chemotherapy in Dogs with Mast Cell Tumors.

Drug(s)	%CR	%PR	ORR	Median Resp. Dur.	Comments
Prednisone	4%	16%	20%	NR	
Vincristine	0%	7%	7%	NR	32% severe toxicity (?)
CCNU (Lomustine)	6%	38%	44%	79 days*	Cum. thrombocytopenia
P/C/V	0%	78%	78%	NR	
COP-HU	23%	35%	59%	53 days	

CR: Complete Response. PR: Partial (>50%) Response. ORR: Overall Response Rate.

P/C/V: Prednisone/Cyclophosphamide/Vinblastine. COP-HU: Cyclophosphamide/

Vincristine/Prednisone/Hydroxyurea. NR: Not Reported

* Excludes patient that experienced CR - Euth. without evidence of disease after 440 days

The information below discusses the use of oral prednisone combined with injectable vinblastine (VBL) for the treatment of canine mast cell tumor, both in the post-surgical setting and in the setting of bulky disease.

Chemotherapy administration - Prednisone is administered orally at an initial dose of 2 mg/kg SID, and this dose was tapered and discontinued over 12 to 26 weeks. VBL was given as a rapid intravenous bolus at **2 mg/m²**. The most common protocol consists of weekly injections for 4 weeks, followed by 4 biweekly injections. In the context of macroscopic disease, treatment is continued for as long as it is felt to be effective.

Side Effects - Adverse effects were noted in approximately 20% of patients, usually after the first dose of VBL. These were considered mild in 15%, and severe in 5%. Mild side effects include self-limiting vomiting (necessitating a 20% dose reduction), neutropaenia without evidence of sepsis (7-day neutrophil count less than 1,000/ μ L), and lethargy/soft stool. Severe side effects consisted of severe, refractory vomiting and febrile neutropaenia after the first VBL dose.

Response - Overall response rate in the "gross disease" population was 7/15 (**47%**), consisting of 4 complete responses and 3 partial responses, with a **median response duration of 153 days**. Survival time was significantly longer in the responding group versus the nonresponders (70 days vs. median not reached, $p = .005$). Overall median survival time in the "gross disease" group was 154 days. As an adjunctive therapy to incomplete surgical resection ("microscopic disease" group), VBL and prednisone treatment conferred a **57%** one and two-year disease free rate. Although this is less than the 85 to 90% two-year disease free rate conferred by surgery plus RT, it is our feeling that this number represents a significant improvement over incomplete resection alone. It should be pointed out that this represents a small case number, and results may vary with a larger sampling of "microscopic disease" patients.

Factors that influenced survival upon univariate analysis are listed below (**See Table 5**). The difference in survival between the "gross disease" and other disease categories underscores the continued importance of surgery as a mainstay of treatment for canine MCT.

Table 5: Univariate Analysis of Prognostic Variables for Effect on Survival Time for 41 Dogs with Mast Cell Tumor Treated with Prednisone and Vinblastine

Variable	Number of Dogs	Median Survival (Days)	<i>p</i> Value	Hazard Ratio (95% CI)
Recurrent				
Yes	10	245 d	0.0012	4.372 (2.273-28.40)
No	31	NR		
Local Treatment				
Gross	17	245 d	0.0031	4.269 (1.697-13.64)
Micro/ALT	24	NR		
AgNOR Frequency				
> 3.04	14	330 d	0.0167	5.266 (1.303-14.18)
≤ 3.04	13	NR		
Histologic Grade				
III	23	331 d	0.0124	3.758 (1.318-9.756)
II	18	NR		
Lymph Node Status				
Positive	22	355 d	0.025	3.370 (1.155-8.302)
Negative	19	NR		
Ulceration				
Yes	6	225 d	0.033	3.183 (1.164-33.89)
No	35	NR		
Prior Chemotherapy				
Yes	5	135 d	0.0486	2.947 (1.010-26.21)
No	36	NR		

Upon multivariate analysis, the overall median time to treatment failure was **317 days**, with 49% progression free at 2 years. After accounting for all other variables, statistically significant prognostic variables for treatment failure were histologic grade ($p = 0.005$), recurrent tumor ($p = 0.001$), and presence of gross disease ($p < 0.001$). Seven of 23 patients (30%) whose disease was controlled at least grossly by surgery ("microscopic" and "adequate local therapy" populations) developed progression of MCT. Recurrence at the site of prior tumor resection occurred in 1 patient, 5 developed disease elsewhere, and 1 had both local recurrence and distant disease. The overall MST was not reached, with a median follow-up of 579 days. 63% of patients were alive at 1 year, and 56% were alive at 2 years. Statistically significant prognostic factors for survival following multivariate analysis were recurrent tumor ($p < 0.001$) and histologic grade ($p = 0.012$).

It is interesting to note that presence of a **recurrent tumor** retained extremely strong prognostic significance for recurrence and survival after multivariate analysis. This suggests strongly that *the time to consider other types of therapy with curative intent* (i.e. aggressive re-resection, radiotherapy, or chemotherapy) *is at the time a MCT is first diagnosed, rather than at the time of recurrence.*

Prednisone and VBL provided longer survival in patients with grade III MCT than has surgery alone has in prior reports, with a MST of 331 days, and 45% of patients with grade III MCT alive at 1 and 2 years. This is an apparent improvement over historical

survival data generated employing surgery alone (Various studies have quoted a median survival time of 13 weeks, a 15% 7-month survival, and a 6% 48 month survival).

Summary:

Combination chemotherapy with prednisone and vinblastine appears to be an effective therapy for canine MCT. In addition to apparently increasing the survival time of high-risk (grade III) patients after surgery, it may also be beneficial for animals with incompletely resected intermediate grade tumors where aggressive local therapy (surgery, RT) is not possible or has been declined. The cost of these drugs is relatively low, particularly in comparison to RT, and they appear to be well tolerated by the majority of canine patients.

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Tumors of the skeletal system

1. Osteosarcoma in dogs

Incidence and Risk Factors

Osteosarcoma (OS) is the most common primary bone tumor in dogs accounting for up to 85% of malignancies originating in the skeleton. Osteosarcoma is estimated to occur in over 8000 dogs each year in the United States however this is probably an underestimation, since not all cases are confirmed nor recorded. The demographics of canine OS have been well reported. It is largely a disease of middle aged to older dogs, with a median age of seven years. There is a large range in age of onset with a reported case in a six-month-old pup, and a small peak in age incidence at 18-24 months. Primary rib OS tends to occur in younger adult dogs with a mean age of 4.5 to 5.4 years. Osteosarcoma is classically a cancer of large and giant breeds. In a review of 1462 cases of canine OS, dogs weighing more than 40 kg accounted for 29% of all cases and only 5% of their tumors occurred in the axial skeleton. Only 5% of OS occur in dogs weighing less than 15 kg but 59% of their tumors originated in the axial skeleton. The breeds most at risk for OS are Saint Bernard, Great Dane, Irish setter, Doberman pinscher, German shepherd and golden retriever; however size seems to be a more important predisposing factor than breed. Males are reported to be slightly more frequently affected than females (1.1 to 1.5:1), with the exception of the Saint Bernard, Rottweiler and Great Dane and for dogs with primary OS of the axial skeleton (except rib and spine) where affected females outnumber males. However, in 544 cases of canine OS of all sites treated at Colorado State University between 1986 and 1994 the male to female ratio was 1:1.2. (Unpublished data) Overall, approximately 75% of OS occurs in the appendicular skeleton, with the remainder occurring in the axial skeleton. The metaphyseal region of long bones is the most common primary site with front limbs affected twice as often as rear limbs and the distal radius and proximal humerus being the two most common locations. It is extremely rare for OS to be primarily located in bones adjacent to the elbow. In the rear limbs, tumors are fairly evenly distributed between the distal femur, distal tibia, and proximal tibia, with the proximal femur a slightly less common site. Primary OS distal to the antebrachio-carpal and tarsocrural joints is relatively rare in dogs. In a study of 116 cases of canine primary OS in the axial skeleton it was reported that 27% were located in the mandible, 22% in the maxilla, 15% in the spine, 14% in the cranium, 10% in ribs, 9% in the nasal cavity or paranasal sinuses and 6% in the pelvis. Documentable multicentric OS at the time of initial diagnosis occurs in less than 10% of all cases. Osteosarcoma of extraskeletal sites is rare, but primary OS has been reported in mammary tissue, spleen, bowel, liver, kidney, testicle, vagina, eye, gastric ligament and adrenal gland.

The etiology of canine OS is generally unknown. Some have speculated a viral cause because OS can occur in littermates and injecting OS cells into canine fetii may experimentally induce OS. However, this is currently not a popularly held view and an etiologic virus has not been isolated. A simplistic theory based on circumstantial evidence is that, since OS tends to occur in major weight bearing bones adjacent to late closing physes, and heavy dogs are predisposed, multiple minor trauma and subsequent injury to sensitive cells in the physal region may occur. This may initiate the disease by inducing mitogenic signals increasing the probability for the development of a mutant lineage. There

are reports of OS associated with metallic implants used for fracture repair, chronic osteomyelitis, and with fractures in which no internal repair was used. Ionizing radiation can induce osteosarcoma. In one study 43 of 403 beagles fed strontium-90 developed primary bone sarcomas. Three of 87 spontaneous tumor-bearing dogs or 3.4% of dogs treated for soft tissue sarcomas developed OS within the field of radiation. Secondary OS developed between 1.7 to 5 years after radiation in that study and the authors speculated that high dose of radiation per fraction may predispose to this serious late effect of irradiation. Osteosarcoma is a rare, late complication of radiation therapy in people and is even less common in dogs. Post irradiation OS in people comprises approximately 2% to 4% of all osteosarcomas reviewed in two large series. Osteosarcomas have been concurrently seen in dogs with bone infarcts. Bone infarcts are uncommon, are of unknown etiology and may be identified as incidental findings by radiography. Bone infarcts are probably not associated with tumor emboli. Osteosarcomas associated with bone infarcts appear to be more common in smaller breeds. It is not clear whether there is any causal relationship between bone infarcts and osteosarcoma. There has recently been a flurry of experimental work and clinical data to support molecular genetic models by which OS may develop. Osteosarcoma tumorigenesis in humans results if both alleles at the retinoblastoma susceptibility locus (Rb gene) are altered. Some workers conclude that Rb gene alteration is pertinent to the genesis of most human OS cases and some other bone and soft tissue tumors. Additional genetic evidence suggests that another event in the development of OS is the homozygous alteration of another gene, p53. Both the Rb gene and p53 have been proposed to act as tumor suppresser genes. Therefore, OS tumorigenesis may be a loss of function of these two, and perhaps other, genes.

Pathology and Natural Behavior

Osteosarcoma, (or osteogenic sarcoma), is a malignant mesenchymal tumor of primitive bone cells. These cells produce an extracellular matrix of osteoid and the presence of tumor osteoid is the basis for the histological diagnosis differentiating OS from other sarcomas of bone. There are many histological sub classifications of OS based on the type and amount of matrix and characteristics of the cells: osteoblastic, chondroblastic, fibroblastic, poorly differentiated and telangiectatic osteosarcoma (a vascular subtype). In dogs, it has not been demonstrated that there is a difference in the biological behavior of the different histological sub classifications. The histological pattern may vary between tumors or even within the same tumor. Small biopsy samples of an OS may lead to misdiagnoses such as chondrosarcoma, fibrosarcoma or haemangiosarcoma. These histological diagnoses from small biopsies must be interpreted with caution. It is important to obtain histological analysis of the entire tumor following definitive excision to confirm the diagnosis.

Osteosarcoma has very aggressive local effects and causes lysis, production of bone or both processes. The local disease is usually attended by soft tissue swelling. Pathological fracture of the affected bone can occur. Metastasis is very common and arises early in the course of the disease, although usually subclinically. Although less than 5% of dogs have radiographically detectable pulmonary metastasis at presentation, approximately 90% will die with metastatic disease, usually to the lungs, within 1 year when amputation is the only treatment. Metastasis via the haematogenous route is most common, however on rare occasions extension to regional lymph nodes may occur. Although the lung is the most commonly reported site for metastasis, tumor spread to bones or other soft tissue sites occurs with some frequency. The biological behavior of OS of the mandible is

probably an exception. Dogs with OS of the mandible treated with mandibulectomy alone had a 1-year survival rate of 71% in one study. Survival of dogs with OS distal to the antebrachioacarpal or tarsocrural joints was somewhat longer (median of 466 days) than survival of dogs with OS of more common appendicular sites however OS in these sites is aggressive with a high potential for metastasis.

History and Clinical Signs

Dogs with OS of appendicular sites generally present with a lameness and swelling at the primary site. Sometimes there is a history of mild trauma just prior to the onset of lameness. This history can often lead to misdiagnosis as a strain, sprain or other orthopedic injury such as cranial cruciate rupture. The pain is likely due to microfractures or disruption of the periosteum induced by osteolysis of cortical bone with tumor extension from the medullary canal. The lameness worsens and a moderately firm to soft, variably painful swelling arises at the primary site. Dogs may present with acute, severe lameness associated with pathologic fractures. Large and giant breed dogs that present with lameness or localized swelling at metaphyseal sites should be evaluated with OS as the most likely diagnosis.

The signs associated with axial skeletal OS are site dependent. Signs vary from localized swelling with or without lameness to dysphagia (oral sites), exophthalmos and pain on opening the mouth (caudal mandibular or orbital sites), facial deformity and nasal discharge (sinus and nasal cavity sites) and hyperesthesia with or without neurological signs (spinal sites). Dogs with tumors arising from ribs usually present because of a palpable, variably painful mass and respiratory signs are not common even where the lesions have large intrathoracic components. Dyspnoea as a sign of malignant pleural effusion is quite rare.

Dogs rarely have respiratory signs as the first clinical evidence of pulmonary metastasis; rather, their first signs are usually vague. With radiographically detectable pulmonary metastasis dogs may remain asymptomatic for many months, but most dogs develop decreased appetites and non-specific signs such as malaise within 1 month. Hypertrophic osteopathy may develop in dogs with pulmonary metastasis.

Diagnostic Techniques and Work-Up

Initial evaluation of the primary site involves interpretation of good quality radiographs taken in lateral and craniocaudal projections. Special views may be necessary for lesions occurring in sites other than in the appendicular skeleton. The overall radiographic abnormality of bone varies from mostly bone lysis to almost entirely osteoblastic or osteogenic changes. There is also an entire spectrum of changes between these two extremes and the appearance of OS can be quite variable. There are some features, however, that are commonly seen. Cortical lysis is a common feature of OS and may be severe enough to leave obvious areas of discontinuity of the cortex leading to pathological fracture. There is often soft tissue extension with an obvious soft tissue swelling and new bone (tumor bone) may form in these areas in a palisading pattern perpendicular or radiating from the axis of the cortex ("sun-burst"). As tumor invades the cortex the periosteum is elevated and new bone is laid down by the cambium layer providing a triangular appearing deposition of dense new bone on the cortex at the periphery of the lesion. This periosteal new bone has been called "Codman's triangle" but this is not pathognomonic for osteosarcoma. Osteosarcoma does not directly

cross articular cartilage and primary lesions usually remain monostotic. The tumors may extend into periarticular soft tissues, however and adjacent bones are at risk because of extension through adjacent soft tissue structures. Other radiographic changes that can attend OS are loss of the fine trabecular pattern in the metaphysis, a vague transition zone at the periphery of the medullary extent of the lesion (rather than a sharp sclerotic margin) or areas of fine punctate lysis. Any one or combinations of these changes may be seen depending on the size, histological subtype, location, and duration of the lesion.

Based on signalment, history, physical exam findings and radiographic findings a presumptive diagnosis of OS can be made. Differential diagnoses of lytic, proliferative or mixed pattern aggressive bone lesions identified on radiographs include other primary bone tumors (chondrosarcoma, fibrosarcoma, haemangiosarcoma); metastatic bone cancer; multiple myeloma or lymphoma of bone; systemic mycosis with bony localization; and bacterial osteomyelitis.

Other primary bone tumors are far less common but may be suspected especially in dogs with unusual signalment or tumor location. Metastatic cancer can spread to bone from almost any malignancy. A careful physical exam is important including a rectal exam with special attention paid to the genitourinary system to help rule out the presence of a primary cancer. Dogs with a history of cancer in the past should have their original biopsy reviewed and should be restaged for the original disease. Common sites for metastatic bone cancer are lumbar and sacral vertebrae, pelvis, and diaphyses of long bones. There are usually other clues for the diagnosis of multiple myeloma such as hyperproteinaemia, and radiographic lesions that are almost entirely lytic usually attend both multiple myeloma and lymphoma of bone. The classic radiographic appearance of myeloma bone lesions are described as "punched-out" areas of lysis.

Systemic mycoses with tendency for bone localization are caused by either *Coccidioides immitis* or *Blastomyces dermatitidis*. These are soil borne organisms found in certain locations in North America (the southwest for coccidioidomycosis and the Mississippi, Missouri, and Ohio River valleys and mid-Atlantic states for blastomycosis), Mexico and Central and South America. Dogs are infected through the respiratory tract or, rarely, from contamination of open wounds. Dogs from endemic areas are at risk and a travel history to such areas is cause for increased suspicion. There is usually a history of respiratory signs six weeks or more prior to the development of bone lesions. There may be radiographic evidence of pulmonary disease although this is more common in the acute phase of the infection. Hilar lymphadenopathy may persist in the chronic or disseminated form and the lung lesions do not usually resemble metastatic cancer nodules. The radiographic appearance of the osteomyelitis caused by these fungal organisms is predominantly of productive and blastic changes in the distal diaphyses, metaphyses, epiphyses or, rarely, in the axial skeleton. Serology may be helpful but is rarely definitive and diagnosis depends on identification of the organisms from histological evaluation of biopsy tissue. An unusual fungal infection that may localize in bone is disseminated aspergillosis caused by *Aspergillus terreus*. This infection is thought to arise because of immunosuppression but predisposing causes have not been identified in infected dogs. Most affected dogs are young to middle aged German shepherds. One dog was reported to be infected with *Aspergillus fumigatum*. These dogs may have lameness, spinal pain, weight loss, inflammatory ocular disease, diskospondylitis, pyrexia, weakness or any combination. Fungal hyphae may be identified in the urine sediment and the organism may be cultured from the urine.

The pathogenesis of bacterial osteomyelitis in adult dogs requires pathogenic bacteria to gain access directly to the bone and is usually not a sequel to bacteremia or septicemia. Common history is of recent surgery, or other penetrating injury that carries bacteria directly to the bone. These lesions usually drain purulent material, and sequestra are often seen on radiographs. Fever or changes in the leukogram consistent with infection do not always accompany this diagnosis, especially in chronic cases.

A diagnosis of primary malignant bone tumor may be suggested by signalment, history and physical examination and radiographic findings. However, a definitive diagnosis lies in correct procurement and interpretation of tissue for histopathology. With new treatments such as limb-sparing, knowledge of the specific tumor type may avoid over extensive or inappropriate treatment of bone tumors thought to be osteosarcoma (e.g., chondrosarcoma or lymphoma). It is crucial to the success of a limb-sparing surgery that the biopsy procedure is planned and performed carefully with close attention to asepsis, haemostasis and wound closure. The skin incision for the biopsy must be small and placed so that it can be completely excised with the tumor at limb-sparing without compromising the procedure. Transverse incisions must be avoided. It has been recommended that the surgeon who is to perform the definitive surgical procedure (especially if this is limb-sparing) should be the person to perform the preoperative bone biopsy.

Bone biopsy may be performed as an open incisional, or a closed needle or trephine biopsy. The advantage of the open techniques is that a large sample of tissue is procured, which presumably improves the likelihood of establishing an accurate histological diagnosis. Unfortunately, this advantage is outweighed by the disadvantages of 1) an involved operative procedure, and 2) risk of post surgical complications such as haematoma formation, wound breakdown, infection, local seeding of tumor and pathological fracture. Although closed biopsy with a Michell trephine yields a diagnostic accuracy rate of 93.8%, there is increased risk of creating pathological fracture than with a smaller gauge needle. This underscores some of the advantages of a closed biopsy using a Jamshidi bone marrow biopsy needle or similar type of needle. Jamshidi needle biopsy has an accuracy rate of 91.9% for detecting tumor versus other disorders and an 82.3% accuracy rate for diagnosis of specific tumor subtype.

The biopsy site is selected carefully. Radiographs (two views) are reviewed and the center of the lesion chosen for biopsy. The skin incision is made so the biopsy tract and any potentially seeded tumor cells can be completely removed at the time of definitive surgery. Care is used to avoid major nerves, vessels and joint spaces. A 4-inch 8- or 11-gauge needle is used. With the dog anesthetized, prepared and draped for surgery, a small stab incision (2 to 3 mm) is made in the skin with a #11 scalpel blade. The bone needle cannula, with the stylet locked in place, is pushed through the soft tissue to the bone cortex. The stylet is removed and the cannula is advanced through the bone cortex into the medullary cavity using a gentle twisting motion and firm pressure. The opposite cortex is not penetrated. The needle is removed and the specimen is gently pushed out of the base of the cannula by inserting the probe into the cannula tip. One or two more samples can be obtained by redirecting the needle through the same skin incision so that samples of the transition zone may also be obtained. Ideal specimens should be 1 or 2 cm in length and not fragmented. Biopsy is repeated until solid tissue cores are obtained. Material for culture and cytology may be taken from the samples prior to fixation in 10% neutral buffered formalin. Diagnostic accuracy is clearly improved when a pathologist thoroughly familiar with bone cancer evaluates samples. After tumor

removal (amputation or limb-sparing) histology should be performed on a larger specimen to confirm the preoperative diagnosis.

Examination for evidence of apparent spread of the disease is important. Regional lymph nodes should be palpated and fine needle cytology performed on any enlarged node. Sites of bone metastasis may be detected by a careful orthopedic examination with palpation of long bones and the accessible axial skeleton. Organomegaly may be detected by abdominal palpation. Usually pulmonary metastases are undetectable by clinical exam but careful thoracic auscultation is important to detect intercurrent cardiopulmonary disorders. High detail thoracic radiographs should be taken during inspiration with the patient awake, and should include three views: a ventrodorsal view or a dorsoventral view and both right and left lateral views. Osteosarcoma pulmonary metastases are generally soft tissue dense and cannot be detected radiographically until the nodules are 6 to 8 mm in diameter. It is relatively rare to detect pulmonary metastatic disease at the time of diagnosis (less than 5% of dogs). Lung computerized tomography (CT) may increase the number of dogs with detected lung lesions at presentation. Bone survey radiography has been useful in detecting dogs with second skeletal sites of osteosarcoma. Bone surveys include lateral radiographs of all bones in the body and a ventro-dorsal projection of the pelvis using standard radiographic technique appropriate for the region radiographed. One hundred and seventy-one dogs with primary bone tumors underwent radiographic bone surveys and thoracic radiography in one study. The findings were that, at presentation, there was a higher yield in finding other sites of OS with radiographic bone survey (6.4%, 11 of 171 dogs) than with thoracic radiographs (4%, 7 of 171 dogs). There are conflicting reports on the usefulness of nuclear scintigraphy (bone scan) for clinical staging of dogs with osteosarcomas. Bone scintigraphy was used in one study to identify suspected second bone sites of OS in 14 of 25 dogs with appendicular primaries. Seven of these lesions were biopsied and confirmed to be osteosarcoma. Another study of 70 dogs with appendicular primary bone tumors resulted in only one scintigraphically-detectable occult bone lesion. In a third report, of 23 dogs with suspected skeletal neoplasia that were evaluated with scintigraphy and radiography, 4 dogs had second skeletal sites suspected to be neoplastic. The suspicious site in one of these dogs was found on histological evaluation, to be normal bone. Nuclear bone scan can be a useful tool for the detection and localization of bone metastasis in dogs presenting for vague lameness or signs such as back pain. Nuclear bone scans are very sensitive but not specific for identifying sites of skeletal tumor location. Any region of osteoblastic activity will be identified by this technique including osteoarthritis and infection. Computerized tomography may be useful to plan surgery especially for tumors located in the axial skeleton. Magnetic resonance imaging can also be used to stage local disease. This is a valuable tool to determine the extent of the soft tissue component of the tumor especially within the medullary canal and in the soft tissue outside the cortex.

A surgical staging system for sarcomas of the skeleton has been devised for people. This system is based on the histological grade (G), the anatomic setting of the primary tumor (T) and regional or distant metastasis (M). There are three stages: stage I, the low-grade (G_1) lesions with out metastasis; stage II, the high-grade (G_2) lesions without metastasis; and stage III, the lesion with regional or distant metastasis regardless of histological grade. The stages are subdivided by the anatomic setting, A being intracompartmental (T_1) and B extracompartmental (T_2). According to this system, most dogs with OS present with stage IIB disease.

The patient's overall health status requires careful assessment. Advancing years do not preclude treatment; however, prolonged anesthesia and chemotherapy may not be tolerated in dogs with organ compromise. Particular attention to the cardiovascular system is important. Coexisting cardiomyopathy or any degree of heart failure may lead to serious complications, particularly during fluid diuresis at surgery or during administration of chemotherapy. An electrocardiogram and echocardiogram should be performed on dogs where the history or physical findings implicate a cardiac disorder. Renal function must be evaluated prior to administration of cisplatin. A minimum database should include a complete blood count, platelet count, serum biochemical analysis and urinalysis. For safe administration of cisplatin, dogs should have > 3,000 polymorphonuclear leukocytes per μl , > 150,000 platelets per μl , a normal BUN and creatinine, and urine specific gravity of 1.030, with no proteinuria or casts in the urine sediment.

Therapy and Prognosis

Occult metastatic disease is present in approximately 90% of dogs at presentation and the median survival is only 3 to 4 months if amputation is the only treatment, therefore some form of systemic therapy is necessary if survival is to be improved. With no treatment at all, dogs become very painful because of extensive destruction of bone and surrounding tissue by their primary tumors and most owners elect euthanasia for their pets soon after diagnosis if no treatment is given. In a multi-institutional study of 162 dogs with appendicular OS treated with amputation alone, dogs younger than 5 years of age had worse survival than older dogs. There is no clear cut evidence that any other easily measured variable, other than mandibular site has prognostic significance. Some studies, however, have weakly related large tumor size and humerus location to poor outcome. Large tumor size has been reported to be a negative prognostic factor for people with osteosarcoma. Dogs presented with stage III disease (measurable metastases) have a very poor prognosis.

Adjuvant treatment

Early work to identify treatments for micrometastatic disease with various adjuvant therapies was generally unsuccessful. In a later study, the median survival was 222 days for dogs treated with amputation and intravenously administered liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (liposome/MTP-PE). The agent MTP-PE is a lipophilic derivative of muramyl dipeptide, which is a synthetic analog of a fragment of Mycobacterium cell wall. There is evidence that liposome/MTP-PE can activate macrophages to destroy malignant cells. Although this study showed that liposome/MTP-PE significantly delayed the time to metastasis and prolonged survival when compared to dogs that received empty liposomes, more than 50% of the dogs were dead by 8 months after surgery. In a follow-up study, dogs randomized to liposome/MTP-PE, following 4 doses of cisplatin (70 mg/m² q 4 weeks) had a median survival time of 432 days (14.5 months) versus 291 days (9.7 months) for those dogs receiving 4 doses of cisplatin. The National Cancer Institute is coordinating a national US trial with Children's Cooperative Oncology Group (CCOG) and the Pediatric Oncology Group (POG) using liposome/MTP-PE in combination with chemotherapy in children following surgery.

Cisplatin used either alone or in combination with doxorubicin on an alternating basis has been demonstrated to improve survival in dogs with OS after amputation. In a report of 36 dogs with appendicular OS treated with cisplatin and amputation seventeen dogs (group 1) were treated with

two doses of IV cisplatin 21 days apart, beginning on average 18 days after amputation and nineteen dogs (group 2) were treated at diagnosis with IV cisplatin and received a second dose 21 days later immediately after amputation. The median survival for group 1 was 262 days, with 1- and 2-year survival rates of 38 and 18%. The median survival for group 2 was 282 days, with 1- and 2-year survival rates of 43 and 16%. The survival of dogs receiving two doses of cisplatin was significantly longer than 35 amputation-alone historic control dogs (median survival 119 days, 1- and 2-year survival rates of 11 and 4%). There was no significant difference between the survival of group 1 and group 2. There is a large body of evidence, however, reported in clinical studies of human OS and laboratory studies with rodents which supports perioperative use of chemotherapy. It seems reasonable to recommend the earliest possible administration of chemotherapy, which is usually at the time of amputation. At Colorado State University (CSU), between three and six doses of cisplatin 21 days apart at 70 mg/m body surface area has been safely administered to 191 dogs with OS after amputation or limb-sparing. Some of these dogs also received cisplatin as implanted OPLA-Pt, which is a biodegradable polylactic acid polymer containing cisplatin (unpublished data). The median survival was 392 days with a 1-year survival rate of 52% and a 2-year survival of 31%. An increasing cumulative dose of cisplatin appears to increase the probability for survival (see **Fehler! Verweisquelle konnte nicht gefunden werden.**).

The recommended dose for cisplatin is 70 mg/m body surface area. In one study a single dose of 90 mg/m was given to twelve dogs and there was no apparent nephrotoxicity in the short term. However, myelosuppression and renal toxicity become serious and life-threatening complications as the dose of cisplatin is increased. Saline diuresis helps prevent nephrotoxicity, which is the dose-limiting toxicity in dogs. The protocol recommended is that described by Ogilvie, et al.

Carboplatin is a second generation platinum compound that is less nephrotoxic than cisplatin with apparently similar anti-tumor effects. In a multi-institutional study of 48 dogs with appendicular OS treated with amputation and up to four doses of carboplatin the median disease-free interval was 257 days, the median survival was 321 days, and 35.4% of dogs were alive at one year (see Table 4). One of the advantages with carboplatin is that it can be given intravenously without the saline diuresis necessary for cisplatin administration. The drug can be given at amputation and every 21 days, provided there are no signs of severe bone marrow suppression. The dose recommended for use in dogs is 300 mg/m administered every 3 weeks for four treatments however the maximum tolerated cumulative dose has not been described.

A poor response to adjuvant doxorubicin as a single agent was determined by one report of 16 dogs with osteosarcoma. In that study doxorubicin was given intravenously at a dosage of 30 mg/m every 3 weeks, beginning 3 weeks after surgery. In a more recent study, doxorubicin was given at the same dosage but every two weeks for five treatments to 35 dogs with appendicular OS and surgical excision was performed either 13 days after the second or third treatment with the subsequent treatment given on the day after surgery. The 1- and 2-year survival rates were 50.5 and 9.7% respectively. Why the 2-year survival is so poor is unclear.

There have been several reports of adjuvant chemotherapy protocols for dogs with osteosarcoma. The results of some of these studies appear in **Fehler! Verweisquelle konnte nicht gefunden werden.** It would seem reasonable that combinations of cisplatin, carboplatin and doxorubicin, drugs shown to be efficacious alone, could further improve survival times.

A measure of the effectiveness of chemotherapy may be the percent tumor necrosis measured in the resected tumor specimen if the chemotherapy was given prior to surgery (neoadjuvant chemotherapy). Evaluation of the response of the primary tumor by determining percent necrosis is considered a valuable determinant of the effectiveness of preoperative treatment in people. If the percent tumor necrosis is low, the response is considered inadequate and the postoperative chemotherapeutic regimen is often modified. Percent tumor necrosis was evaluated in resected specimens from dogs with OS treated with various preoperative regimens. Mean percent tumor necrosis was: untreated tumors (n = 94) 27%, radiation therapy alone (n = 23) 82%, two doses of intra-arterial (IA) cisplatin at 70 mg/m/dose (n = 14) 45%, two doses of IV cisplatin at 70 mg/m/dose (n = 6) 24%, two doses of IA cisplatin at 70 mg/m/dose and radiation therapy (n = 45) 82%, and 10 doses of IV cisplatin at 10 mg/m/dose and radiation therapy (n = 8) 78%. There was no significant difference between percent tumor necrosis in untreated osteosarcoma compared to those receiving IV cisplatin alone, but a significant increase in percent tumor necrosis was present in all other groups. Percent tumor necrosis was strongly correlated with local tumor control after limb-sparing, as 91% of dogs with > 90% tumor necrosis had local control, while 78% of dogs with 80 to 89% tumor necrosis had local tumor control and only 30% of dogs with > 79% tumor necrosis had local control. Since those dogs with radiation as part of their preoperative treatments had higher mean percent tumor necrosis, radiation in combination with chemotherapy may still play a role in the local preoperative management of osteosarcoma. Percent tumor necrosis in resected primary tumors from dogs with OS treated with intravenous doxorubicin ranged from 0 to 87% (mean, 24.9%) in one report. Interestingly there was a significant direct correlation between survival time and percent necrosis in that study.

A drug delivery system has been developed which can release a very high dose of chemotherapy into a surgical wound and cause slow release of relatively low concentrations of chemotherapy systemically. The system is a biodegradable polymer called open cell polylactic acid containing cisplatin (OPLA-Pt). When OPLA-Pt was implanted in normal dogs no systemic toxicity and no impediment of cortical allograft healing was identified at doses of up to 80.6 mg/m. Serum pharmacology data revealed approximately a 30 fold increase in area under the curve (AUC) for systemic platinum exposure compared to a similar dose of intravenous cisplatin. Local wound concentrations of platinum are up to 50 times those achievable from a single intravenous dose. This drug delivery system may potentially be important to the control of microscopic local cancer after limb sparing because very high doses of cisplatin can be delivered to the tumor bed after incomplete surgical removal. Also the control of microscopic distant disease may be achieved because cisplatin escapes from the implanted device to the circulation for an extended period of time. Thirty nine dogs with stage IIB, appendicular OS were treated with amputation and one dose of OPLA-Pt implanted in the muscles of the amputation stump at the time of surgery. The median survival was 240 days and the 1-year survival rate was 41.2% (see Table 4). This is at least equivalent to the improvement in survival probability when two intravenous doses of cisplatin are used with amputation. We are now investigating the effect of repeated doses of slow release chemotherapy for control of micrometastatic cancer in the canine OS amputation model.

Surgery

Amputation of the affected limb is the standard treatment for canine appendicular osteosarcoma. Even large and giant breed dogs can function well after limb amputation and most owners are pleased with their pets' mobility and quality of life after surgery. Severe preexisting orthopedic or neurological conditions may cause poor results in some cases and careful preoperative examination is important. With no treatment dogs experience increasing pain from the primary tumor site. Surgery alone must be considered palliative for osteosarcoma. After surgery alone euthanasia is usually requested by owners when their dogs become symptomatic for metastatic disease.

Although most dogs function well with amputation, there are some dogs where limb-sparing would be preferred over amputation, such as dogs with severe preexisting orthopedic or neurological disease, very large dogs, or dogs with owners who absolutely will not permit amputation. Until recently, only a few reports of limb-sparing in dogs, with limited follow-up, have appeared in the literature. More than 200 limb-sparing procedures have been performed at CSU through September, 1994. Limb function has been good to excellent in most dogs and survival has not been adversely affected by removing the primary tumor with marginal resection as compared to radical margins, as with amputation.

Suitable candidates for limb-sparing are dogs with osteosarcoma clinically and radiographically confined to the leg, where the primary tumor affects < 50% of the bone determined radiographically and dogs that are in otherwise good general health. Most dogs treated at CSU with limb-sparing received either some form of preoperative treatment, (IA cisplatin, IV cisplatin, radiotherapy to the tumor bone, or a combination of radiotherapy with IV or IA cisplatin) or OPLA-Pt implantation at surgery. Most dogs had cisplatin given intravenously after surgery. Results from 21 dogs treated with radiation therapy alone given in large doses per fraction prior to limb-sparing were unsatisfactory for preservation of life or limb. Many of the dogs treated with preoperative IA cisplatin on two occasions 21 days apart, with the last treatment 21 days prior to surgery, showed marked decrease in the degree of vascularization of the tumor. This usually represented a high degree of induced tumor necrosis in the resected specimen, especially when combined with radiation therapy, and facilitated limb sparing.

The most suitable cases for limb-sparing are dogs with tumors in the distal radius or ulna. Dogs with tumors in proximal humeral sites may also be potential limb-sparing candidates. Dogs with tumors located in the distal tibia are not as suitable, since the infection rate is high in these dogs due to minimal soft tissue coverage. Tumors located in the proximal tibia or distal femur present special problems, since it is usually impossible to save the knee joint. Dogs with limb-sparing and stifle arthrodeses generally have poor function. Preservation of knee function using osteochondral allografts has been attempted in three dogs. In one dog with a small chondrosarcoma of the medial femoral condyle, a hemicondylectomy was performed, with reconstruction with an osteochondral allograft. This dog had excellent function for 8.5 months, at which time euthanasia was performed because of symptomatic pulmonary metastases. In one dog, a distal femoral OS was removed and the distal femur was replaced with an osteochondral allograft. This dog had only fair function and died due to metastatic disease 5 months after diagnosis. The lateral half of the proximal tibia with half of the tibial plateau was removed from a dog with chondrosarcoma. The tibia was reconstructed with an osteochondral allograft and OPLA-Pt was implanted. This dog is alive, free of measurable cancer and has excellent function 3 years after surgery.

Limbsparing is a complicated process and requires a supply of allografts (bone bank) and, more importantly, a coordinated team effort between surgical and medical oncologists, radiologists, pathologists and technical staff. A description of the surgery follows. Second-generation cephalosporin antibiotics are administered IV immediately preoperatively, intraoperatively and for 24 hours postoperatively. Meticulous aseptic technique is used.

For a distal radial site, the dog is placed in lateral recumbency, with the affected limb uppermost. A skin incision is made on the dorsolateral aspect of the antebrachium from a point just distal to the elbow, to just proximal to the metacarpophalangeal joint. Any biopsy tracts are excised *en bloc*. Soft tissue is dissected to the level of the tumor pseudocapsule. Care is taken not to enter the tumor. The bone is cut with an oscillating bone saw 3 to 5 cm proximal to the proximal radiographic margin of the tumor. The *extensor carpi radialis muscle* is transected and the distal part of this muscle and its tendon are removed with the tumor. The common digital extensor tendon usually is closely involved with the tumor pseudocapsule, and it is usually transected proximal and distal to the tumor, and also removed with the mass. The distal margin is usually at the level of the radiocarpal joint. The joint capsule is incised, keeping close to the proximal row of carpal bones. The ulna is sectioned sagittally with an osteotome and the medial ulnar cortex adjacent to the tumor is removed en bloc with the radius. For tumors that have extension to the ulna, the ulna is also cut with a bone saw and the distal 1/3 or more is removed with the tumor. Care is taken to preserve as much vasculature as possible, especially on the palmar surface. Large vessels associated with the tumor are ligated and divided. Surgical haemostatic staples are very useful. The specimen is radiographed, then submitted for histological evaluation, including assessment of completeness of surgical margins and percent tumor necrosis.

A fresh-frozen cortical allograft is thawed in 1 liter of an antibiotic in saline solution, the articular cartilage is removed, the graft is cut to fit, and the medullary cavity reamed to remove fat and cellular debris. The articular cartilage of the proximal carpal bones is removed and the allograft is stabilized in compression using Association for the Study of Internal Fixation (ASIF/AO) principles. A dynamic compression plate with a minimum of three screws proximal and four screws distal to the graft is used; 3.5 mm broad plates of up to 22 holes size are appropriate in most cases but for very large dogs 4.5 mm narrow or broad plates are selected. The plate is fastened in the patient to the allograft with two or three screws, removed from the surgery site, and the medullary canal of the allograft is filled with polymethyl methacrylate bone cement containing amikacin (1 g amikacin to 40 g of polymer powder). This provides support for the screws during revascularization of the graft and acts as a reservoir for antibiotics. The healing of the allograft is not significantly impeded by the presence of the cement. The plate extends proximally in the host radius for at least 3 screws and distally to a level just proximal to the metacarpophalangeal joint.

The wound is thoroughly lavaged with saline and it is at this point that OPLA-Pt may be implanted. A closed suction drain is inserted adjacent to the allograft and the wound is closed. The leg is supported in a padded bandage. The drain is removed the day after surgery in most cases. It is most important to prevent self-mutilation (licking) after surgery and Elizabethan collars should be used as necessary. No external coaptation is used and most dogs use the limb fairly well by 10 days after surgery. Postoperative swelling can be considerable but usually resolves by 2 weeks. Although decreased exercise is recommended for the first 3 to 4 weeks to allow soft tissues to heal, no exercise

restriction need apply after this time. In fact, it is important that limb use is encouraged even in early postoperative times so that flexure contracture of the digits does not occur.

The principles of resection are the same for other sites; however, because of abundant soft tissue in the area, wider margins are often attained with proximal humerus resections. Proximal humerus resections are, however, more difficult, and limb use immediately following surgery is usually poor but improves to good but rarely excellent over about 1 to 2 months. The allograft selected for reconstruction of proximal humeral defects can be a distal femur from the opposite side. The femoral allograft is placed so that the medial condyle sits in the glenoid and the femoral diaphysis contacts the distal humerus with the caudal part of the allograft facing cranially. That is the femur is placed up-side-down and back-to-front. The plate then extends from the dorsocranial side of almost the entire length of the scapular spine to cover the dorsal aspect of the humerus with the allograft in compression and scapulohumeral arthrodesis is performed. Vigorous physiotherapy is important after surgery in these dogs.

There is no significant difference in survival rates for dogs treated with amputation and cisplatin compared to dogs treated with limb-sparing and cisplatin. Overall, limb function has been satisfactory, with approximately 80% of dogs experiencing good to excellent limb function.

Limb-sparing requires a dedicated owner and clinical team. Complications can arise in any or all phases of treatment (chemotherapy, radiation, or surgery). Serious complications as a direct result of chemotherapy (e.g., sepsis and renal failure) are extremely rare. High dose radiation therapy may complicate wound and allograft healing and potentiate allograft infection. Moderate dose radiation in combination with chemotherapy may, however, be useful for control of local disease, as indicated by percent tumor necrosis data. The major complications related mainly to surgery are recurrent local disease and allograft infection. In the first 200 dogs that have had limb-sparing surgeries performed at CSU, the one-year local recurrence free rate determined by Kaplan-Meier life tables was 76.3%. Local disease control was improved with certain treatments such as pretreatment with moderate doses of radiation and intra-arterial cisplatin. When OPLA-Pt was implanted at the time of tumor removal the one-year local recurrence free rate was 89.9%. Some dogs had their locally recurrent disease resected *en bloc* and remained disease-free for an extended period. Eighty eight dogs (40%) developed allograft infections. The majority had their infections adequately controlled with systemic antibiotics with or without local antibiotics (antibiotic-impregnated polymethyl methacrylate beads). Many of these dogs continued to have evidence of infection; however, their function was not severely affected by it. In severe and uncontrolled infections allografts had to be removed and a small number of dogs required amputation. An unexpected finding was that dogs with allograft infections were twice as likely to survive compared to dogs with limb-sparings without infected allografts. The reason for this is unclear but could be related to activation of immune effector cells and a response to cytokines, such as interleukins or tumor necrosis factor, elaborated in the face of chronic bacterial infection.

Bone tumors originating in proximal sites of the scapula can be successfully removed by partial scapulectomy. Dogs function well with partial scapulectomy; however gait abnormalities may occur after scapulectomy by disarticulation at the scapulohumeral joint. Mandibulectomy and maxillectomy are appropriate surgeries for bone tumor primaries of oral sites. Tumors of periorbital sites can be removed by orbitectomy. Rib tumors can be removed by thoracic wall resection and the defect reconstructed with polypropylene mesh with plastic plates for large defects, or by diaphragmatic

advancement for caudally located defects. Small primary tumors of the ulna can be removed by partial ulnectomy, and reconstruction with allografts or bone substitutes may not be necessary. Certain primary bone tumors of the pelvis can be removed by techniques of hemipelvectomy and, although these surgeries are difficult, function and cosmetic outcome have been excellent.

Radiation

The combination of external beam radiation therapy and limb-sparing has been described. It appears that radiation therapy can cause considerable necrosis of primary OS in dogs. Palliative radiation for metastatic bone disease is discussed in the next section, however palliative radiation for primary OS has also been described. This may be a treatment option for dogs with stage III disease at presentation (that is distant metastasis to lung for example) or where the owner does not want to pursue any attempts at permanent local control. Another area where radiation likely plays a role in treating OS in dogs is for OS of vertebrae. At CSU, 14 dogs with spinal OS and 6 dogs with spinal fibrosarcoma were treated from 1986 to 1994. Fourteen of these dogs had surgery to decompress the spinal cord and 9 dogs were treated with OPLA-Pt implanted in a distant intramuscular site and 12 were given intravenous cisplatin. Fourteen dogs were treated with fractionated external beam radiation therapy. All dogs had surgery, radiation therapy or both while no dog was treated with chemotherapy alone. Eight dogs improved neurologically after treatment and seven remained the same. All three dogs presenting with non-ambulatory paraparesis regained ambulatory status after treatment. The median survival after treatment was relatively short, however at approximately 4.5 months.

Metastatic Disease

The usual cause of death in humans and dogs following amputation as the sole treatment for osteosarcoma is diffuse pulmonary metastasis. Resection of pulmonary metastasis from osteosarcoma or other solid tumors has been reported in people. There is a report of 36 dogs treated with pulmonary metastasectomy for osteosarcoma. Lesions located subpleurally were gently lifted from the lung parenchyma by thumb forceps and a single pursestring of 2-0 or 3-0 polygalactan 910 suture was tied around the base of normal tissue. Larger lesions located deeper in the lung parenchyma were removed by complete or partial lobectomy using surgical staples. No chemotherapy was given after these surgeries. Although the initial treatments varied between dogs, the median survival time of the entire group was 487 days. The median survival after pulmonary metastasectomy was 176 days (range 20 to 1495 days). The criteria established for case selection for pulmonary metastasectomy in order to maximize the probability long survival periods are: 1) primary tumor in complete remission, preferably for a long relapse-free interval (> 300 days); 2) one or two nodules visible on plain thoracic radiographs; 4) cancer only found in the lung (negative bone scan); and perhaps 3) long doubling time (> 30 days) with no new visible lesions within this time.

In another study, 45 dogs with measurable metastatic OS were treated with various chemotherapy regimes (cisplatin, doxorubicin, mitoxantrone). Only one dog had a partial remission, which lasted 21 days. All other dogs experienced progressive disease and the median survival time from the time metastatic disease was diagnosed was 61 days (range, 14 to 192 days). Cisplatin, doxorubicin, and mitoxantrone chemotherapy appear to be ineffective for the treatment of measurable metastatic OS in the dog.

A change over recent years in the pattern of metastatic disease in human osteosarcoma has been described. This change is primarily an increase in bone metastases. Possible explanations for this change include: a change in the behavior of this cancer independent of treatment; selective killing of metastatic cancer by chemotherapy in certain sites, such as lung, which allows metastasis in other sites to become clinically relevant; lung resection and chemotherapy have improved survival and bone sites become clinically relevant; more sensitive detection methods which allow previously undetectable metastases to be seen; or, more complete and detailed necropsies compared to those performed previously, which identify asymptomatic metastatic sites. Since the advent of adjuvant chemotherapy with increasing survival times there has been an increase in the number of treated dogs presenting with signs referable to bone metastases. In one report of 35 dogs treated with doxorubicin, 32 dogs were euthanized because of distant metastasis. Approximately one third were euthanized because of bone metastases. Nuclear scintigraphy is a useful way of identifying sites of bone metastasis. For dogs with solitary bone metastases and no evidence of cancer elsewhere metastasectomy may be indicated although the subsequent disease free interval is generally short. An alternative is to treat metastatic bone lesions with palliative radiation. A protocol of three 10 Gy fractions of high energy photons delivered over a three week period on days 0, 7, and 21, for a total dose of 30 Gy has been described for palliative treatment of OS in dogs. A useful and safe protocol used at CSU is a coarse fractionation scheme delivered as high-energy photons at 4.5 Gy per fraction for five consecutive daily fractions to a total dose of 22.5 Gy. Dogs can remain pain free for over 6 months. Unfortunately, the metastatic lesions usually become symptomatic in about 2 to 3 months after radiation. A second course using the same fractions has been successful for further temporary pain relief in a few dogs. For short term pain control, the nonsteroidal anti-inflammatory drug, piroxicam may be given at 0.1 to 0.4 mg/kg daily for 3 to 5 days then every 48 hours. This appears to give temporary pain relief to most dogs with OS lesions. Dogs must be carefully monitored for signs of gastrointestinal toxicity and the drug withdrawn if these signs occur. Corticosteroids must not be administered at the same time because this combination can predispose to the development of gastric or duodenal ulceration. It is also not advisable to give corticosteroids or piroxicam concurrently with cisplatin or in dogs with decreased renal function. There has been some work that suggests feldene may have some anti-tumor effects. Radiopharmaceuticals (such as strontium-90), bisphosphonates, diphosphonates and other compounds have been used to palliate pain from metastatic bone cancer in people. Samarium-153-ethylenediamine-tetramethylene-phosphonic acid (Sm-EDTMP) is a radiopharmaceutical that has been used to treat metastatic and primary bone tumors in dogs. In both normal beagle dogs and in tumor bearing dogs, Sm-EDTMP caused transient bone marrow depression (for approximately 4 weeks) of all cell lines.

Comparative Aspects

Animal models for the study of human diseases are important to our understanding of the mechanism and etiology of disease and for the development and refinement of therapeutic strategies. Spontaneously developing diseases in animal populations are particularly useful for study. Canine osteosarcoma has many similarities to human osteosarcoma and can serve well as a valuable comparative model for study (see Table 5). Osteosarcoma is more common in dogs than humans; therefore, case accrual can be rapid in dogs. Since disease progression is more rapid in dogs than humans, results of treatment protocols can be reported earlier than would those of similar trials in humans. Research costs are less for clinical trials in dogs compared to those in human clinical trials

and, from an animal welfare standpoint, no disease is induced and dogs with cancer can be helped through the course of the research.

Osteosarcoma is an uncommon cancer of humans affecting mainly children in their second decade of life and it remains a very serious, aggressive solid tumor. Fortunately there has been a great improvement in survival rates with the use of established multi-drug adjuvant protocols. Some centers boast five-year survival rates of 80-90% which contrasts to the 20% expected five-year survival rates of 15 years ago. Limb sparing programs are becoming more common and many survivors of OS retain functional, pain-free limbs.

2. Bone surface osteosarcoma

Osteosarcoma usually originates from elements within the medullary canal of bones (intraosseous-OS) however there are forms of this cancer that originate from the outside surface of bones. Periosteal OS is a high-grade form of surface OS and seems to arise from the periosteal surface but has invasive characteristics seen radiographically. There is cortical lysis with extension of the tumor into the bone and surrounding soft tissues. These tumors are histologically similar to intraosseous OS and have similar aggressive biological behavior. Parosteal OS, or juxtacortical OS, arises from the periosteal surface of bones but appear less aggressive than periosteal OS both radiographically and in terms of biological behavior. Parosteal osteosarcomas are relatively uncommon and have a moderately well circumscribed radiographic appearance. The tumors grow out from the periosteal side of a cortex and cortical lysis is usually very mild if apparent at all on radiographs. Histologically these tumors look more benign compared to intraosseous or periosteal-osteosarcoma. These tumors contain well-differentiated cartilage, fibrous tissue and bone with sparse regions of sarcoma cells adjacent to tumor osteoid. Histological specimens must be evaluated carefully because it is often easy to miss the areas of tumor cells and misdiagnose the lesion as osteoma, chondroma or reactive bone. These tumors generally do not invade the medullary canal and tend to grow out from the bone on broad pedicles. Diagnosis is based on typical histological and radiographic findings.

Parosteal OS is usually slow growing but can induce pain at the local site. Metastases can occur but the prognosis for survival is much better than for intra-osseous osteosarcoma. Control of parosteal OS can be achieved by en bloc resection of the tumor with the adjacent cortical bone. This has been reported for tumors of the zygomatic arch. If the full thickness cortex needs to be removed for tumors on long bones, reconstruction may be performed using autogenous corticocancellous bone such as a rib or ilial crest or allogeneic cortical bone. The margins of resection must be carefully evaluated for signs of tumor infiltration. Extension of malignant cells up to the cut edge signifies the need for either further surgery (removal of more cortical bone with the entire previous surgical field or limb amputation) or perhaps adjuvant radiation or chemotherapy.

3. Multilobular osteochondrosarcoma

Multilobular osteochondrosarcoma (MLO) is an uncommon tumor that generally arises from the skull of dogs. Many names have been used to describe this disease including chondroma rodens and multilobular osteoma. These tumors have a characteristic radiographic appearance: generally the

borders of the tumor are sharply demarcated with limited lysis of adjacent bone and there is a coarse granular mineral density throughout. Histologically these tumors are composed of multiple lobules each centered on a core of cartilaginous or bony matrix that is surrounded by a thin layer of spindle cells. A histological grading system has been described. These tumors have the potential to recur locally following incomplete resection and metastasis can occur. In one report the average age of affected dogs was 7.5 years and there was no breed or sex predilection. A little over half the dogs developed metastases after treatment with a median time to metastasis of 14 months. The median survival time was 21 months. Local tumor recurrence and metastasis after treatment appears to be partially predicted by histological grade. When metastatic lesions are identified by thoracic radiography, dogs may remain asymptomatic for their lung disease for up to one year or more. Local tumor excision with histologically complete surgical margins appears to offer good opportunity for long-term tumor control. The role of chemotherapy and radiation therapy in the management of MLO is not well defined.

4. Other primary bone tumors of dogs

It can be difficult to distinguish chondroblastic osteosarcoma from chondrosarcoma and fibroblastic osteosarcoma from fibrosarcoma and telangiectatic osteosarcoma from haemangiosarcoma when only small amounts of biopsy tissue are evaluated. This makes interpretation of older reports difficult in terms of trying to establish the true incidence of the different types of primary bone tumors. This also underscores the importance of evaluating the entire excised specimen to validate the preoperative biopsy. All too often a bone malignancy thought to be relatively low grade from preoperative biopsy is up-graded to a true OS once the histology of the surgical specimen is reviewed. This changes both the prognosis and post surgical treatment plan. Primary bone tumors other than OS make up somewhere between 5 and 10% of bone malignancies in dogs. These tumors are chondrosarcomas, haemangiosarcomas and fibrosarcomas.

CHONDROSARCOMA

Chondrosarcoma (CS) is the second most common primary tumor of bone in humans and dogs and accounts for approximately 5-to10% of all canine primary bone tumors. Anaplastic cartilage cells that elaborate a cartilaginous matrix characterize chondrosarcomas histologically. There is a spectrum of degree of differentiation and maturation of the cells within and between each tumor. Histological grading systems have been devised. The etiology is generally unknown although CS can arise in dogs with multiple cartilaginous exostosis. In a recent clinicopathological study of 97 dogs with CS the mean age was 8.7 years (range, one to 15 years) and golden retrievers were at a higher risk of developing CS than any other breed. There was no sex predilection and 61% of the tumors occurred on flat bones. Chondrosarcoma can originate in the nasal cavity, ribs, long bones, pelvis, extraskeletal sites (such as the mammary gland, heart valves, aorta, larynx, trachea, lung and omentum), vertebrae, facial bones, digits and *os penis*. The nasal cavity is the most common site for canine chondrosarcoma.

Chondrosarcoma is generally considered to be slow to metastasize. Tumor location rather than histological grade was prognostic in one study, however histological grade was found to be important for predicting survival for tumors of the same anatomical site of origin. The reported median survival

of dogs with nasal CS ranges from 210 days to 510 days with treatments various treatments (radiation therapy, rhinotomy and radiation therapy and rhinotomy alone). Clinical signs were present for a long time, up to one year, before treatment in one study. Metastatic disease is not a feature of nasal CS in dogs. The reported median survival for dogs with CS of ribs varies widely. Reports prior to 1992 contained few cases that were treated with intent to cure but 15 dogs with rib CS treated with *en bloc* resection in a recent study had a median survival of 1080 days. The median survival for dogs with CS of long bones was 201 days in one report of 7 dogs treated with amputation with or without adjuvant chemotherapy and 540 days in another study of 5 dogs treated with amputation alone. Death was usually associated with metastatic disease. A reliable adjuvant chemotherapeutic agent is not known for canine chondrosarcoma.

HAEMANGIOSARCOMA

Primary haemangiosarcoma (HS) of bone is rare and probably accounts for less than 5% of all bone tumors. This disease generally affects middle-aged to older dogs and can occur in dogs of any size. This is a highly metastatic tumor and virtually all dogs affected will develop measurable metastatic disease within six months of diagnosis. Metastases can be widely spread throughout various organs such as lungs, liver, spleen, heart, skeletal muscles, kidney, brain, and other bones. Dogs can present with multiple lesions making it difficult to determine the site of primary disease. Histologically, HS is composed of highly anaplastic mesenchymal cells, which are precursors to vascular endothelium. The cells are arranged in chords separated by a collagenous background and may appear to be forming vascular channels or sinuses. Cellular pleomorphism and numerous mitotic figures are features of this highly malignant disease. There is profound bone lysis and the malignant cells aggressively invade adjacent normal structures. The lesion however may be confused with telangiectatic osteosarcoma especially if the diagnosis is based on small tissue samples. Often the dominant radiographic feature is lysis however HS does not have an unequivocally unique radiographic appearance and diagnosis is based on histopathology.

If HS is diagnosed, the dog must be thoroughly staged with thoracic and abdominal films, bone survey radiography or bone scintigraphy and ultrasonographic evaluation particularly of the heart and abdominal organs. Right atrial HS may be present without clinical or radiographic signs of pericardial effusion. The prognosis is very poor and even dogs with HS clinically confined to one bony site have less than a 10% probability of surviving one year if the tumor can be completely excised. Cyclophosphamide, vincristine and doxorubicin have been used in combination as an adjuvant protocol and the reported median survival for dogs with non-skeletal HS is 172 days. Doxorubicin as a single agent adjuvant seems to be as effective as the combination of drugs with some long-term survivors although the overall survival prognosis is still poor.

FIBROSARCOMA

Primary fibrosarcoma (FS) is also a rare tumor of dogs and probably accounts for less than 5% of all primary bone tumors of dogs. Unfortunately, the difficulty in distinguishing FS from fibroblastic OS histologically (especially from small tissue samples) renders study of this tumor difficult. In a recent study 11 dogs thought to have FS were studied. On re-evaluation of complete resection specimens the histological diagnosis was changed to OS in 6 dogs. Histological characteristics of FS have been described as interwoven bundles of fibroblasts within a collagen matrix permeating cancellous and cortical bone but not associated with osteoid produced by the tumor cells. Host bone derived new bone can be seen, however, especially at the periphery of the tumor.

Complete surgical resection of the primary lesion is recommended for dogs with FS clinically confined to the primary site. This treatment may be curative although metastatic potential may be considerable. There is no good evidence that adjuvant chemotherapy is of any benefit in preventing metastatic disease. It has been postulated that primary FS of bone has a propensity to metastasize to such sites as heart, pericardium, skin and other bones rather than lung.

5. Metastatic tumors of bone

Almost any malignant tumor with the capacity to metastasize can spread to bone via the haematogenous route. The lumbar vertebrae and the pelvis are common sites for cancer spread possibly because these are predilection sites for bone metastasis from the common urinogenital malignancies such as prostate, bladder, urethral and mammary cancer. Metastatic lesions in long bones frequently affect the diaphysis probably because of the proximity to the nutrient foramen. Nuclear scintigraphy is a very sensitive technique to detect bone metastasis. A whole skeleton bone scan is recommended when metastatic bone cancer is suspected because it is common for there to be multiple sites of bone metastasis even if the patient is symptomatic for tumor in only one bone.

6. Benign tumor of bone

OSTEOMAS

Osteomas are benign tumors of bone. Radiographically these are well-circumscribed dense bony projections, which are usually not painful to palpation. Histologically they are composed of tissue almost indistinguishable from reactive bone. The diagnosis is made after considering physical exam, radiographic and histological findings. The most important differential diagnosis is MLO when the lesion occurs on the skull. Treatment for osteoma is simple surgical excision, which is usually curative.

MULTIPLE CARTILAGINOUS EXOSTOSES

Multiple cartilaginous exostoses (MCE) are considered a developmental condition of growing dogs. There is evidence that the etiology of this condition may have a heritable component. The actual incidence of MCE is difficult to determine since affected dogs may show no signs and the diagnosis is often incidental. Lesions occur by the process of endochondral ossification when new bone is formed from a cartilage cap analogous to a physis. Lesions are located on bones that form from endochondral ossification and lesions stop growing at skeletal maturity. Malignant transformation of MCE lesions has been reported but generally they remain as unchanged, mature, bony projections from the surface of the bone from which they arose.

Dogs typically are presented because of a moderately painful palpable mass on the surface of a bone or bones. The pain and lameness is thought to be due to mechanical interference of the mass with the overlying soft tissue structures. Radiographically there is a bony mass on the surface of the affected bone that has quite a benign appearance with fine trabecular pattern in the body of the mass. To obtain a histological diagnosis, biopsy material must be collected so sections can include the cartilaginous cap and the underlying stalk of bone. Histologically this cartilaginous cap gives rise to an orderly array of maturing bone according to the sequence of endochondral ossification. The

cortical bone surfaces of the mass and the adjacent bone are confluent. A strong presumptive diagnosis is made by evaluation of the physical findings, history and radiographic findings.

Treatment involves conservative surgical excision but this is only necessary if signs do not abate after the dog is skeletally mature. Because of the likelihood of a heritable etiology, affected dogs should not be bred. Owners should also be advised of the possibility of late malignant transformation. Dogs with a previous history of MCE should be carefully evaluated for bone malignancy if signs return later in life.

BONE CYSTS

Cysts are rare, benign lesions of bone. Affected animals are often young and present because of mild or moderate lameness however pathological fracture can occur through cystic areas of long bones leading to severe lameness. There appears to be a familial tendency in Doberman Pinschers and Old English Sheepdogs. The majority of the veterinary literature pertaining to bone cysts centers on several small series of cases or single case reports. The nomenclature in various reviews of canine bone cysts is confusing. By definition, a cyst is a fluid-filled sac lined by epithelium. The only true cyst of primary intraosseous origin is a simple bone cyst (SBC, or unicameral bone cyst). These lesions are usually in metaphyseal regions of long bones and they can adjoin an open growth plate. Sometimes, however, unicameral bone cysts can be diaphyseal or epiphyseal. Neither the etiology nor the pathogenesis is known but it is speculated that the lesions may be the result of trauma to the growth plate interfering with proper endochondral ossification. Others have theorized that with the rapid resorption and deposition of bone occurring in the metaphysis of a young animal, a cyst might develop if resorption is so rapid that a focus of loose fibrous tissue forms. The focus of fibrous tissue may then obstruct the thin walled sinusoids causing interstitial fluid to build up and form a cyst. The theory, which appears to be at least partially substantiated, is the synovial "rest" thesis. It is suggested that during fetal development a "rest" of synovial or presynovial tissue becomes misplaced or incorporated into the adjacent osseous tissue. If this tissue remains or becomes functional then by the effect of synovial secretion a cyst would develop in the bone. Cysts have been described to occur in bone just below articular cartilage (subchondral bone cysts or juxtacortical bone cysts). In these it has often been possible to demonstrate direct communication with the articular synovial membrane. Malignant transformation of SBC is not known to occur in small animals although there has been one documented case in a human patient. Radiographically, SBC are single or, more commonly, multilocular, sharply defined, centrally located, radiolucent defects in the medullary canal of long bones. Variable degrees of thinning of the corteces with symmetrical bone "expansion" is often a feature of the radiographs. The diagnosis cannot however, be reliably made from interpretation of radiographs. Lytic OS can be misdiagnosed as SBC. Diagnosis of a SBC relies on the histological finding of a thin fibrous wall lined by flat to slightly plump layers of mesothelial or endothelial cells. Treatment consists of meticulous curettage and packing the space with autogenous bone graft.

Aneurysmal bone "cysts" (ABC) are spongy, multiloculated masses filled with free flowing blood. The walls of an ABC are rarely lined by epithelium and the lesion is probably an arteriovenous malformation. A proposed pathogenesis of ABCs is that a primary event such as trauma or a benign bone tumor occurs within the bone or periosteum. This event disrupts the vasculature resulting in a rapidly enlarging lesion with anomalous blood flow, which damages the bone mesenchyme. The bone reacts by proliferating. As the vascular anomaly becomes stabilized the reactive bone becomes

more consolidated and matures. It is important to differentiate these lesions from OS or other malignant lesions of bone. The age of affected dogs ranges from 2 to 14 years. Treatment can be achieved by *en bloc* resection and reconstruction, but extensive curettage with packing of the defect with autogenous bone graft can be effective. Cryosurgery has also been recommended.

7. Primary bone tumors of cats

Incidence and risk

Cancer involving bones of cats is rare. An estimate of the incidence of all bone tumors in cats is 4.9 per 100,000. Anywhere between 67 to 90% of bone tumors in cats are histologically malignant and tumors occur in long bones approximately twice as often as in axial skeleton sites and the hind limbs are affected nearly twice as often as the front limbs. Osteosarcomas account for 70 to 80% of all primary malignant cancer of cats. The disease in cats differs from dogs in that the primary lesions occur more often in hindlimbs in cats and the disease is far less metastatic than in dogs. Osteosarcoma generally affects older cats (mean 10.2 years) but the age range of reported cases is large, 1 to 20 years. In one study males outnumbered females but the opposite was found in a second study. Osteosarcoma was reported to arise after a limb fracture was repaired with an intramedullary pin in one cat. A case of suspected radiation induced osteosarcoma has been reported in a cat.

Multiple cartilaginous exostosis, (MCE), is a disease which occurs after skeletal maturity in cats. This is in contrast to dogs where exostoses develop before closure of growth plates. Also, in contrast to dogs, the lesions seldom affect long bones, are rarely symmetric and are probably of viral rather than familial origin. There does not appear to be any breed or sex predisposition although early reports of this condition were in the Siamese. Affected cats range in age from 1.3 to 8 years (mean 3.2 years). Virtually all cats with multiple cartilaginous exostosis will test positive for the FeLV virus. This disease is included in the discussion of primary bone tumors because of its aggressive natural behavior.

Pathology and Natural Behavior

Osteosarcoma of cats is composed of mesenchymal cells embedded in malignant osteoid. There may be a considerable amount of cartilage present and osteoid may be scant. A feature of some feline OS cases is the presence of multinucleate giant cells, which may be numerous. Reactive host bone and remnants of host bone are often present in specimens. Tumors are seen to be invasive however some surrounding soft tissue may be compressed rather than infiltrated. There is often variation of the histological appearance within the tumor with some portions having more fibrosarcomatous appearance and others more cartilaginous and so on. Some authors have described subtypes that resemble those seen in dogs; chondroblastic, fibroblastic, and telangiectatic as well as the giant cell variant. These features however do not appear to confer any prognostic predictive value. Osteosarcomas in cats can be of the juxtacortical type.

In cats with OS of a limb where there are no clinically detectable metastatic lesions, amputation alone may be curative. In one study of 15 cats, the median survival after amputation alone was 24 months. The metastatic potential is much less than for the same disease in dogs or humans.

Osteochondroma may occur singly in cats but there is a form, which is multicentric (osteochondromatosis). The lesions are composed of hard, irregular exostoses having a fibrous and cartilaginous cap. Endochondral ossification occurs from the cartilage cap, which extends to a variable thickness. This cap tends to blend with adjacent tissue making its surgical removal difficult. Cats usually develop multiple sites of disease and there is a potential for malignant transformation and metastasis. The presence of FeLV virus is also foreboding for these cats.

History and Clinical Signs

The most common signs of OS are deformity and lameness depending on the location of the lesion. The lesions may appear radiographically similar to the OS in dogs however some cats have lesions arising from the periosteal surface (juxtacortical OS). It is very rare for cats to have metastatic osteosarcoma.

Cats with multiple cartilaginous exostosis have rather rapidly progressing, conspicuous, hard swellings over affected sites causing pain and loss of function. Common sites for lesion development are the scapula, vertebrae, and mandible however any bone can become affected. Radiographically the lesions are either sessile or pedunculated protuberances from bone surfaces with indistinct borders with the normal bone. There may be a loss of smooth contour with evidence of lysis particularly if there is malignant transformation.

Diagnostic Workup

Both OS and MCE may be suspected by the radiographic appearance of the lesions and the FeLV status of the cat. Definitive diagnosis is made by histopathological evaluation of properly collected biopsy tissue.

Therapy and Prognosis

For OS of a limb, amputation is recommended. No adjuvant therapy is known to be efficacious and without adjuvant treatment the median survival of cats with OS is two years.

Cats with MCE have a guarded prognosis. Lesions may be removed surgically for palliation however local recurrences are common or new, painful, debilitating lesions may occur. No reliably effective treatment is known for this condition in cats.

Other primary bone tumors of cats

Fibrosarcoma is the second most common primary bone tumor of cats. Chondrosarcoma is reported to be next in terms of frequency and haemangiosarcomas rarely involve bones of cats. Little is known about the biological behavior of these rare lesions however metastases have been seen in cats with chondrosarcoma and hemangiosarcoma.

TABLES

Table 3 Table showing survival data for dogs with OS treated with amputation or limb sparing with varying total cumulative doses of cisplatin.

NUMBER OF DOGS STUDIED	NUMBER OF DOSES OF CISPLATIN AT 70mg/m	MEDIAN DISEASE FREE INTERVAL (Days)	MEDIAN SURVIVAL (Days)	% 1-YEAR SURVIVAL
117	2	229	280	41.3
40	4	244	414	51.8
12	6	392	392	55.6

Table 4 Table showing commonly used adjuvant chemotherapy agents and the survival outcome for dogs with osteosarcoma where amputation has been performed.

DRUG	DOSE REGIME & # DOGS	DISEASE FREE	SURVIVAL	COMMENTS
Cisplatin	70 mg/m IV on two occasions, every 21 days. n = 26	median 177-226 days	38-43% at 1 year, 16-18% at 2 years median 262-282 days	No significant difference between survival data for dogs given cisplatin before amputation compared to those treated after amputation.
Cisplatin (some dogs treated with limb sparing)	60 mg/m IV on 1 to 6 occasions, every 21 days n = 22	not reported	45.5% at 1 year, 20.9 at 2 years median 325 days	Apparent increase in treatment failures due to bone metastases.
Cisplatin	40-50 mg/m IV on 2 to 6 occasions, every 28 days n = 11	median 165 days	median 300 days	.
Cisplatin	50mg/m IV on 2 occasions 2 and 7 weeks after amputation n = 15	not reported	30% at 1 year median 290 days	
Cisplatin	50 mg/m IV on up to 9 occasions, every 28 days n = 16	not reported	62% at 1 year median 413 days	Trend for dogs receiving higher cumulative doses of cisplatin to have long survival times.
Carboplatin	300 mg/m on four occasions every 21 days n = 48	median 257 days	35.4% at 1 year median 321 days	Maximum tolerated cumulative dose has not been described for dogs
Doxorubicin	Doxorubicin at 30 mg/m IV on day 1 and cisplatin	median 210	37% at 1 year	No significant difference was

and cisplatin	at 60 mg/m IV on day 21 cycle repeated once in 21 days n = 19	days	median 300 days	found between survival data from this study and survival data from a single agent cisplatin study
Doxorubicin	30 mg/m on five occasions every 2 weeks	not reported	50.5% at 1 year and 9.7% at 2 years	Percent necrosis of tumor predicted survival
OPLA-Pt	80 mg/m implanted at the time of amputation n = 37	median 256 days	41.2% at 1 year median 278 days	New trials ongoing with an injectable polymer containing cisplatin

Table 5 Modified with permission from Withrow SJ, Powers BE, Straw RC and Wilkins RM. Comparative Aspects of Osteosarcoma; Dog Versus Man. Clin Orthop And Rel Res. 270: 159-167,1991.

<i>Variable</i>	<i>Dog</i>	<i>Human</i>
Incidence in U.S.	>8,000/year	1,000/year
Mean age	7 years	14 years
Race/breed	Large or giant purebreds	None
Body weight	90% > 20 kg	Heavy
Site	77% long bones Metaphyseal Distal radius > proximal humerus Distal femur > tibia	90% long bones Metaphyseal Distal femur > proximal tibia Proximal humerus
Etiology	Generally unknown	Generally unknown
% clinically confined to the limb at presentation	80-90%	80-90%
% histologically high grade	95%	85-90%
DNA index	75% aneuploid	75% aneuploid
Metastatic rate without chemotherapy	90% before 1 year	80% before 2 years
Metastatic sites	Lung > bone > soft tissue	Lung > bone > soft tissue
Improved survival with chemotherapy	Yes	Yes

Reconstructive surgery

Forward

During the earlier part of my surgery residency the majority of the reconstructive procedures I did were related to trauma and burn cases. There are many patients in small animal practice that can benefit from the various plastic and reconstructive procedures we will discuss in these seminars. Reconstructive surgery becomes very important in the management of cancer patients where there is a need to address large defects after removal of neoplastic disease. By the middle of 1986 my career was focused on, and dedicated to, treating small animals with cancer. This has been my mission since then. I have had the opportunity to use many reconstructive techniques frequently during my career as a surgical oncologist. I hope I can share my experience in this area of surgery with you and that this information will help you manage cancer patients, trauma patients and others.

I have drawn heavily from the textbook written by Dr Michael Pavletic in the preparation of these notes. His textbook entitled, "Atlas of Small Animal Reconstructive Surgery", second edition is published by WB Saunders Co, Philadelphia, 1999, and makes a valuable addition to anybody's library especially for surgeons involved in soft tissue and reconstructive surgery of small animals. I highly recommend this textbook.

Introduction

Like many other cancer therapies, curative surgery for patients with solid tumours is achieved at the risk of normal tissues. Where the advantage gained by aggressive, wide surgical margins outweighs the disadvantages there is "therapeutic gain". The surgical oncologist must consider this in a global sense before embarking on "radical" surgical exercises. There are, however, many settings where complete surgical excision may be curative and it is paramount that surgical margins are not compromised for the sake of ease of closure.

"Above all else, get the cancer out! In the stress of the event you will think of something for closure"
- SJ Withrow.

Soft tissue defects may be managed in several ways and it is the prepared surgeon who will be able to offer his or her patients the best opportunity for low morbidity, rapid recovery and return to function after excisional surgery for cancer.

Besides being familiar with the technology of plastic and reconstructive surgery (the "nuts and bolts"), I cannot overemphasise the importance of solid knowledge of wound healing, wound management and atraumatic surgical technique.

Although a thorough review of wound healing and wound management is beyond the scope of this particular seminar series, I will take time at the start of these seminars to present some principles of good tissue handling. "Poor tissue handling can defeat the best surgical plans." (Mike Pavletic)

During the lectures I will also present techniques of reconstructive surgery that I have found useful over the years. I will present this information in a case based format. The following outline of my lecture is provided so you can make notes in the margins as necessary. I have also included a summary of Thoracic wall tumours as I hope to cover some of the reconstructive surgery issues involved in managing dogs with defects left after removing these tumours.

Management of Lateral Thoracic Wall Masses in Dogs

Masses involving the lateral chest wall of dogs are seen infrequently in general veterinary practice. Such lesions are, however, usually primary malignant tumours of ribs. They pose a serious clinical problem because full thickness chest wall resection is necessary for successful management. The work-up, surgical procedure, after-care, adjunctive therapy, follow-up, and potential complications will be presented.

There have been 295 dogs reported in the literature with chest wall tumours and of these 201 have documented long term follow-up. Chondrosarcoma, osteosarcoma, haemangiosarcoma and fibrosarcoma are the common tumours affecting the ribs with the first two mentioned histologies being the most common. Dogs with chondrosarcoma of the ribs have the best prognosis following resection with reported median survival times up to 250 weeks. Dogs with malignant rib tumours treated conservatively without surgery have a poor prognosis with reported median survival times of 2 to 15 weeks depending on the histology. Wide surgical margins including at least one unaffected rib cranial and caudal to the lesion and dorsal and ventral margins allowing 2-3 cm of grossly unaffected rib are necessary for successful *en block* resection of malignant primary rib tumours. Reconstruction involves the use of polypropylene mesh, diaphragmatic advancement, *latissimus dorsi* muscle flaps, or a combination of these with or without augmentation using omental pedicle grafts. Analgesia can be effectively provided pre-emptively, intra-operatively and postoperatively by intercostal nerve blocks, opiates either delivered by systemic administration (constant rate infusion or intermittent intravenous or subcutaneous injections) or by transdermal patches, epidural morphine, intrapleural local anaesthesia, and non-steroidal anti-inflammatory drugs as well as newer and alternative analgesic strategies. Adjuvant chemotherapy drugs are usually recommended for dogs with osteosarcoma. Carboplatin, cisplatin and doxorubicin either as single agents or in some combination have demonstrated efficacy in treating dogs with osteosarcoma. The efficacy of chemotherapy drugs in the adjuvant setting for treating dogs with chondrosarcoma has not been demonstrated. In the author's experience, dogs with haemangiosarcoma of the ribs have very poor prognoses, as metastatic disease, either measurable or occult, is almost invariable. However, two dogs in one study lived 48 and 52 weeks after surgery and survival times as long as 112 weeks have been reported. Dogs with rib fibrosarcoma have been reported to have a median survival of 26 weeks with a range of 16-64 weeks. Metastatic disease has been reported in dogs with chest wall tumours especially those with haemangiosarcoma and osteosarcoma. Recurrence is not common after wide resection with reported incidences of 10-15%. Histologically determined complete surgical margins confer an improved probability for local control.

Early wide surgical excision is recommended in the management of tumours of the canine lateral thoracic wall. This treatment has been reported to be associated with low long-term morbidity and excellent survival probabilities for dogs with certain histological types of primary rib cancer.

Mammary gland tumors

Canine Mammary Gland Tumours

Mammary gland tumours (MGT) are common in the bitch especially in countries where speying is not commonly practiced, such as Scandinavia. The incidence of MGT also appears to be greater in bitches treated with injectable progestins for oestrus prevention. Female dogs are less likely to develop MGT if they are speyed early in life. The risk of MGT in male dogs is less than 1% of that in female dogs. The median age for dogs with MGT is between 10 and 11 years and it is extremely rare for dogs younger than 4 years old to develop this cancer. Some pure breed dogs may be predisposed with the spaniel breeds, poodles and dachshunds over represented in some studies.

Half of dogs presented with MGT have single masses. The other half has multiple masses developing simultaneously or subsequently in the mammary tissue. Masses may be associated with the nipple or, more commonly, associated with the gland itself. About 70% of canine MGT develop in the caudal mammae (4 and 5).

Aetiopathogenesis

It is clear that the disease has a hormonal dependant aetiology. The risk for malignant tumour development in dogs speyed before the first oestrus is 0.5%. Dogs speyed after the first oestrus have an 8% risk and this increases to 26% if the dog is speyed after the second oestrus compared to the risk in intact dogs. Risk reduction or the protective effect of speying for the development of malignant MGT is lost if the animal is speyed late in life (after 2-3 years of age). A protective effect of early pregnancy seen in women has not been demonstrated in dogs.

Ovarian steroid hormones (oestrogen and progesterone) are mitogenic for mammary cells due to binding to the rich oestrogen and progesterone receptors (ER and PR) on these cells. Malignant canine MGT have ER and PR in less than 50% of cases with far less metastatic lesions displaying these receptors. So there appears to be a loss of the receptors as tumours become more undifferentiated and presumably this corresponds to a decrease in the steroid dependency of these cells for their growth. There may be over expression of a growth hormone (GH) gene in some MGT cells that may be progesterone induced. This GH gene possibly results in GH having local effects via induction of insulin-like growth factor-I (IGF-I) expressed by mammary stromal cells. As well as an increase in GH production induced by progestins, a rise in blood levels of IGF-I and IGF-II occurs, which may stimulate mammary cell proliferation. GH effects on differentiation and the interplay between other growth factors and their receptors complicate the whole process.

Genes play a role in the transmission of growth signals from the cell surface to the nucleus. There has been no evidence that the *ras* genes are over expressed in canine MGT but there is evidence (from mRNA studies) that *c-erbB-2* (or *c-neu*) is an oncogene over expressed in some canine MGT. The tumour suppressor gene p53 is mutated in some canine MGT. Alterations in a second tumour suppressor gene, *BRCA1*, occur in some tumours studied in dogs. The whole story of gene alterations in the aetiopathogenesis of canine MGT still needs to be told and work continues.

Another factor in the pathogenesis and prognosis of MGT studied is nuclear DNA content abnormalities studied by flow cytometry. About half of canine malignant MGT had abnormalities

(DNA aneuploidy). This reflects genetic instability and can be seen in some benign MGT too, possibly reflecting a potential for malignant transformation.

Obesity at an early age appears to be a risk factor in dogs. It is a known risk factor in women and rodents. So nutrition plays some role in tumour development and it appears from one study that homemade meals were associated with an increase risk of MGT compared to commercial diets.

Tumour Behaviour

Classically, this disease in dogs has been called a "50:50 cancer". That is, about half of the dogs presented to veterinarians with mammary masses have malignant disease and half have benign lumps. Half of those dogs with malignant tumours will be cured by appropriate excisional surgery.

Most MGT are epithelial (carcinoma). Pure sarcomas (fibrosarcoma, osteosarcoma, etc.) are rare. Similarly, a rare diagnosis is a tumour with both malignant cells from epithelial and connective tissue lineage, carcinosarcoma. The latest revision of the WHO classification attempts to divide tumours into groups with prognostic implication. It appears from one study that ductular carcinomas make up about 20% of the malignant tumours of the canine mammary gland and adenocarcinomas of other histiogenic origin made up the majority of the remaining tumours. Ductular carcinomas were 8 times more likely to be fatal than the adenocarcinomas. All the carcinosarcomas caused the death of the host. In another study, a pathological staging system was used and the degree of differentiation and invasiveness were predictive of tumour aggressiveness.

Carcinomas generally metastasize via the lymphatic route. Carcinoma that metastasizes to the inguinal lymph nodes may enter the pudendal lymphatics and spread to the internal iliac nodes. Other common metastatic sites include lung, liver, kidney and bone.

Inflammatory Carcinoma

Inflammatory carcinoma of the breast is considered a separate entity with respect to biological behaviour. These MGT grow extremely rapidly invading lymphatics readily causing oedema and inflammation for the skin and adjacent tissue. All or part of the mammary chain may be involved with a diffusely swollen and poorly demarcated, red, often pruritic lesion resembling an acute dermatological infection ("hot spot") or mastitis. Cytological evaluation of aspirates or impression smears has been useful in diagnosing this entity.

These dogs may develop disseminated intravascular coagulation and a coagulation profile may be indicated as part of the work-up for these dogs. Metastasis is common.

Surgery is not indicated as a treatment for this. Most of these cannot be resected, and if they are resected, they tend to recur within weeks to a month after surgery. Short-term benefits of radiation therapy have been reported but cures are elusive. In our clinical experience, response to chemotherapy has been poor. Overall the outlook for these dogs is very bleak.

Work-up

The aim of the clinical work-up is to establish staging. This is the TNM classification:

1. Tumour (T) – the most important features to note with the primary tumour are growth characteristics (recent rapid growth vs. long stable history), size, clinical evidence of

invasiveness (fixation to adjacent structures), ulceration and evidence of inflammatory carcinoma.

2. Lymph nodes (N) – evaluate for extension to regional lymph nodes (inguinal, axillary, presternal, internal iliac, and prescapular nodes).
3. Metastases (M) – lung and bone (lumbar vertebrae especially)

Other components of the work-up pertain to general health evaluation and starts with a detailed history taking and physical exam. Ancillary tests include CBC, serum biochemistry, routine urinalysis and coagulation profile if indicated (see inflammatory carcinoma). Thoracic radiography in both lateral projections and dorsoventral or ventrodorsal projections is used to detect lung involvement. Abdominal radiograph is useful to detect bone metastases to the lumbar vertebrae and abdominal ultrasonography can help detect enlarged retroperitoneal nodes.

Cytology of the primary tumour rarely helps in the diagnosis but may rule out diseases masquerading as MGT such as mast cell tumours. Evaluation of a fine needle aspirate or impression smear may also help prompt diagnosis of inflammatory carcinoma.

Pre-operative biopsy is generally not indicated and the definitive diagnosis is usually made on histological evaluation of an excisional biopsy.

Treatment

Surgery is the mainstay for treating MGT in dogs where there is not clinical evidence of metastatic disease. Half of the dogs with malignant MGT will be cured with surgery alone. The technique used largely depends on the size and extent of the tumour. In dogs, MGT should be removed with the lowest “dose” of surgery able to completely remove the cancer. Once the specimen is removed we recommend “inking” the surgical margins and fixing it and the regional lymph node where this has been removed in 10% neutral buffered formalin. The excised tumour must be evaluated for tumour type and grade as well as completeness of resection (margins). The node should be evaluated for extension of disease. Other tests such as flow cytometry, AgNORs, S-phase fraction, steroid receptor assays are rarely performed on excised tumour tissue from dogs at routine diagnostic laboratories.

Surgery

Mammary cancer in the dog should be removed by the simplest procedure that will remove all known cancer in the mammary gland. That is not to say that incomplete resection or debulking surgery is acceptable.

Lumpectomy

Here the surgeon makes an incision over the skin and removal of a nodule (<5 mm) from the breast with a small rim of normal tissue. This is only suitable for benign nodules. Further surgery is indicated if the biopsied nodule is malignant.

Mamnectomy

This is the removal of one mammary gland where the mass (> 10 mm) is located in the substance of the gland and is displaying some fixation to the skin or fascia. The involved skin or fascia must be

removed with the mass. It is often easier to remove glands 4 and 5 together due to their close anatomical relationship.

Regional Mastectomy

This was proposed some time ago based on the complex relationship of the mammary gland lymphatic drainage in the dog. Based on the premise of lymphatic drainage, tumours involving glands 1, 2, or 3 should be removed en bloc. Similarly, tumours involving 4 or 5 should be removed en bloc. Basically, however, it is more important to remove the entire known tumour by the simplest procedure rather than going through the semantics of determining the lymph drainage pattern of the affected gland.

Unilateral or Bilateral Mastectomy

Glands 1 to 5 can be removed as a unit if multiple tumours or several large tumours preclude rapid and wide removal by lesser procedures.

Simultaneous bilateral mastectomy can rarely be performed in dogs in my experience except for those individuals with very pendulous mammary glands. It is the preferred technique for cats, however. If both sides need to be removed from dogs, then a staged unilateral mastectomy (two unilateral mastectomies 2-3 weeks apart) is the preferred technique.

Lymph Node Removal

The inguinal node is removed when glands 4 and 5 are removed and should be dissected from the specimen after surgery and submitted separately to complete the staging. If the axillary or inguinal nodes are large or cytologically positive for cancer they must be removed. Removing positive nodes does not influence survival outcome other than helping staging and predicting outcome.

Chemotherapy

The role of adjuvant chemotherapy has not been established in dogs although some workers report promising results with Doxorubicin and Cyclophosphamide. For dogs with high-grade lesions or node positive disease, adjuvant chemotherapy may offer some benefit. This still has to be substantiated in proper, controlled clinical trials.

Radiation therapy

As with chemotherapy, no reliable information on the value of radiation is yet available.

Biological Response Modifiers

Studies have been completed using levamisole, *Corynebacterium parvum*, Bacillus Calmette-Guérin (BCG), and liposome muramyl-tripeptide phosphatidylethanolamine (L-MTP). No validated, clinically applicable immunomodulating approach is available that can be considered to have proven therapeutic effectiveness.

Hormonal Therapy

It still appears that spaying dogs at the time of treatment (surgery) for their malignant MGT does not influence prognosis. This is still hotly debated in many circles despite years of argument, evaluation of retrospective data and laboratory investigations. There has not been any well-designed

prospective study to clearly address the issue of ovariohysterectomy as an adjunct treatment for dogs with malignant mammary tumours.

Tamoxifen (antioestrogen) does not appear to have any beneficial effects for dogs with MGT and can produce moderate to severe side effects.

Summary of Canine MGT Prognostic Factors

Good	Poor	Indifferent
<3cm	>3cm	Age
Well circumscribed	Invasive	Breed
Lymph node (-)	Lymph node (+)	OHE status
Lymphoid cellular reactivity (+)	Lymphoid cellular reactivity (-)	Weight
	Inflammatory carcinoma	Type of Sx (simple vs. radical)
ER or PR (+)	Ulceration	
Carcinoma	Sarcomas	
Well differentiated	ER (-)	Number of tumours
Complex	Carcinoma	Gland(s) involved
Tubular/Papillary	Poorly differentiated	
AgNOR count – low	Simple	
	Solid, anaplastic	
	AgNOR count - high	

Feline Mammary Gland Tumours

Where about half of the dogs presented with mammary masses have malignant tumours, over 90% of cats with mammary nodules have malignant disease. Mammary gland tumours are the third most common cancer of cats following haemopoietic cancers and skin tumours. Domestic shorthaired cats and Siamese cats may have higher incidence rates than other cats. Siamese cats may have twice the risk of any other breed of developing MGT.

The disease has been reported in cats as young as 9 months old and as old as 23 years with a mean age of 10 years old. Cats spayed at 6 months had approximately 7-fold reduced risk of MGT compared to intact cats. Cats receiving drugs containing synthetic progestins or oestrogen-progestin combinations have a 3-fold greater risk of developing mammary masses (benign and malignant) compared to untreated cats.

Many of the tumours, especially the larger ones, are invasive, adhere to the skin and are ulcerated. Lymphatic and lymph node invasion is common. More than 80% of cats with malignant MGT in several studies had metastases at the time of euthanasia.

Histology is usually adenocarcinoma (80%). Sarcomas, squamous cell carcinomas, and mucinous carcinomas are less common.

Mammary tumour pulmonary metastases appear radiographically as interstitial (milliary) densities. Sternal lymphadenomegally is sometimes present. Biopsy is recommended of feline mammary masses. Radical mastectomy is the treatment of choice as it significantly reduces the chance of local tumour recurrence. The inguinal nodes are removed and evaluated for tumour extension. Axillary nodes are only removed if enlarged or cytologically positive for tumour extension.

Chemotherapy with doxorubicin or doxorubicin and cyclophosphamide has been recommended although trials are underway and results demonstrating efficacy are pending.

The prognosis for cats with MGT is usually guarded. Two thirds of cats where their tumours were removed by conservative surgery developed local tumour recurrence. The most significant prognostic factors affecting recurrence and survival for cats with MGT are tumour size, extent of surgery and histological grading. Tumour size is the single most important factor. Cats with a tumour size of greater than 3 cm in diameter will have a median survival time of 4 to 6 months. Cats with a tumour size of 2 to 3 cm in diameter will have a median survival time of 2 years, and cats with tumours less than a 2 cm diameter will have a median survival time over 3 years.

Perianal tumors

Almost any tumour can occasionally affect the perineum and perianal region. Mast cell tumours, soft tissue sarcomas, other skin tumours, lymphoma and so on are examples but the most common are those of the sebaceous glands; the perianal tumours (often called circumanal or hepatoid tumours).

Perianal tumours are common in the male dog and rare in the female dog or the cat. Perianal adenomas are the most common making up over 80% of perianal tumours in the intact male dog.

Perianal adenomas commonly occur in older, intact male dogs and are thought to be androgen dependant where as perianal adenocarcinomas (the evil cousins) occur in castrated and intact male dogs and are not thought to rely on a source of androgen for their growth. Perianal adenomas in females appear to be largely restricted to speyed animals. In rare occasions, testosterone secretion from the adrenal gland may stimulate the development of perianal adenomas. Dogs with Cushing's disease may be prone to developing these lesions and it may warrant investigation particularly when adenomas occur in females.

Perianal adenomas and adenocarcinomas derive from sebaceous glands. Apocrine gland carcinomas develop from the apocrine glands lining the anal sacs and older, speyed female dogs are over represented in most studies of this cancer in dogs. A true hormonal dependence for apocrine gland carcinoma has not been shown. Apocrine gland adenocarcinoma is very rare in the cat.

Presentation

Dogs with benign lesions generally present with a perianal mass that has been growing slowly over months to years. The lesions usually cause no obvious pain or discomfort and may be single or multiple. Most occur on the hairless regions around the anus, although they may extend into haired adjacent skin and may even occur on the tail base, scrotum and prepuce. Despite their benign behaviour they can look aggressive with areas of ulceration and fixation to deeper structures.

The malignant form, perianal adenocarcinoma, usually has a more rapid growth history but can look grossly very similar to perianal adenoma. Characteristically they are firmer, more commonly ulcerated and frequently adhere to adjacent structures such as the rectum and even the pelvis. These tumours can become quite large. Difficulty with defaecation leading to obstipation is a late clinical sign. A perianal mass in a castrated male dog must be considered suspicious for adenocarcinoma.

Dogs with anal sac adenocarcinoma (apocrine gland carcinoma) may not present because of signs directly referable to the primary tumour, which may be small (5 – 10 mm). These dogs may have hypercalcaemia and the presenting complaint by the owner may be that the dog is polydipsic, polyuric, anorexic, has vomiting and so on. Also it is not uncommon for these dogs to be straining to defaecate due to pelvic canal obstruction from palpably enlarged internal iliac (sub lumbar) lymph nodes. The primary tumour can usually be palpated on rectal examination as a nodule in one of the two anal sacs located ventrolaterally on either side of the anal sphincter.

Work-up

The intact male presenting with a perianal mass to our clinic receives a complete physical examination and a detailed history is taken from the owners. Once it is established that the dog is otherwise healthy, (minimum data base blood work and urinalysis are usually evaluated) and adenoma or adenocarcinoma is suspected then the dog is taken to surgery and the lesion is usually

excised and the dog castrated. Preoperative biopsy is considered if the lesion is large and cannot be excised easily. Fine needle aspiration cytology is useful to rule out other cancers, such as mast cell tumours, but cannot be relied upon to differentiate perianal adenoma from perianal adenocarcinoma. If the histopathology is consistent with adenoma then no more treatment is necessary. If the disease is adenocarcinoma then abdominal ultrasonography to evaluate lymph nodes and liver is performed and thoracic radiography is done for staging. Further surgery is usually necessary to obtain clean margins and adjuvant chemotherapy is considered.

A perianal mass in the castrated dog or if there is recurrence of the mass in the recently castrated dog previously diagnosed with adenoma always necessitates biopsy. Adenocarcinoma must be suspected in this scenario.

Dogs with tumours of the anal sac receive the same physical examination and history evaluation. Large caudal abdominal nodes are frequently palpated via abdominal palpation or rectal exam or both. These dogs are often suffering from the effects of hypercalcaemia and require prompt laboratory evaluation and attention. Abdominal radiography and ultrasonography are performed. Thoracic radiography is also recommended. Renal complications from hypercalcaemia can occur in these dogs and renal parameters need to be carefully scrutinized from blood work and urinalysis. Biopsy of the anal sac mass establishes the definitive diagnosis however these dogs have a characteristic presentation and rarely require a tissue biopsy before treatment.

Treatment

Castration and tumour removal or cryosurgery is usually all that is required to cure dogs with perianal adenoma. Perianal adenocarcinomas are locally invasive and do not respond to castration. Wide surgical margins need to be obtained. It is possible to remove over 50% of the anal sphincter and regain continence after a short period of temporary faecal incontinence. Regional node metastases can often be resected. Lymphadenectomy is generally performed by ventral midline laparotomy although I have performed a dorsal approach to the rectum to remove sub sacral nodes on occasion. Following subtotal lymphadenectomy, external beam radiation therapy can help prevent disease progression although we have experienced good results with doxorubicin based chemotherapy protocols.

Treatment of anal sac apocrine gland carcinomas requires wide resection of the primary with lymphadenectomy in most cases. Radiation of the nodes and primary site follows. We have treated dogs with excision of the primary and lymphadenectomy followed by doxorubicin at 30 mg/m² every 21 days for 5 treatments with quite good results. Hypercalcaemia usually resolves within days of surgery.

Prognosis

Generally, intact male dogs with perianal adenoma treated with castration and excision have an excellent prognosis with over 90% cured.

Sebaceous gland adenocarcinoma in the male dog is difficult to cure but dogs with early stage disease can do well after wide surgical excision. Tumours less than 5 cm in diameter (T2NoMo or less) had survivals in excess of 70% at 2 years with wide surgical excision.

Anal sac carcinomas carry the worst prognosis with approximately 50% 1-year survivals even with surgery, lymphadenectomy and adjuvant therapy. Metastasis at diagnosis and hypercalcaemia appear to be poor prognostic indicators.

More work needs to be done to determine the roll of adjuvant radiation and chemotherapy in the management of this disease although preliminary data looks encouraging.

Cancer of the oral cavity

INTRODUCTION

Collectively, oral cancer accounts for 6% of canine cancer and is the fourth most common cancer overall. In the cat, it accounts for 3% of all cancers. In the past there was very little the veterinarian could effectively do to help pets with oral cancer. Recent knowledge about tumor biology, new surgical techniques and radiation therapy has allowed effective treatment of many cats and dogs with malignant oral disease. It is the purpose of these notes to review cancer of the oral cavity for the benefit of the practicing veterinarian to allow understanding of the biological behavior of these diseases and the principles of their management.

The most common oral cancers in the dog are malignant melanoma, squamous cell carcinoma, fibrosarcoma and acanthomatous epulis. In the cat, squamous cell carcinoma is the most common oral tumor followed by fibrosarcoma in prevalence. Other oral tumors and tumor-like lesions of dogs and cats will also be covered in these notes (mandibular osteosarcoma, multilobular osteochondrosarcoma, histologically low grade but biologically high grade sarcomas, tonsillar squamous cell carcinoma, tongue tumors, viral papillomatosis, canine eosinophilic granuloma complex, epulides, inductive fibroameloblastoma, nasopharyngeal polyps, eosinophilic granuloma in cats and undifferentiated malignancy of young dogs).

PATHOLOGY AND NATURAL BEHAVIOR

The oral cavity is a very common site for a wide variety of malignant and benign cancers. Although most cancers are fairly straightforward histologically, some have confusing nomenclature or extenuating circumstances to warrant discussion.

Fibrosarcoma

Oral fibrosarcoma will often look surprisingly benign histologically and even with large biopsy samples the pathologist is forced to read out fibroma or low-grade fibrosarcoma. If the cancer in question is rapidly growing, recurrent, or invading bone, however, the clinician should dictate treatment as for malignant cancer. Fibrosarcoma is very locally invasive but metastasizes in less than 20% of cases (usually to the lungs).

Malignant Melanoma

Malignant melanoma can present a confusing histopathological picture if the tumor or the biopsy section does not contain melanin (1/3 of all cases). A histopathological diagnosis of undifferentiated sarcoma should be looked upon with suspicion for possible underlying melanoma. Melanoma has a strong predilection to metastasize to regional lymph nodes and then lung. Metastasis to lung only or other sites is not uncommon.

Squamous Cell Carcinoma

Squamous cell carcinoma is usually a straightforward histological diagnosis. It is the most common feline oral malignancy. Severe and extensive involvement of bone is common in the cat. The metastatic rate in the cat is somewhat unknown since so few cats have their local disease controlled to observe the long term metastatic potential. Metastasis in the canine is very site-dependent with

the rostral oral cavity having a low metastatic rate and the caudal tongue and tonsil having a high metastatic potential.

Acanthomatous Epulis

The terminology for the epulides and dental tumors has been confusing in the past because no universally accepted nomenclature existed. The clinician was left bewildered by the different terms used by different pathologists for the same tumor. The terminology used in these notes is that of Dubielzig which has largely become the accepted norm. The "traditional" epulides are similar to gingival hyperplasia in appearance and are usually confined to one or two sites at the gum margin. They are slow growing, firm and generally covered by intact epithelium. Most are firmly attached while some are pedunculated. These are classified as fibrous epulides or ossifying epulides, depending on the presence or absence of bone. A third class of epulis has been termed acanthomatous epulis instead of the previous term of adamantinoma. Some pathologists use the terms interchangeably. It has been concluded that the acanthomatous epulis is indeed a form of ameloblastoma, although its microscopic appearance differs from that of the lesions described by Dubielzig and Thrall. Gardner and Baker have suggested the term, *canine acanthomatous ameloblastoma*. For our purposes we chose to use the term, *acanthomatous epulis*. These are much more locally invasive than the other epulides, and virtually always invade bone. They do not metastasize. Another dental tumor uncommonly encountered in the oral cavity of dogs is the keratinizing ameloblastoma.

HISTORY AND SIGNS

Most patients present with a mass in the mouth noticed by the owner. The owner however, rarely notices cancer in the caudal pharynx and the patient will present for signs of increased salivation, weight loss, halitosis, bloody discharge, dysphagia or occasionally cervical lymphadenopathy. In fact, a common presenting sign for active retrieving dogs with cancer in the caudal parts of their mouths is blood on the *Frisbee*. Loose teeth in a patient with generally good dentition, should alert the clinician to possible underlying neoplastic bone lysis (especially in the cat). Facial deformity is usually a sign of very advanced disease.

DIAGNOSTIC TECHNIQUES AND WORK-UP

The diagnostic evaluation for oral cancers is critical due to the wide ranges of cancer behavior and therapeutic options available. If the cancer is suspected, thoracic radiographs can be performed prior to biopsy. The most likely cancers to have positive chest radiographs at the time of diagnosis are melanoma and squamous cell carcinoma of the caudal oral and pharyngeal area. Most animals will require a short general anesthesia for careful palpation, regional radiographs and a biopsy. Lesions that are not covered by intact epithelium and that are easily accessible may be biopsied with the animal conscious (allowing for the particular animal's temperament).

Appropriate radiographic views of the local site should be performed with the animal under general anaesthesia. This applies to animals with cancers that are adherent to bone, other than fibromatous or ossifying epulides. When 40% or more of the bone mineral is lost, lysis may be observed. However, apparently normal radiographs do not rule out bone invasion. If the tumor is fixed to bone

it can generally be assumed that there is at least microscopic invasion of the adjacent bone. It is inappropriate to scrape malignant disease from the bone surface even if there is no apparent lysis of the underlying bone on radiographs. Where there is evidence of lysis, regional radiographs will assist in determining the clinical stage of cancer and the extent of resection when surgery is indicated.

Regional lymph nodes (mandibular and retropharyngeal) should be carefully palpated for enlargement or asymmetry. When abnormal (or even just palpable), they should be aspirated via a fine needle. This is especially important for melanoma and caudally situated squamous cell carcinoma. Some authors have suggested lymph node removal for staging purposes but there is no evidence that prophylactic lymph node removal for cancer of the oral cavity improves survival rates.

The last step to perform, while the patient is still anesthetized, is a large incisional biopsy. Oral cancers are commonly infected, inflamed or necrotic and it is important to obtain a large specimen. Electrocautery may distort the specimen and should only be used for haemostasis after blade incision. Large samples of healthy tissue at the edge and center of the lesion will increase the diagnostic yield. The biopsy site should be located in such a position as to be easily included in a future resection. For small lesions (epulides, papillomas or labial mucosa melanoma), curative intent resection (excisional biopsy) may be undertaken at the time of initial evaluation. For more extensive disease, waiting for biopsy results to accurately plan treatment is encouraged.

Cytological preparations of oral cancers may not help in obtaining a diagnosis due to the necrosis and inflammation, which commonly accompanies these conditions.

THERAPY

Surgery, cryosurgery and irradiation are the principal treatments for animals with oral cancer. When feasible, surgical excision is the most economical, fastest and most curative treatment. Radical surgeries such as mandibulectomy and partial maxillectomy are well tolerated by small animals and are indicated for lesions with extensive bone invasion, which are not histological types that respond well to radiation or are too large for cryosurgery. Margins of at least 2 cm are necessary for malignant cancers such as squamous cell carcinoma, malignant melanoma, and fibrosarcoma in the dog. Squamous cell carcinoma in the cat should have even wider margins, due to their high local recurrence rates.

Cryosurgery may be indicated for lesions less than 1 cm in diameter, which are fixed or minimally invasive into bone. Larger lesions should generally be surgically resected. More extensive lesions in bone will often result in a fracture (mandible) or oronasal fistula (maxilla) if aggressively frozen. Cancer of soft tissue only should be surgically excised rather than frozen.

Hyperthermia offers no advantage over cryosurgery or surgery if it is used alone. In fact, bone penetration is less reproducible with heat versus cold treatment. Hyperthermia at moderate temperatures (42 to 43°C) may, however, be used as an effective adjunct to irradiation.

Radiation therapy is utilized under three general settings:

1. Known responsiveness for such tumors as dental (acanthomatous epulides or adamantinoma) or squamous cell carcinoma.
2. An inoperable cancer of any histology.

3. Known postoperative residual disease to "clean up" the remaining cancer.

Local and regional disease control is the goal of treatment. No known effective chemotherapeutic agents exist for cancers likely to metastasize (malignant melanoma, squamous cell carcinoma or fibrosarcoma). Adjuvant immunotherapy with BCG or levamisole has failed to improve survivals for malignant melanoma in the dog. A slight improvement in survival was demonstrated for patients with advanced local stage malignant melanoma when treated with surgery and *Corynebacterium parvum* versus surgery alone. In a randomized clinical trial evaluating the efficacy of adjuvant liposome encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE) in dogs there was a trend for an improvement in survival and disease free interval in treated dogs, which was most, pronounced in dogs with stage I disease. The role of immunomodulation in the management of oral malignant melanoma is still poorly defined. There are ongoing trials including a "tumor vaccine" study.

PROGNOSIS

The prognosis for acanthomatous epulides is excellent with surgery or irradiation. Recurrence rates for these tumors after aggressive resection are less than 5%. Radiation therapy will control in excess of 90% of these tumors. A peculiar syndrome of a malignant cancer developing in the irradiated site may occur in up to 20% of patients. By all accounts this risk of a second malignancy is probably an over estimate, however the tumors may be of epithelial or mesenchymal origin and usually take several years to develop. The outlook for squamous cell carcinoma is very site and species dependent. Canine squamous cell carcinomas in the rostral mouth are curable with surgery or irradiation, while those of the tonsil or base of the tongue are highly metastatic and likely to recur locally or regionally. Local control of feline squamous cell carcinoma is poor with either surgery or radiation therapy. One-year survivals rarely exceed 10% in the cat.

Overall, approximately 25% of canine oral malignant melanomas will survive one year or more. The only known variables, which have prognostic significance, are size (< 2 cm diameter do better) and ability of first treatment to afford local control. Dogs with tumors < 2 cm diameter have a median survival of 511 days as opposed to dogs with lymph node involvement or tumors greater than 2 cm diameter whose median survival is 164 days. Dogs with recurrent malignant melanoma have worse survival probabilities than dogs with primarily treated disease where local control is achieved. Age, breed, sex, degree of pigmentation, microscopic appearance, and anatomic site are not prognostic.

Local control of fibrosarcoma is more of a problem than metastasis. The best one-year survival rates with almost any treatment are no better than 25-40%. Fibrosarcomas are generally considered radiation resistant. Mean survival after radiation of 17 dogs was only 7 months. Radiation combined with regional hyperthermia improved local control rates to 50% as measured at one year in a series of 10 cases.

OTHER ORAL TUMORS AND TUMOR LIKE LESIONS

Canine Mandibular Osteosarcoma

Canine osteosarcoma, (OS), is an aggressive primary bone cancer with a high metastatic potential. Primary OS occurs more commonly in the appendicular skeleton than the axial skeleton and in one study of 457 cases of canine OS, 25.4% were primary to the axial skeleton and 27% of these were

located in the mandible. Dogs with OS of the skull or mandible have been thought to have a better prognosis than dogs with OS of appendicular sites because of a lower metastatic rate. Osteosarcoma primarily located in limbs of dogs is highly metastatic. The median survival for dogs with appendicular OS treated with amputation alone is 19.2 weeks. It appears, however that OS of some axial sites, such as the pelvis and rib, are as potentially metastatic as OS of the limbs. Recent studies of canine mandibular osteosarcoma treated with mandibulectomy report 1-year survival rates of between 35 and 42 per cent. Osteosarcoma of the jaw of people differs from OS of the long bones mainly because of a lower metastatic rate. A recent study conducted with participants from the Veterinary Cooperative Oncology Group was performed to identify clinicopathological and treatment outcome features of mandibular OS in dogs.

A search of hospital records from January 1980 to March 1992 from participating institutions was conducted for dogs with OS of the mandible with no clinical evidence of metastasis at presentation (stage IIb), where treatment was instituted and follow-up information was available.

Fifty-one dogs treated for osteosarcoma of the mandible were retrospectively studied. Treatments were partial mandibulectomy (n=32), partial mandibulectomy and chemotherapy (n=10), partial mandibulectomy and radiation therapy (n=3), partial mandibulectomy, radiation therapy and chemotherapy (n=4) and radiation therapy alone (n=2). The overall 1-year survival rate was 59.3%. Dogs treated with surgery alone had a 1-year survival rate of 71% that is higher than for dogs with appendicular osteosarcoma treated with surgery alone, ($p \leq 0.001$, hazard ratio=0.29). There was no apparent effect of type of treatment, institution where treatment was given or histological type. Histological score and, to a lesser extent, histological grade were predictive of survival outcome.

Histologically Low Grade But Biologically High Grade Sarcomas (Hlg Bhg)

Proliferation of fibroblasts with abundant production of collagenous tissue has been reported to occur in the head and oral region of dogs. Various names have been given to lesions of this type: low grade fibrosarcoma, maxillary fibrosarcoma, nodular fasciitis, fibrous epulis, fibroma, chronic inflammation and granulation tissue. This tumor is characterized by an innocuous histological appearance but demonstrates aggressive biologic behavior evidenced by invasion into surrounding soft tissue and bone as well as metastasis. This disease has been reported to occur predominantly in the maxilla of large breed dogs. Recognition of the aggressive nature of this lesion despite deceptively benign histology is imperative to facilitate early appropriate therapy.

A recent retrospective study at CSU was performed to describe the clinical, radiographic and histological findings as well as treatment outcome of 25 dogs with confirmed histologically low-grade fibrosarcoma (HLG BHG) of the maxilla and mandible. Most dogs had prolonged clinical histories and previous biopsies of the affected regions that were often interpreted as benign fibrous connective tissue. The most common breed represented was the golden retriever (54%). Skull radiographs were evaluated for 22 dogs and 16 dogs (72%) had evidence of bone lysis. At presentation, none of the dogs had radiographic evidence of pulmonary metastasis. Upon subsequent examinations and necropsy, the incidence of pulmonary metastasis was 12%. The incidence of regional lymph node metastasis was 20%. The histological appearance of all specimens was similar and characterized by a proliferation of fibrous connective tissue with moderate to low cellularity that aggressively infiltrated adjacent normal tissue. Treatment modalities varied considerably. Surgical excision in combination with radiation therapy, surgery alone, radiation therapy alone and radiation therapy used adjunctively

with localized hyperthermia demonstrated prolonged survival times. The clinical behavior and histological characteristics of these lesions most closely resemble aggressive fibromatoses in man.

Multilobular Osteochondrosarcoma

Multilobular osteochondrosarcoma (MLO) is an infrequently diagnosed bony and cartilaginous tumor generally arising from the canine skull. It is said to be the most common "benign" canine bone tumor arising from this site. Reports in the literature are confused by inconsistent nomenclature. Names used to describe this tumor in animals include chondroma rodens, multilobular osteosarcoma, calcifying aponeurotic fibroma, multilobular osteoma, multilobular chondroma, cartilage analogue of fibromatosis, juvenile aponeurotic fibroma, and multilobular osteoma and chondroma. Despite this inconsistent nomenclature, most reports describe tumors with similar radiographic and histological appearance as well as characteristic locally destructive behavior that is slowly progressive. The tumors are likely to recur after incomplete resection and infrequently have been reported to metastasize to the lungs. Similar lesions have been described in cats, a horse and human beings.

The characteristic histological feature of MLO is a mass forming multiple lobules, each of which consists of central cartilaginous or bone matrix surrounded by a thin layer of spindle cells. The histological grade of primary lesions can be determined using a scheme recently described (Table III).

The gross and microscopic pathologic features of MLO have been described; numerous single case reports exist and 1 case series was reported. The latter describes MLO-like lesions in 4 dogs. A retrospective study of 16 dogs with MLO, mostly seen at CSU documented the clinicopathological behavior of the disease. The mean age of affected dogs was 7.5 years, a single breed did not appear to be over represented and males were affected as frequently as were females. All of the primary lesions affected the mandible, maxilla or cranium.

Excision was the only treatment in 11 dogs, 2 dogs had radiotherapy in addition to excision, and 1 dog had radiotherapy and chemotherapy after excision. Twelve treated dogs had follow-up information available. Of the 12 treated dogs, 7 had local recurrence (58%), with median time to recurrence of 14 months. Seven dogs (58%) developed metastatic disease after treatment, with median time to metastasis of 14 months. The median disease-free interval was 12 months, and the median survival time was 21 months.

The relatively high metastatic rates in the dogs of this study, compared with those of previous studies, was likely attributable to the prolonged survival after more aggressive treatment of the primary disease. In most other studies, dogs were either euthanatized at time of diagnosis or were not followed for a long enough period for metastasis to develop. Dogs can survive for many months with pulmonary metastasis from MLO and not have clinical signs of tumor.

Recently, histological grade has been shown to be a prognostic indicator for MLO in dogs. Dogs with grades-1, 2 and 3 primary lesions had a median survival of 50, 22 and 11 months respectively, which were statistically significantly different. Excision with histologically complete surgical margins offers good opportunity for long-term tumor control.

Tonsillar Squamous Cell Carcinoma

This cancer is ten times more common in animals living in urban vs. rural areas, implying an etiologic association with environmental pollutants. Most primary tonsillar cancer is squamous cell carcinoma.

Lymphosarcoma can affect the tonsils but is usually accompanied by generalized lymphadenopathy. Other cancer, especially malignant melanoma may metastasize to tonsil as well. Cervical lymphadenopathy, ipsi- or contralateral, is a common presenting sign, even with very small primary cancers. Fine needle aspirates of these lymph nodes or excisional biopsy of the tonsil will confirm the diagnosis. Thoracic radiographs will be positive in a large percentage of cases. This disease is considered generalized at diagnosis in over 90% of patients. Simple tonsillectomy is almost never curative but probably should be done bilaterally due to the high percentage of bilateral disease. Cervical lymphadenectomy, especially for large and fixed nodes, is rarely curative and should be considered diagnostic only. Regional radiation (pharynx and cervical lymph nodes) is capable of controlling local disease in over 75% of the cases, however, survival still remains poor with only 10% of affected animals alive at one year. Cause of death is local disease early and systemic disease (usually lung metastasis) later. To date, no known effective chemotherapeutic agents exist for canine or feline squamous cell carcinoma although bleomycin has been utilized with very limited success.

Tongue Tumors

Cancer confined to the tongue is rare. White dogs appear to be at higher risk for squamous cell carcinoma, even though lack of pigment would not seem to be as much a problem as it is in other, more exposed areas of the body (nose, eyelids and ears). The most common cancer of the canine tongue is squamous cell carcinoma (~50%) followed by granular cell myoblastoma, melanoma, mast cell, fibrosarcoma and a wide variety of histological types. Feline tongue tumors are usually squamous cell carcinoma and most are located on the ventral surface near the frenulum. Presenting signs are similar to other oral cancers and mass lesions. Ulceration may be seen (especially with squamous cell carcinoma).

Under general anesthesia, the tongue may be biopsied with a wedge incision and closed with horizontal mattress sutures. Hemorrhage may be profuse until sutured. Regional lymph nodes should be aspirated for staging purposes if palpable. Treatment is generally with surgery and irradiation is reserved for inoperable cancer or cancer metastatic to lymph nodes. Partial glossectomy can be performed for the rostral one-half (mobile tongue) or longitudinal one-half of the tongue. Eating and drinking may be slightly impaired but good hydration and nutrition can be maintained postoperatively. Grooming in cats will be compromised with up to 50% removal and may result in poor hair coat hygiene.

The prognosis for tongue tumors will vary with the site and type of cancer. Cancer in the rostral (mobile) tongue has a better behavior for any of the following reasons:

1. Earlier detection since the owner can see the lesion
2. The caudal tongue may have richer lymphatic and vascular channels to allow metastasis
3. Rostral lesions are easier to operate with wide margins.

Even so, the one-year survival with surgery or radiation for squamous cell carcinoma of the tongue is rarely over 25%. Metastasis is common to regional lymph nodes and beyond.

Granular cell myoblastoma is a curable cancer. These cancers may look large and invasive but are almost always removable. Permanent local control rates exceed 80%. They may recur but serial surgeries are usually possible. This cancer is rarely metastatic. Local control in four of five tongue

melanomas was obtained by surgery and the metastatic rate was less than 50% in this small series. The behavior of other tongue cancers is generally unknown due to the rarity of these conditions.

Viral Papillomatosis

This condition is horizontally transmitted by a viral agent (papovavirus) from dog to dog. Affected animals are generally young. The lesions appear wart-like and are generally multiple in the oral cavity, pharynx, tongue or lips. A biopsy can be performed if necessary but visual examination is usually diagnostic. Most patients never suffer any significant side effects of this disease while an occasional dog will have such marked involvement as to require surgical debulking in order to permit swallowing. The majority of patients will undergo a spontaneous regression of disease within four to eight weeks, which resists a subsequent viral challenge. For resistant cases, a wide variety of treatments have been tried: crushing of lesions *in situ* to "release" antigen, autogenous vaccines and chemotherapy. These methods are seldom required and the prognosis is excellent. There is, however, a small subset of dogs affected with oral papillomatosis where the disease is so severe that they cannot eat or swallow food. These dogs may have lesions as far distally as the esophagus and stomach. Dogs with this form of papillomatosis may not respond to treatment.

Canine Oral Eosinophilic Granulomas

This disease affects young dogs (one to seven years) and may be heritable in the Siberian husky. It is histologically similar to the feline disease with eosinophils and granulomatous inflammation predominating. The granulomas typically occur on the lateral and ventral aspects of the tongue. They are raised, frequently ulcerated and may mimic more malignant cancers in appearance. Treatment with corticosteroids or surgical excision is generally curative although spontaneous regression may occur. Recurrences are uncommon.

Epulides

Benign, gingivally located proliferations of tissue in the dog are termed epulides and may be fibromatous or ossifying. They are usually firm, 1 to 4 cm, and variably fixed to the bone at the gum line. Mild ulceration may occur but most are covered by epithelium. Epulides do not generally invade bone and treatment is with conservative blade excision. The rare recurrent lesion may require more aggressive destruction of the base with electrocautery or cryosurgery. They are rare in the cat.

Keratinizing Ameloblastoma

These tumors are persistently invasive and recur if not removed with an adequate margin of normal tissue. They do not metastasize.

Inductive Fibroameloblastoma

This rare odontogenic tumor affects primarily young cats (6 months to 2 years) and has a predilection for the region of the upper canine teeth and maxilla. Radiographically the tumor site shows variable degrees of bone destruction, production and expansion of the maxillary bones. Teeth deformity is common. Smaller lesions are treated with surgical debulking and cryosurgery or premaxillectomy. Larger lesions will respond to radiation. Local treatment needs to be aggressive but control rates are good and metastasis has not been reported.

Nasopharyngeal Polyps In Cats

This disease tends to affect young cats usually less than two years old. No definitive breed or sex predilection is known. Clinical signs include sneezing, swallowing problems, rhinitis and difficulty in breathing. Firm, fleshy masses can be seen or palpated in the caudal pharynx or above the soft palate. Occasionally, masses can be visualized in the external ear canal. Skull radiographs may reveal fluid or tissue in the tympanic bullae. Most lesions originate in the bullae or eustachian tube and grow toward the pharynx to become a pedunculated mass. Treatment through the oral cavity is by traction and ligation of as much of the stalk as possible, however recurrences are common if that is the sole treatment. If radiographs reveal tissue in the bullae, a combined oral removal and bullae osteotomy may be required to affect a cure. The disease is not truly neoplastic but rather primarily or secondarily inflammatory.

Eosinophilic Granuloma In The Cat

This condition is also known as rodent ulcer, indolent ulcer or most commonly eosinophilic granuloma. It occurs more commonly in females with an average age of five years. The etiology is unknown.

Any oral site is at risk but it is most common on the upper lip near the midline. The history is usually that of a slowly progressive (months to years) erosion of the lip. Biopsies are often necessary to differentiate the condition from true cancers.

Various treatments are proposed including (in order of author preference): prednisone at 1 to 2 mg/kg BID x 30 days orally or IM methyl prednisolone acetate at 20 mg/cat SQ every two weeks; megestrol acetate; hypoallergenic diets; radiation; surgery or cryosurgery. The prognosis for complete and permanent recovery is only fair, although rare cases may undergo spontaneous regression.

Undifferentiated Malignancy Of Young Dogs

This condition is seen in dogs less than two years of age (range 6 to 22 months). Most patients are large breeds and there is no sex predilection. The disease is manifest by a rapidly growing mass in the area of the hard palate, upper molar teeth and may include the maxilla and orbit. Biopsies reveal an undifferentiated malignancy of undetermined histogenesis. Most patients present with lymph node metastasis and at necropsy five of six in our series had metastasis beyond the head and neck. No effective treatment has been proposed although conceptually, chemotherapy would be necessary. Most patients are euthanatized within 30 days of diagnosis due to progressive and uncontrolled tumor growth.

Medical records from 6 dogs with histologically confirmed undifferentiated tumors of the oral cavity and periorbital region were recently reviewed in a study from CSU. The mean age of the 6 dogs was 17.5 months (range; 12 to 25 months). All dogs were purebreds with no single breed re-presented more than once. The dogs were all medium to large breed dogs (body weight > 25 kilograms). Four dogs were male (intact; n=2, castrated; n=2) and two dogs were spayed females. All 6 dogs were presented with the primary complaint of a swelling or mass located on the caudal maxilla or in the periorbital region. Four dogs had signs referable to conjunctivitis and exophthalmos secondary to the physical presence of the growing mass. Complete blood count, serum chemistry profile, and urinalysis when performed (n=3dogs) were all normal. Thoracic radiographs (n=3 dogs) and

abdominal radiographs (n=1 dog) did not reveal any abnormalities. Radiographs of the skull were performed in 3 dogs. There was evidence of osteolysis of the maxilla in two dogs. Computerized tomography was performed in 2 dogs and revealed a soft tissue mass medial to the orbit invading periocular muscles and exhibiting osteolysis of the frontal bone and caudal maxilla in both dogs.

Histopathology revealed similar features in all instances. The tissue consisted of sheets of pleomorphic, spindlyoid to polygonal cells with indistinct cytoplasmic borders. The nuclei were pleomorphic, vesicular and prominent nucleoli were present. Mitotic figures were numerous. Necrosis was evident in all samples. A scant amount of fibrous stroma was present and cells were highly invasive into surrounding soft tissue and bone. The cell of origin was difficult to ascertain. The diagnosis in each case was undifferentiated sarcoma.

Three dogs had euthanasia performed immediately after diagnosis. Postmortem examination was performed on 1 of these dogs. Therapy was attempted in the three remaining dogs. Treatment consisted of cyclophosphamide, vincristine, prednisone and radiation therapy (n=1), surgical excision and doxorubicin (n=1), and radiation therapy and doxorubicin (n=1). Metastatic disease occurred in all three of the treated dogs. Euthanasia was then performed 7 days, 30 days and 105 days respectively, after initiation of therapy.

At postmortem examination performed in three dogs (treated, n=2; untreated, n=1) extensive sites of metastatic disease were identified. There was residual local disease in all three dogs including the 2 dogs that underwent treatment. Foci of metastasis were found in both regional and distant lymph nodes (n=3), in the lungs (n=2), the liver (n=2), pancreas (n=1), and kidneys (n=1).

It was concluded from this small case series that undifferentiated tumors that originate in either the caudal maxilla or periorbital region in dogs less than 2 years of age although uncommon, are locally invasive and have a very high metastatic potential. This disease is refractory to treatments used so far, including multimodal treatments, and is an extremely aggressive, life-threatening cancer of young dogs. A very poor prognosis should be given for dogs diagnosed with this disease.

COMPARATIVE ASPECTS

The vast majority of oral cavity cancer in man is squamous cell carcinoma. It is associated with alcohol and tobacco use and usually occurs in patients over 45 years old.

Treatment is generally with surgery, radiation or both. Chemotherapy has a limited role for local disease but has shown promise, often in combination with radiation, for advanced stage cancer.

Prognosis is strongly correlated to histological grade, stage and site (pharynx and caudal tongue worse than rostral tongue and oral cavity).

MANDIBULECTOMY

Mandibulectomy is the resection of variable sections of the mandible and closure of the ostectomy site with lingual, labial, and buccal mucosa and submucosa flaps. No replacement of bone or stabilization is required. Appearance, owner acceptance, and function generally are excellent following a mandibulectomy. The amount of tissue removed varies with the tumor type, stage and location. As a guide, five mandibular removal procedures have been described: (a) unilateral rostral body mandibulectomy (from as far back as the molar teeth forward to symphysis), (b) bilateral rostral body mandibulectomy (a bilateral version of the former technique), (c) total hemimandibulectomy

(horizontal body and vertical ramus on one side), (d) vertical ramus mandibulectomy (with or without temporomandibular joint removal), and (e) segmental horizontal body mandibulectomy.

Indications

Mandibulectomy is performed for local control of cancer of the mandible, for treatment of chronic mandibular osteomyelitis, and as a salvage procedure for mandibular fractures with severe bone or soft tissue injury. Removal of oral tumors is the most common indication for mandibular resections.

As previously stated, oral tumors tend to be locally aggressive and slow to metastasize except for malignant melanoma, caudally located oropharyngeal squamous cell carcinoma and undifferentiated malignancies of young dogs. Morbidity and mortality often result, however, from local disease rather than distant metastasis. Many animals die or euthanasia is performed because of signs of local disease, such as pain, prehension difficulties, halitosis and dysphagia.

Control of local disease is the first goal of most surgical treatments for oral cancer. However, curettage, debulking or other forms of intralesional resections of oral tumors fail because of recurrence of the tumor at the primary surgical site. Mandibulectomy accompanied by soft tissue resection for oral tumors has the potential for providing prolonged remission or cure in certain malignancies. If nothing else, the quality of life can be dramatically improved even though distant metastasis may ultimately occur for some tumor types.

Preoperative Evaluation

Routine haematological and biochemical profiles, as well as urinalysis, should be performed on all candidates for mandibulectomy for anesthetic considerations and to identify any co-existing medical problems. In cases of oral neoplasia, the tumor should be clinically staged (see

DIAGNOSTIC TECHNIQUES AND WORK-UP, page 102), before definitive treatment is selected. Staging requires a deep incisional biopsy under general anesthesia for histopathological analysis and analysis of a regional lymph node aspirate and thoracic radiographs to detect regional and distant metastasis. Preoperative staging helps the veterinarian determine the appropriate treatment and prognosis and also helps the client in deciding whether to pursue therapy (based on the prognosis related to the type and stage).

Radiographs of the mandible taken under general anesthesia should be obtained preoperatively in all cases of oral cancer to help plan surgical margins. The views taken may include lateral, ventrodorsal, and oblique views, as well as open mouth views if the tumor involves the rostral part of the mandible. Fine detail screen with high contrast film at low KVP is recommended. Tumors that are adherent or "fixed" to the underlying mandible, even if there is no radiographic evidence of invasion, are candidates for mandibulectomy (fixation implies at least microscopic invasion of the tumor into bone).

General Surgical Considerations

When mandibulectomy is performed for treatment of an oral neoplasm, at least a 1 to 2cm grossly visible tumor-free margin should be obtained on all cut surfaces. The removed mandible should be radiographed to aid in determining whether adequate bony disease-free surgical margins were obtained. The specimen should be dipped in India ink or specific margins marked. Incisions can be made into large lesions to aid fixation (care must be taken so the pathologist does not confuse these

cuts with actual surgical margins and the tumor should remain intact somewhat like a bread loaf would be if not completely sliced). The entire specimen is then placed in 10% buffered formalin and submitted for histological evaluation. The pathologist should be requested to specifically note any extension of cancer cells to a cut edge. Because the pathologist generally does this randomly, preplacing sutures (tagging) suspect edges, marking with ink, or submitting suspect areas in separate containers will greatly increase the accuracy of this determination. Tumor extension to the cut margins generally implies the need for additional surgery, adjunctive irradiation or, rarely, chemotherapy.

Mandibulectomy is considered a contaminated or, at best a clean contaminated surgery. Many authors have recommended the administration of therapeutic levels of antibiotics at the time of surgery. Parenteral prophylactic antibiotic therapy can be given just before surgery or intraoperatively and continued for a maximum of 24 hours after surgery in cases in which osteomyelitis is not already established. The antibiotic chosen should be effective against the bacterial flora normally found in the oral cavity, which includes gram-positive cocci (e.g. staphylococcus species and streptococcus species) and gram-negative rods (e.g. *Proteus* and *Pasteurella* species). The first-generation cephalosporins, penicillins, and synthetic penicillins are generally considered effective prophylactic oral antibiotics.

Polypropylene, polydioxanone, and polyglactin 910 suture (3-0 or 4-0) are recommended for wound closure following mandibulectomy. (Polypropylene [Prolene], polydioxanone [PDS], and polyglactin 910 [coated Vicryl], Ethicon, Inc, Somerville, NJ) These relatively nonreactive sutures minimize oral mucosa irritation and maintain adequate tensile strength during the critical early period of healing. Although polypropylene suture shows the least tendency to incite oral mucosa ulceration, it is nonabsorbable and thus must be removed. Heavy sedation or general anesthesia often is required to adequately visualize the oral cavity for its removal. Polydioxanone's advantages are that it is monofilament and absorbable. Its absorption is very slow, however, and food tends to cling to the suture over a period of time, resulting in oral mucosa ulceration if the knots are not buried or if the exposed suture is not removed after the wound has healed. Polyglactin 910, while being absorbable, is a braided suture and tends to drag through the delicate oral mucosa. Bacteria and food tend to cling to it; this material has the greatest tendency of these three sutures to cause oral mucosa irritation. Personal preference, cost, and availability should be considered when selecting a suture. A reverse-cutting swaged-on needle has been found beneficial in suturing the tough fibrous soft tissues of the oral cavity. This type of needle causes little surgical trauma.

SURGICAL TECHNIQUES

Depending on the type of mandibulectomy performed, the hair is clipped and the area over the anticipated surgery site is prepared. The oral cavity should be swabbed with a 10% dilution of povidone-iodine solution. (Betadine solution, Purdue Frederick Co, Norwalk, CT 06856). A mouth speculum may be placed between the teeth on the normal side to keep the mouth open. The surgical area is draped off as aseptically as possible with a water-impermeable draping material.

The patient should be fasted for 12 hours before the procedure. Abnormalities in fluid or electrolyte balance should be corrected prior to surgery. The choice of preanesthetic medication is based on the preoperative evaluation and personal preference. A narcotic is recommended for its analgesic effect. Following induction, an endotracheal tube should be inserted and anesthesia maintained with a gas

inhalant and oxygen. A cuffed endotracheal tube is mandatory to prevent aspiration of blood and fluid. The tube is anchored to the muzzle to minimize its interference during surgery. Isotonic crystalloid fluid therapy is started immediately after induction at an initial dose of 10 ml/kg/hr. At times, hemorrhage is brisk and the fluid rate should be increased as dictated by the situation. The patient is placed on a protected hot water blanket and monitored at all times with a continuous electrocardiogram and preferably with either direct or indirect blood pressure measurements. Before the surgical procedure is begun, the cuffed endotracheal tube should be checked to ensure that an airtight seal has been created with the trachea to prevent the aspiration of blood.

Unilateral Rostral Body Mandibulectomy

Tumors or injuries involving the incisors, lower canine, or first two premolars on one side are indications for unilateral rostral body mandibulectomy. The soft tissues medial to this region must be free of tumor in order to obtain a tumor-free margin and have adequate soft tissues for closure. A bilateral rostral body mandibulectomy should be considered if the medial soft tissue structures are involved or if an adequate tumor-free margin cannot be obtained.

The animal is placed in lateral recumbency with the affected side upper-most. The labial mucosa is incised at a minimum of 1 cm outside the visible limits of the tumor. The dissection is continued around the body to the sublingual mucosa until the symphysis and the caudal limit of the proposed osteotomy is exposed. The sublingual and mandibular salivary gland ducts open under the body of the tongue on the sublingual caruncle and are generally preserved. If excising this area is necessary, an attempt should be made to ligate these ducts.

Following exposure of the symphysis, the tough fibrous joint is split with an osteotome and mallet to separate the two sides of the mandible. If the tumor has crossed over or is adjacent to the symphysis, the rostral osteotomy should be performed off center between the incisors or adjacent to the canine tooth on the opposite side in order to completely excise the symphyseal joint. Because the body of the mandible is very dense and brittle, an oscillating saw or Gigli wire is used to make the caudal osteotomy. (A hobby saw or Hack saw blade could substitute quite well in this task). Some authors suggest tapering the osteotomy at the occlusal margin to decrease suture line tension on the mucosal closure. This may require the removal of an additional tooth. Hemorrhage from the mandibular medullary cavity is from the mental artery and vein and at times may be brisk. It is best to control bleeding by carefully picking up the offending artery with mosquito hemostats and ligating it with suture. If hemorrhage is controlled with cautery or bone wax there is a risk that, in recovery when blood pressure increases profuse hemorrhage may ensue dictating the need to re-operate. No attempt is made to stabilize the sides of the mandible.

A one-layer simple interrupted suture closure of sublingual mucosa to the labial mucosa attached to the skin is accomplished with 3-0 or 4-0 suture.

Bilateral Rostral Body Mandibulectomy

Bilateral rostral body mandibulectomy is indicated for tumors or injuries that cross the midline rostral to the second premolar. This procedure is more commonly used in cancer patients compared to the former procedure because tumors frequently extent bilaterally at the time of diagnosis.

The patient can be placed in lateral, dorsal, or sternal recumbency. The ventral recumbency position affords good exposure of the oral cavity for suturing, however, it makes sawing the bone a little cumbersome if a large power instrument is used. My preference is to position the animal in dorsal recumbency with the maxilla fastened to the table with tape. This procedure is similar to unilateral rostral body mandibulectomy except that a bilateral resection is performed. No attempt is made to fasten the two sides of the mandible together. The bodies are not pulled together but are allowed to remain in a normal anatomic position. In the case of small resections, the caudal aspect of the symphysis can be left intact, providing stability and better excellent cosmetics. Redundant skin may need to be removed before it is sutured to the sublingual mucosa during closure. This is easily accomplished by excising a V-shaped wedge of skin with the apex located ventrally. The excision can be performed at the most rostral tip of the exposed skin or just lateral to this point. The location selected should be based first on location of the tumor and second on cosmetics. It is imperative that any adherent skin overlying the tumor be removed *en bloc* to ensure a tumor-free margin. During suturing of the labial mucosa attached to skin to the sublingual mucosa, an attempt should be made to create a soft-tissue ridge rostrally to help keep saliva in the mouth. Holes drilled with a 0.045 inch "K-wire" in the stumps of the mandible can serve as anchor points for suturing the deep tissue in the reconstruction of a chin. This helps relieve tension from the mucosal layer and helps prevent dehiscence.

Total Hemimandibulectomy

Total hemimandibulectomy involves removal of one the entire side of the mandible. This procedure is indicated for tumors or injuries involving a large segment of the mandible or for those tumors (e.g. malignant melanoma, fibrosarcoma, osteosarcoma) that can extend into the medullary cavity of the mandible.

The animal is positioned in lateral recumbency with the involved mandible upper-most. The commissure of the lip is first incised at the canthus, full thickness, to the rostral edge of the vertical ramus. The incision is then continued through the skin, avoiding the underlying masseter muscle to the level of the temporomandibular joint. Branches of the facial artery and vein are divided and ligated or cauterized as necessary. The parotid duct is generally dorsal to this incision.

The labial and buccal mucosa is then incised, to ensure at least a 1-cm tumor-free margin. This incision is begun at the symphysis and is extended caudally to the angle of the mandible. The mandibular and sublingual salivary ducts may be ligated at this time. The dissection is carried completely around the horizontal body of the mandible; the genioglossus, geniohyoideus, and mylohyoideus muscles are cut where they attach to the medial surface of the mandible or at some distance from the mandible depending on the location and size of the tumor. The sublingual mucosa is incised to free the lateral border of the tongue. As much mucosa as possible is saved to aid closure and to allow mobility of the tongue after reconstruction. Once the horizontal body is free of soft tissue attachments, the symphysis is cut with an osteotome and mallet. This allows free lateral movement of the affected mandible, enhancing visualization for caudal dissection.

The masseter muscle is next sharply dissected from the ventrolateral surface and ventral margin of the ramus of the mandible. The hemimandible may then be retracted out of the wound. The digastricus muscle is then incised at its insertion on the ventrocaudal border of the horizontal mandible or at some point sufficiently distant from gross tumor. With lateral retraction of the

mandibular body, the pterygoideus muscles are incised where they insert medially on the ventrocaudal surface of the angle of the mandible. Extreme care is necessary at this time to avoid accidental cutting of the mandibular alveolar artery, a branch of the maxillary artery, prior to its identification and ligation; profuse hemorrhage results if it is prematurely incised. This vessel passes across the lateral surface of the medial pterygoideus muscle before entering the mandibular canal. The mandibular foramen is located ventromedial and just rostral to the border that extends between the angular and coronoid processes of the mandible. The artery can generally be easily palpated where it enters the foramen but if there is excessive retraction of the mandibular segment the artery may be occluded and a pulse may not be palpable. If there is no palpable pulse in this area, release some of the retraction and the artery is then generally easily identified. After the capsule of the temporomandibular joint is visualized and incised both medially and laterally, the joint is luxated. This allows removal of the temporalis muscle as it inserts on the coronoid process of the mandible and of any remaining loose fascial attachments.

Closure is specific to each case, depending on the amount of soft tissue excised, but in all cases dead space must be closed, followed by mucosal apposition in the caudal third of the incision. A three-layer suture closure is recommended. The deep layer consists of opposing the pterygoideus, masseter, and temporalis muscles. If this does not inadequately close the dead space, a drain may be placed to exit ventrally. The remaining closure sequence entails the stromal layer located below the mucosa followed by a mucosal layer. A continuous suture pattern works best in the mucosa to obtain a watertight seal.

In the caudal third of the incision, the oral mucosa lateral to the base of the tongue and oropharynx is sutured to the mucosa of the soft and hard palate. In the middle third of the incision, the upper buccal and labial mucosa is sutured to the sublingual mucosa remaining lateral to the tongue. This is continued to the rostral edge of the commissure incision. Because removal of the entire hemimandible results in loss of lateral support for the tongue, lateral drifting of the tongue often occurs. Closing the commissure of the lip farther rostrally can help maintain the normal position of the tongue. To do this, the margin of the upper lip, where it previously met the lower lip to form the commissure, is incised full thickness along its margin to the level of the first premolar or canine tooth. A three-layer suture closure, consisting of the mucosa, subcutaneous tissue, and skin, is then performed. Because of excess tension at the rostral extent of the suture line when the mouth is opened, a vertical mattress suture with buttons or rubber stent is recommended. To complete the closure, the symphyseal oral mucosa is sutured to the lower labial mucosa as described for a unilateral rostral body mandibulectomy.

Vertical Ramus Mandibulectomy

Vertical ramus mandibulectomy is indicated for tumors or injuries involving the angle or vertical ramus of the mandible. This procedure is versatile enough to allow preservation of the temporomandibular joint or excision of the entire hemimandible caudal to the last molar.

The animal is placed in lateral recumbency with the affected side upper-most. A curved skin incision is made over the length of the ventral aspect of the zygomatic arch. Multiple small vessels are encountered, and several thin superficial muscles are incised as they cross lateral to the zygomatic arch. The periosteum is incised over the lateral surface of the zygomatic arch. With a periosteal elevator, the temporalis and masseter muscles are subperiosteally elevated off the dorsal and medial

aspect and the ventral aspect of the zygomatic arch. Care should be taken not to injure the infraorbital artery, nerve, and vein as they course just medial to the zygomatic arch. Once the zygomatic arch is free of soft tissue attachments, it is cut with an oscillating saw or Gigli wire at its rostral and caudal margins; an osteotome should not be used because it tends to shatter the hard, brittle bone of the zygomatic arch. Following osteotomy, the zygomatic arch is removed. Bleeding at the cut edges of the osteotomy site can be stopped with electrocautery or bone wax. Some authors recommend preserving this piece of bone by covering it in a blood-soaked gauze sponge, and placing it in a safe area for later use. If cancer or injury has invaded or destroyed this bone, it should not be reimplanted into the body. I rarely reuse the excised zygomatic arch. The vertical ramus on that side will no longer exist after this surgery so the ipsilateral muscles of mastication will atrophy. This tends to make the zygoma appear very prominent so replacing the zygomatic arch does not improve the cosmetic appearance. In fact animals have a more appealing appearance if this bone is not replaced.

The masseter muscle is elevated ventrally from the lateral surface of the vertical ramus. The temporalis muscle is similarly elevated from the medial and rostral aspect of the mandibular ramus. Care should be taken, as the medial dissection is continued ventrally, to avoid the mandibular alveolar vessels and nerve. These structures cross the lateral surface of the medial pterygoideus muscle and enter the mandibular foramen located just rostral and ventral to the temporomandibular joint. If the temporomandibular joint is to be included in the excision, the vessels must be divided and ligated and the medial pterygoideus muscle incised and elevated from the ventromedial aspect of the mandibular angle. The mandible is cut ventral and rostral to the involved bone with an oscillating saw or Gigli wire. Depending on the extent of the lesion to be removed, one may preserve the temporomandibular joint or include the joint in the excised bone. At this point, the ramus can be easily removed by incising any loosely attached muscle and fascia; the temporomandibular joint is dislocated if necessary.

Following copious lavage with physiologic saline, the muscle groups at the angle of the mandible are closed together to obliterate dead space. If you chose, the zygomatic arch may be replaced and stabilized with a 20-gauge interfragmentary wire at its rostral and caudal margins. A 0.045-inch Kirschner wire can be used to drill the holes for insertion of the orthopedic wire. The fascia of the masseter and temporalis muscles is then reattached to the zygomatic arch by encircling, nonabsorbable sutures. If the bone is not replaced then closure is accomplished by suturing the fascia of the masseter and temporalis muscles together. Closure is completed with placement of subcutaneous and skin sutures.

Segmental Horizontal Body Mandibulectomy

Segmental horizontal body mandibulectomy is indicated for benign disease processes and for low-grade malignancies that do not penetrate cortical bone extensively and are confined to the horizontal body between the first premolar and the last molar. With a mandibulectomy to remove cancer, however, adequate (1 cm or greater) disease-free surgical margins must be obtained. If in doubt, it is wise to do a total hemimandibulectomy procedure.

The animal is placed in lateral recumbency with the affected side upper-most. The labial and lingual mucosa is incised 1cm outside the visible limits of the tumor. Dissection is continued completely around the mandibular body until it is exposed for 360 degrees. An oscillating saw or Gigli wire is then used to cut the mandibular body 1 cm rostral and caudal to the lesion. Some authors

recommend making the osteotomy angle away from the lesion toward the occlusal surface of the mandible. Bleeding from the exposed medullary cavity can be stopped with ligation of the divided vessels as described for rostral mandibulectomy. A one-layer closure of sublingual mucosa to the remaining labial mucosa attached to the skin is accomplished with 3-0 or 4-0 suture material.

Postoperative Care And Complications

Where there is exposed nerves in the dissection, such as the branches of the trigeminal nerve (alveolar nerve) the prineureum or the stump of transected nerves may be infused with bupivacane with a 25 gauge needle on a syringe to induce post-operative, regional anesthesia to aid recovery. Analgesics generally are indicated for the first 24 hours postoperatively, particularly after the more aggressive procedures. Maintenance parenteral fluids (20 ml/kg TID) also are recommended during this time. Antibiotics generally are not given for longer than 24 hours postoperatively.

Water and soft foods may be given the day following surgery for all types of mandibulectomy. Sloppy foods should be avoided and it is preferable to feed soft canned dog food made into "meat balls" that can be easily swallowed. Hot dogs are a good alternative food for the first several days after surgery. Most animals are able to maintain hydration and caloric intake by 24 to 48 hours after surgery. Pharyngostomy or gastrostomy tubes are rarely necessary. It is possible for the animal to eat more abrasive food after about ten days and a return to the normal diet is advised at this time.

Despite the "radical" nature of these surgeries, complications are relatively rare. Postoperative infection is rare unless a deep-seated infection was present at the time of surgery. The abundant blood supply to the oral cavity is a major reason for the low incidence of infection.

If dehiscence occurs at the surgery site, delaying closure for 7 to 10 days, to allow better delineation of necrotic tissue and development of a healthy granulation bed, is recommended. Dehiscence generally results from self-induced trauma by the animal, excessive use of electrocautery, premature feeding of hard foods before adequate healing, or excess tension at the suture line.

Excess tension is most often noted at the rostral extent of the cheiloplasty following hemimandibulectomy or at the occlusal bone margin following horizontal body ostectomy. Angling the occlusal bone margin away from the lesion and suturing the mucosa over the tapered bone can achieve tension-free closure of the mucosal suture line at the level of the ostectomy. Often, this requires extraction of an additional tooth.

Drooping of the tongue to one side of the mouth can occur following hemimandibulectomy if a cheiloplasty is not performed. Desiccation of the surface of the tongue may result, and the animal's appearance may not be acceptable. Prehensile function of the tongue generally is normal, however.

If ostectomy is performed caudal to the second premolar bilaterally, drooping of the tongue may occur following bilateral rostral mandibulectomy. This is a result of loss of support to the base of the tongue. Despite the unusual appearance and the excessive drooling these animals function well. As long as the owner is prepared for the "long tongue look" there is no reason to deny treatment of dogs with extensive local disease if a potential cure can be achieved with a large mandibulectomy

Following mandibulectomy, it is not uncommon for edema or a "false" ranula to develop at the base of the tongue on the surgery side. This condition is self-limiting and generally resolves within seven days. Removal of the sublingual and mandibular salivary glands is not necessary for resolution of this

condition. Ligation or surgical trauma and inflammation with occlusion of the ducts of these glands at the time of surgery leads to atrophy of the glands.

The only long-term complication that commonly occurs after a mandibulectomy is shifting of the lower jaw toward the operated side. This shift results from loosening of a portion of the mandibular support at either the temporomandibular joint or the symphyseal region. The malocclusion that results generally is clinically insignificant. Occasionally, filing down or extracting the remaining lower canine tooth may be necessary because of chronic irritation and ulceration of the hard palate mucosa. Also, because of malocclusion, excessive dental plaque accumulation can be expected after mandibulectomy.

Follow-up

In cases in which mandibulectomy is performed for tumor excision, periodic checks should be performed at 1, 3, 6, 9, and 12 months. The animal should be evaluated for local recurrence, nodal metastasis, and distant metastasis.

MAXILLECTOMY AND PREMAXILLECTOMY

Maxillectomy involves surgical removal of various portions of the maxillary, incisive, and palatine bones or combinations of parts of these bones with closure of the resulting oronasal defect with a labial mucosal-submucosal flap. The remaining bony structure of the muzzle maintains stability and contour, eliminating the need for bone replacement. Closure of the maxillectomy site is limited by the availability of normal labial and buccal mucosa. Tumors that extensively involve the labia or cross the midline of the hard palate may not be resectable. Appearance and function generally are excellent following maxillectomy.

Indications for partial maxillectomy and premaxillectomy are similar to those for mandibulectomy. These include oral neoplasia, chronic osteomyelitis, maxillary fractures with severe bone and soft-tissue injury; another indication is oronasal fistula. Partial maxillectomy and premaxillectomy are most often performed for local disease control of oral cancer.

Various basic techniques for partial maxillectomy and premaxillectomy have been described and include: unilateral premaxillectomy, bilateral premaxillectomy, and various levels of lateral maxillectomy. An aggressive surgery for cancer involving the bones of the periorbital area is orbitectomy.

Preoperative Evaluation

The preoperative workup for maxillectomy is similar to that for mandibulectomy. The minimum database required includes a complete blood count, biochemical profile, urinalysis, and thoracic radiographs for detection of distant metastasis. Regional lymph node aspiration should also be evaluated for cytological evidence of regional metastasis. Evidence of systemic disease or metabolic abnormalities may preclude or alter the mode of therapy and prognosis.

Radiographs of the skull and tumor site should be taken under general anesthesia. Lateral, ventrodorsal, and oblique radiographs are recommended. High quality radiographs, appropriate positioning, and an adequate number of views are essential for thorough evaluation of the skull. The radiographic assessment should include evaluation of cortical bone continuity, alterations in bone

density, periosteal new bone formation, and involvement of adjacent soft tissues. Computerized tomography (CT scan) is often very valuable in preoperative staging and often greatly helps plan the surgical approach.

An incisional biopsy for accurate tissue identification is also important before definitive therapy is undertaken. The biopsy site should be selected so that the complete resection of the mass is not compromised. The entire biopsy tract must be removed *en bloc* with the tumor at the definitive surgery.

General Surgical Considerations

Boundaries for partial maxillectomy or premaxillectomy for oral neoplasms with or without cortical bone penetration and destruction are determined by oral examination, preoperative radiographs and CT scan. A 1cm or greater tumor-free margin should be the goal.

As a rule, the oronasal defect created following resection of tumors that cross the midline is more difficult to close than a defect created from resection of tumors that do not cross the midline. Availability of normal labial, buccal, and palatine mucosa generally is the limiting factor. The excised tissue should be routinely radiographed to determine whether adequate bony disease-free surgical margins were obtained.

Specimens should be placed in 10% buffered formalin and submitted for histological sections. It is important that the pathologist ascertain any extension of neoplasia to a cut edge. Marking suspect areas with suture at the time of surgery, or submitting these areas in separate containers, will greatly increase the accuracy of this determination. Inking the specimen, as described for mandibulectomy, can facilitate the determination of surgical margins. Tumor extension to a cut margin generally implies the need for additional surgery or adjunctive therapy such as irradiation. Perioperative antibiotics are recommended. Antibiotic therapy for more than 24 hours is not indicated unless dictated by the situation. While surgery of the oral cavity is considered clean-contaminated, infection is rarely a postoperative complication.

Polyglactin 910, polydioxanone, and polypropylene suture (3-0 and 4-0) with swaged-on reverse-cutting needles are recommended (Polyglactin 910 [coated Vicryl], polydioxanone [PDS], and polypropylene [Prolene], Ethicon, Inc., Somerville, NJ). These sutures produce minimal tissue reaction and are well tolerated in the mouth. The soft tissues of the oral cavity are often very fibrous and tough, making a cutting needle easier and less traumatic to pass than a tapered needle. Use of electrocautery should be kept to a minimum. Incisions within the oral cavity made with electrocautery are more likely to have delayed healing or to break down than incisions made with a scalpel.

The choice of preanesthetic medication and induction agents is based on preoperative evaluation, personal preference, and expertise. The use of a narcotic is recommended for its analgesic effects. Following induction, general anesthesia should be maintained with a gas inhalant and oxygen. An endotracheal tube with an inflatable cuff is used to prevent aspiration of blood and fluid. The tube should be secured to the lower jaw to minimize surgical interference. A balanced electrolyte solution (10 mg/kg/hr) is started immediately after induction and continued throughout the surgery until the animal has recovered. Because hemorrhage can be profuse during surgery, a patent intravenous access catheter must be maintained at all times. Cross-matched or DEA1 negative whole blood for

transfusion should be available especially for more extensive resections. Depending on the extent of disease and the type of resection to be performed, clipping of hair is either not necessary or minimal.

Temporary unilateral or bilateral carotid artery occlusion has been found by some authors to decrease blood volume loss and improve visualization of the surgical field during maxillectomies, especially hemimaxillectomy and caudal maxillectomy. After removal of the tissue to be excised, blood flow is re-established to allow maximum circulation to the surgical site. The blood flow to the nasal cavity and palatine mucosa originates from terminal branches of the maxillary artery; the main branches include the sphenopalatine, major and minor palatine, infraorbital, and dorsal and lateral nasal arteries. Experimentally and clinically, the common carotid artery has been permanently occluded both unilaterally and bilaterally in dogs without causing neurological or ischemic deficits. This may not be true, however, in the cat.

As a general principle, haemorrhage control during aggressive oral surgery must be looked on somewhat philosophically. The tissue of the mouth is very well endowed with blood supply. This is why we can get away with these large resections without massive infection and necrosis. At the same time there is real risk for considerable blood loss during surgery. If the surgeon adopts a meticulous approach to haemostasis and tries to keep a dry field, the animal will likely die of blood loss because the surgery time will be extremely prolonged and it is very difficult to control all the mucosal hemorrhage. A more appropriate tact is to keep moving. Make your incision plans and cut and keep cutting, stopping only to address large vascular structures that require division and ligation. Using this technique I have avoided the need to perform carotid ligation.

SURGICAL TECHNIQUES

Positioning of the patient is critical in order to visualize the entire surgical field. The animal positioned in dorsal recumbency with the mouth taped open affords excellent exposure to the hard palate. The lower jaw, tongue, and endotracheal tube are taped to an anesthesia screen. Movement of the head should be restricted by adhesive tape. For orbitectomy procedures the animal is generally placed in lateral recumbency.

The oral cavity is prepared by repeated flushing and swabbing with a 10% dilution of povidone-iodine solution (Betadine solution, Purdue Frederick Co., Norwalk, CT 06856). The surgical site is draped off with water-impermeable drapes applied to the mucocutaneous junction of the upper labia. The lower jaw is draped off as best as possible.

As noted previously, temporary occlusion of the carotid artery may decrease blood loss and improve visualization during a maxillectomy. Although occlusion can be achieved quickly and easily, this procedure requires strict asepsis; thus, the carotid artery should be occluded before the maxillectomy is begun if the same instruments are to be used for both procedures.

Making a ventral cervical midline incision starting at the larynx and extending caudally begin the occlusion procedure. The paired sternohyoideus muscles are separated and retracted laterally to expose the ventral surface of the trachea. The carotid sheath on the affected side is localized dorsolateral to the trachea by palpation and exteriorized by blunt dissection. The sheath is incised, and the common carotid artery is separated from the vagosympathetic trunk and internal jugular vein. The common carotid artery can be temporarily occluded with a bulldog vascular clamp or Rommel-type tourniquet. The other carotid artery is then isolated and occluded if desired. The neck incision is covered with a moistened gauze sponge and protected with sterile drapes during the

maxillectomy procedure. Before closing the oronasal defect, blood flow through the common carotid artery should be re-established. Any residual vessels that require occlusion can be detected at this time before suturing the defect closed. Clean instruments and a change of surgical gloves are required for closure of the neck incision.

Unilateral Premaxillectomy

Unilateral premaxillectomy is indicated for lesions that are located rostral to the second premolar and do not come up to or cross the midline. The labial and gingival mucosa rostral and lateral to the tumor is incised at least 1cm from the gross margins of the lesion. The incision is continued through the hard palate mucosa caudal and medial to the lesion. Hemorrhage from the hard palate mucosal incision generally is profuse and large vessels such as the major palatine artery require ligation. Applying pressure can control other hemorrhage. An oscillating bone saw or osteotome and mallet is used to cut the underlying bone following the mucosal incision lines. The incised segment of bone is freed of soft-tissue attachments and levered *en bloc* with the tumor out of the surgical site taking care not to fracture the specimen.

The oronasal defect created is covered with a labial mucosal-submucosal flap. The flap should be designed so that sufficient tissue is obtained to cover the defect without tension. The flap should consist of mucosa, submucosa, and as much subcutaneous tissue as possible. The surgeon often can establish a tissue plane when undermining the labial mucosa-submucosa with Metzenbaum scissors. The mucosal surface of the flap faces the oral cavity. Blood supply is the critical factor for the survival of the mucosal-submucosal flap. It is important that the base of the pedicle be of sufficient width to allow adequate vascularity to reach the tip of the flap. The flap is sutured into position with a two-layer closure. The first or deep layer consists of simple interrupted sutures placed through holes predrilled in the nasal mucosa and bony hard palate with 0.045-inch "K wire". The second or superficial layer is a simple continuous pattern with the knots buried to appose the palatine mucosa to the labial flap.

Bilateral Premaxillectomy

Bilateral premaxillectomy is indicated for lesions that come up to or cross the midline and are rostral to the second premolar. In essence, this procedure is similar to the unilateral procedure except that the entire rostral bony floor of the nasal cavity is excised. The oronasal defect can be closed with a single layer of labial mucosa-submucosa. This flap is developed from the lip and has its base caudally located so that when it is sutured in place it is analogous to a 90⁰ transposition flap.

Lateral Maxillectomy

The most aggressive of the lateral maxillectomy procedures, hemimaxillectomy is indicated for tumors that involve the majority of the hard palate on one side without crossing the midline. It involves removal of the oral mucosa, teeth, and portions of the incisive, maxillary, palatine, and zygomatic bones. The mucosal incision is begun rostrally at the labial-gingival junction dorsal to the middle incisors and is continued lateral and caudal to the level of the last molar tooth. Medially, the incision begins between the central incisors and extends along the midline of the hard palate. The two incisions are joined together just caudal to the last molar tooth at the junction of the hard and soft palate. Hemorrhage is often profuse and is controlled with pressure, ligation, and electrocautery. An

ostectomy is then performed along the incision lines with either an oscillating saw or osteotome and mallet. Intravenous fluid therapy should be increased as indicated by the rate and volume of blood loss. Whole blood transfusion may be necessary.

The caudal osteotomies are at the rostral base of the zygomatic arch. The terminal branches of the maxillary artery are in this region and need to be identified, divided and ligated. Major branches encountered include the infraorbital, sphenopalatine, and minor palatine vessels. Once the ostectomy incisions are complete, the tissue to be resected is levered loose, soft-tissue attachments are excised, and the section is removed intact from the surgical site. Residual bleeding can be controlled at this time. If temporary occlusion of the common carotid artery has been performed, blood flow should be reestablished to allow identification of cut vessels.

The oronasal defect created is closed with a single-layer labial and buccal mucosal-submucosal flap. The base of the lip flap is located ventrally at the lip margin. This tends to indent the contour of the muzzle. The base of the flap must be wide and long enough to support adequate vascularity to the mucosal-submucosal tissue. The blood supply to the lip is extensive, coming predominantly from terminal branches of the infraorbital (dorsonasal and lateral nasal) and facial arteries (dorsolabial and angular artery of the mouth). These terminal branches anastomose with each other and to their fellow vessels on the opposite side.

Undermining the labial mucosa and submucosa from the maxillectomy site toward the lip margin creates a lip margin-based flap. The mucosa-submucosa flap must be of adequate size and sufficiently undermined so that it can be brought into apposition with the mucoperiosteum of the hard palate without tension. The flap is secured with two layers of sutures as previously described for premaxillectomy. The oropharynx is suctioned of blood before the animal is allowed to recover from anesthesia.

Central Maxillectomy

A relatively easy procedure to perform, central maxillectomy is indicated for tumors located between the canine tooth and the first molar tooth on one side of the hard palate. The procedure is a "regional" hemi maxillectomy. The animal's appearance following surgery generally is excellent because the premaxilla and caudal hard palate are preserved. The major palatine artery requires ligation as it exits the major palatine foramen to supply the hard palate mucosa midway between the alveoli and midline at the caudal border of the fourth premolar. Depending on the dorsal extent of the maxillectomy, the infraorbital artery may or may not require ligation. Following ostectomy of the involved maxillary and palatine bones of the skull, the defect between the nose and mouth is closed with a labial mucosal-submucosal flap with its base at the lip margin.

Caudal Maxillectomy

Caudal maxillectomy is indicated for tumors involving the maxilla caudal to the third premolar on one side. Variable portions of the zygomatic, palatine, and lacrimal bones can be excised during this procedure. The infraorbital, sphenopalatine, and major and minor palatine vessels are ligated if encountered during the resection. Removal of the ventral and ventromedial margin of the orbit does not usually result in a sunken globe and the cosmetic result is usually excellent. The oronasal defect created is closed with a flap composed of labial and buccal mucosa and submucosa.

Orbitectomy

Periorbital tumors are infrequently diagnosed in companion animals but can have devastating consequences. These tumors are often malignant and can originate from, or invade into, the eye, its neurovascular supply, eyelids, retrobulbar space, nasal cavity, paranasal sinuses, oral cavity and brain. Initial presenting signs can be non-specific and include facial swelling, exophthalmia, or pain upon opening the mouth. Unfortunately by the time many periorbital tumors are diagnosed they can be large and invasive. The treatment of choice in many instances is wide surgical resection. Orbitotomy techniques have been described in veterinary medicine. Standard approaches include dorsal and lateral orbitotomy, modified lateral orbitotomy, and the transconjunctival approach. These techniques are useful for obtaining tissue for biopsy and for removing small, encapsulated masses but are inadequate for complete excision of larger, invasive tumors.

When the tumor is attached to or invades the bones comprising the orbit an orbitectomy is indicated. Orbitectomy has been infrequently mentioned in veterinary literature. A recent paper describes orbitectomy for the treatment of malignant disease in 24 dogs and 6 cats. Long disease free intervals were attained and survival times in excess of 15 months were achieved in the majority of cases in the study. The surgical procedure is, however, technically demanding. Despite this, in the hands of experienced oncological surgeons, complications are usually minimal and wide surgical margins can be achieved.

Surgical Technique

Animals are positioned in lateral recumbency. A first generation cephalosporin antibiotic (Cefazolin) is administered (22 mg/kg) intravenously every 2 hours during the procedure, beginning with induction of anesthesia, and then continuing every 8 hours after surgery for 24 to 48 hours. A wide area is clipped and the field is aseptically prepared for surgery. Care is taken to protect the eye if it was to be preserved. Temporary tarsorrhaphy is occasionally performed to cover the globe.

Surgical approach varies with location of the tumor. The dog and cat have an open orbit. The lateral wall is incomplete and is composed of a thick fibrous orbital ligament that connects the frontal bone to the zygomatic arch. The bones that comprise the orbit include the maxilla, frontal, zygoma, and palatine, lacrimal and sphenoid bones. Incisions are centered over the tumor and include any biopsy tracks or previous surgical scars. An attempt is made to remove the tumor intact and surrounded by a one to two centimeter layer of normal tissue whenever possible.

A total orbitectomy involves a combination of individual approaches. A dorsal approach is used to expose the frontal bone overlying the nasal cavity and frontal sinus. The temporalis muscle overlying the portion of the frontal bone is incised, elevated and retracted ventrally and rostrally to expose the caudal margin of the orbit. An intraoral approach is used to isolate the caudal hemimaxilla. The buccal mucosa is incised lateral to the edge of the tumor located on the maxilla. The mucoperiosteum of the palatine bone is incised medial to the caudal molars and is elevated medially. The exposure of the maxilla is then continued dorsally to join the exposure of the frontal bone. The zygomatic arch and the orbital ligament define the lateral orbit. The temporalis and masseter muscle insertions on the zygomatic arch are incised to expose the zygomatic arch. If the tumor extends lateral to the orbit, portions of the masseter muscle ventral to the zygomatic arch are also removed with the tumor. If the coronoid process of the mandible is involved the vertical ramus is exposed ventral to the tumor and a transverse osteotomy of the ramus is performed. The coronoid process is

then removed with the entire mass. On occasion the entire vertical ramus and a portion of the mandibular body may be also removed.

Osteotomies are performed using an oscillating bone saw, an osteotome and mallet, an air drill, or a combination of these instruments. The zygomatic arch is osteotomized at its most caudal border and could be extended to include the temporomandibular joint. If the maxilla is involved, a caudal hemimaxillectomy is performed (see Caudal Maxillectomy, page 122). The hemimaxillectomy is continuous with the rhinotomy over the nasal cavity and frontal sinus, which can be extended into a craniotomy if necessary. The medial orbital wall is removed by osteotomy of the lacrimal and frontal bone to complete the resection.

The orbit and tumor are freed from any residual soft tissue attachments and removed as one piece. Haemostasis is maintained with electrocautery and ligatures. The optic nerve is severed as it exits the optic foramen. Excessive traction of the optic nerve is avoided in order to prevent iatrogenic damage to the optic chiasm resulting in blindness in the contralateral eye.

Partial orbitectomy consists of either removal of the superior orbit (e.g. frontal bone) or the inferior orbit (e.g. zygoma and maxilla). Inferior orbitectomy consists of excision of the zygomatic arch or both the zygomatic arch and the caudal hemi-maxilla. As in the total orbitectomy procedure if the vertical ramus of the mandible is involved it is removed with the zygomatic arch. A superior orbitectomy involves excision of a portion of the frontal bone and removal of the medial aspect of the orbital wall. Enucleation is only performed if the eye or its neurovascular supply or a significant percentage of the eyelid is infiltrated with tumor or is in close proximity to the tumor border.

The defect is closed by apposition of any subcutaneous tissue using absorbable sutures. Care is taken to reestablish the compartments of the oral and nasal cavities. If a caudal maxillectomy is performed the oral and nasal cavities are reestablished by suturing the labial mucosa of the upper lip to the hard and soft palate. Attachment of soft tissues to the palatine bone of the palate is facilitated by pre-drilling holes in the bone through which sutures can be passed. If a craniotomy has been performed a temporalis muscle flap may be used to cover and protect the exposed brain. Surgical sites are drained if necessary for 24 hours. Skin is reapposed with nylon sutures.

Postoperative Care

The animal should be supported for the first 24 hours after surgery with parenteral fluids and analgesics. Antibiotics given perioperatively generally are not indicated for more than 24 hours after the surgery. Water is allowed after recovery from anesthesia, and soft foods are offered 24 to 48 hours after surgery. Pharyngostomy and gastrostomy tubes rarely are necessary.

The surgical site should be evaluated daily for five days for evidence of dehiscence. Mucopurulent nasal discharge during the healing period is generally an indication of suture line dehiscence. Suture line tension, excessive use of electrocautery, ischemic necrosis of the mucosal-submucosal flap, and tumor recurrence are the major causes of dehiscence. Except for tumor recurrence, most problems result from technical error by the surgeon and can be eliminated by following proper technique and minimizing surgical trauma. If the sutures holding the flap in place break down within the first 3 to 5 days following surgery, the animal should be reanesthetized and the flap resutured. If dehiscence occurs later, it is best to wait 2 to 3 weeks before attempting reclosure of the oronasal defect. This delay allows tissue inflammation to subside and clearer demarcation of necrotic and healthy tissues.

At the time of resuturing, rebiopsy of this surgical site is *always* indicated. What appears as granulation tissue can easily be tumor recurrence. Approximately 20 to 30% of maxillectomies have some degree of dehiscence during the postoperative period. Not all, however, are of clinical significance. Dehiscence is most commonly noted following caudal or hemimaxillectomies, when tumors cross the midline, and whenever the mucosa has been sutured next to a tooth on the occlusal margin of the ostectomy. Extracting an additional tooth, elevating the palatine and labial gingiva, and suturing the mucosal flaps over the alveolar bone can achieve a tension-free closure at the level of the occlusal ostectomy.

Indentation of the muzzle contour can occur following partial maxillectomy and repair with a labial mucosal-submucosal flap, resulting in an objectionable appearance or ulceration of the surgical site from a mandibular tooth. Such indentation generally results from an insufficient amount of normal labial tissues; it sometimes occurs following closure with a lip margin-based mucosa flap. It generally can be corrected by incising the base of the labial flap 3 weeks following surgery to allow the lip to return to its normal position.

With a bilateral premaxillectomy, removal of the bony hard palate caudal to the canine teeth may result in shortening of the nose. In some cases, the upper lip may actually be positioned caudal to the lower canines when the mouth is closed. Drooping of the nares and rostral muzzle will also occur when the mouth is open. Dogs appear to breathe through the nostrils in a normal fashion, however. If the nasolacrimal duct is transected or ligated following any of the maxillectomy procedures, mild crusting of the nares and epiphora on the ipsilateral side should be expected.

Follow-up

Animals should be evaluated at 1 month and then every 3 months during the first postoperative year. Evaluations should include both visualization and palpation of the oral cavity, muzzle, and regional lymph nodes. Thoracic radiographs, depending on tumor type, may also be indicated for detection of distant metastasis. If gross evidence of local tumor recurrence or suspicious areas is detected, an incisional biopsy should be made. Skull radiographs may be beneficial but are often difficult to evaluate, especially in the distinction of tumor and bony reactions resulting from surgical trauma. Complete surgical excision with adequate tumor-free margins generally is difficult to obtain following documentation of local tumor recurrence.

Paraneoplastic Syndromes

One way cancer may affect the host body is by distant systemic disturbances known as paraneoplastic syndromes. Paraneoplastic syndromes may occur by tumours producing and releasing substances such as polypeptide hormones that act at distant sites. Often the cause of paraneoplastic syndromes is not known. The following is a broad listing of paraneoplastic syndromes giving examples of some tumours that may be associated:

Cancer cachexia

Many tumours

Ectopic hormone production

hypercalcaemia

Lymphoma

Mammary adenocarcinoma

Multiple myeloma

Epidermoid carcinoma

Anal sac apocrine gland carcinoma

Parathyroid tumours

Gastric carcinoma

Thyroid carcinoma

Nasal carcinoma

Thymoma

Hypoglycaemia

Islet cell tumour

Hepatocellular carcinoma

Oral melanoma

Haemangiosarcoma

Salivary gland adenocarcinoma

Hepatocellular adenoma

Plasmacytoid tumour

Lymphoma

Leiomyosarcoma

Erythropoietin producing

Primary or metastatic renal tumours

Lymphoma

Hepatic tumours

Nasal fibrosarcoma

TVT

ACTH producing

Primary lung tumour

Hypertrophic Osteopathy

Primary lung tumour

Rhabdomyosarcoma bladder

Lung metastases

Oesophageal sarcomas

Haematological-Haemostatic Abnormalities

Anaemia

Many tumours

Disseminated intravascular coagulation

Haemangiosarcoma

Inflammatory carcinoma

Mast cell tumours

Many other tumours

Leukocytosis

Lymphoma

Many tumours

Thrombocytopaenia

Lymphoma

Mammary adenocarcinoma

Nasal adenocarcinoma

Mast cell tumour

Haemangiosarcoma

Fibrosarcoma

Hyperproteinaemia

Multiple myeloma

Lymphoma

Renal manifestations

Nephrotic syndrome

Multiple myeloma

Renal disease due to hypercalcaemia, amyloid, paraproteins

Many tumours

Fever

Many tumours

Neurologic Abnormalities

Lymphoma

Myelomonocytic neoplasia

Thymoma

Beta cell tumour

Primary lung tumour

Gastric Ulceration

Mast cell tumour

Cancer cachexia

Weight loss with associated metabolic abnormalities seen in many cancer patients when normally adequate nutritional intake is present is called cancer cachexia. This may be a fairly common paraneoplastic condition in animals with cancer. The metabolic abnormalities underlying this condition may continue for some time even after the tumour has been controlled.

Hypercalcaemia

There are many causes of hypercalcaemia. Not an exhaustive list includes:

- hyperalbuminaemia
- hypercalcaemia of malignancy
- primary hyperparathyroidism
- hypervitaminosis D
- renal disease (familial renal dysplasia and CRF)
- osteolytic bone disease
- plant toxicity
- calciferol-containing rodenticides
- certain granulomatous diseases
- severe hypothermia
- disuse
- osteoporosis

Calcium is usually measured by colourimetric methods so lipaemia or haemolysis can lead to a spurious result. Also a fraction of the calcium is carried in the blood bound to proteins so an elevated albumin can lead to an elevated calcium measurement (unless just the active ionized fraction is measured as a serum ionized calcium measurement). The most common cause of true hypercalcaemia in dogs is hypercalcaemia of malignancy (paraneoplastic syndrome). Lymphoma is the most common cause. Many dogs with hypercalcaemia secondary to lymphoma have the mediastinal form. The mechanisms involved include; lytic bone metastasis, true hyperparathyroidism that occurs simultaneously with the malignant disease, ectopic tumour-produced parathormone (PTH) or PTH-related peptide (PTH-rp), tumour-produced prostaglandins (PGE₁, PGE₂), and tumour-produced osteoclast activating factor (OAF). PTH-rp is a common cause in such tumours as lymphoma and anal sac apocrine gland adenocarcinoma.

The clinical signs associated with hypercalcaemia are largely referable to altered renal function: polydipsia, polyuria, vomiting, and dehydration. Elevated calcium can also affect the gastrointestinal, cardiovascular and neurological systems causing a wide variety of signs including anorexia, bradycardia, weakness even stupor, coma and seizures.

It is important to identify the cause of hypercalcaemia. The most important treatment for hypercalcaemia of malignancy is to remove the cancer causing this paraneoplastic disorder. It is impossible to treat cancer unless it is properly diagnosed so make sure an accurate diagnosis is obtained before starting treatment (especially with glucocorticoids). It is reasonable to start some emergency symptomatic relief from the hypercalcaemia by using 0.9% NaCl (45-80 ml/kg/hr) intravenously together with furosemide (1-4 mg/kg BID IV or PO). Prednisolone is very effective in lowering serum calcium but may also cause tumour lysis if lymphoma is the cause thus masking the diagnosis. **Do not use corticosteroids until lymphoma has been ruled out.** Other drugs to reduce serum calcium include Calcitonin 4 –8 MRC units/kg SQ), Mythramycin 25 µ/kg IV once or twice weekly, diphosphinate (investigatory), gallium nitrate also mainly used in people.

Hypoglycaemia

Insulinoma is one of the most common causes of hypoglycaemia in the dog. There are, however other tumours that can cause hypoglycemia: hepatocellular carcinomas and adenomas, plasmacytoid tumours, lymphoma, leiomyoma, melanoma, haemangiosarcoma, and salivary gland adenocarcinoma. Interestingly, dogs with hypoglycaemia associated with extrapancreatic tumours have low to low normal insulin levels in their blood. Possible reasons for the low blood glucose in these cases is the secretion by the tumour of insulin-like substances, accelerated utilization of glucose by the tumour, and failure of gluconeogenesis or glycogenolysis by the liver. The most likely differential diagnoses for hypoglycaemia in the dog is: insulinoma (hyperinsulinism), hepatic dysfunction, adrenocortical insufficiency, hypopituitarism, extrapancreatic tumours, starvation, sepsis, and laboratory error.

Clinical signs usually occur with blood glucose levels below 45 mg/dl. Signs are predominantly neurological; weakness, disorientation, seizures progressing to convulsions, coma and death.

Extrapaneatic tumours are usually easily identified. Insulinomas are often very small, however and difficult or impossible to image. Insulin-producing tumours may be diagnosed by demonstrating elevated insulin in association with low blood glucose levels. Periodic sampling during a 72 hour fast may be necessary to identify times when there is dramatic hypoglycaemia. The amended insulin-glucose ratio and the insulin-glucose ratio (AIGR) have been advocated as ways to help diagnose insulin-producing tumours in small animals. The AIGR is:

$$\frac{\text{Serum insulin } (\mu\text{U/ml X 100})}{\text{Serum glucose (mg/dl)} - 30}$$

AIGR values above 30 suggest a diagnosis of an insulinoma or other insulin-producing tumour.

Surgical removal is the treatment of choice for tumours producing hypoglycaemia. Partial pancreatectomy is recommended to remove insulinomas and post operative pancreatitis and diabetes mellitus may be complications. The majority of insulinomas are malignant and many are high stage at the time of diagnosis (liver and lymph node extension). It is important to biopsy live and liver nodules and to remove regional nodes for staging at the time of surgery. High stage, young age and very high serum insulin concentrations have been associated with shorter survivals. Medical management includes feeding small frequent meals and using drugs such as prednisone (0.5 to 2 mg/kg divided BID PO), diazoxide (10 to 40 mg/kg divided BID PO) or propranolol (10 to 40 mg/kg TID PO). Combined surgical and medical management of insulinomas has been associated with remission times of one year or more.

Hypertrophic Osteopathy

Hypertrophic osteopathy is a bony disease of dogs and cats, often associated with primary and metastatic lung tumours. Other tumours such as oesophageal sarcomas, bladder rhabdomyosarcomas have also been associated with this paraneoplastic syndrome. Pneumonia, heartworm disease, congenital and acquired heart disease, focal lung atelectasis have also been implicated in this condition. The disease results in increased peripheral blood flow and periosteal new bone proliferation on diaphyseal locations of long bones. This often starts with the digits and extends as far proximally as the femora and humeri. Initially there is soft tissue swelling with pain and heat in the limbs and radiographic evidence of periosteal new bone arranged in fine palisades perpendicular to the diaphysis occurs later. The cause is not known however successful treatment with vagotomy suggests a neurovascular mechanism.

Removal of the cause (tumour) can cause complete resolution of signs and resolution of the bony changes. Other treatments include glucocorticoids, vagotomy and other surgical procedures and the use of analgesics (NSAID's).

Other paraneoplastic syndromes will be discussed in lecture and readers are directed to reviews in current oncology texts for further information.