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Multimodality therapy for head and neck cancer

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For the purposes of this article, head and neck tumors include nasal tumors, oral tumors, and tumors of the salivary glands, thyroid glands, and ear canals. As a group, these tumors remain a treatment challenge in both human and veterinary medicine. Generally, surgery is considered the mainstay of treatment for head and neck tumors. Tumors that cannot be completely resected and those associated with significant metastatic potential are considered appropriate candidates for multimodality therapy. Although there are now years of anecdotal experience in veterinary medicine to indicate that multimodality approaches to these tumors increase control rates, there are few studies to date that have accumulated enough cases to make strong recommendations. The rate of development of distant metastases can be reduced with systemic chemotherapy, but an overall effect on survival remains to be definitively shown. Those studies that are available are included in this review. In addition, several decades of information accumulated through human clinical trials are summarized briefly.

Nasal tumors

With the possible exception of extremely small well-defined tumors, surgery alone is not indicated in the treatment of nasal tumors. Most nasal tumors are carcinomas or soft tissue sarcomas and are treated with radiation therapy. Radiation therapy alone has increased reported median survival times from the 3 to 7 months reported for surgery, chemotherapy, or immunotherapy [1–5] to 8 to 31 months [6–11]. Significant variation exists between protocols instituted and degree of staging employed. Elective treatment of regional lymph nodes does not seem to be indicated, because

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regional spread of nasal tumors is unusual. All agree that there is unavoidable morbidity associated with the administration of conventional external beam radiation therapy.

Side effects of radiation therapy are usually separated into acute and late effects. Acute effects are generally related to inflammatory reactions in the tissues within the radiation field. The temporary or permanent nature of these effects is usually related to dose and site. Late effects develop over several months to years but are irreversible and more likely to affect the patient's quality of life. For example, ocular effects that can be expected to develop in the treatment of nasal tumors include cataracts and keratoconjunctivitis sicca [12]. Although these side effects are quite acceptable for most owners as the cost of controlling the tumor, they are discouraging to deal with in the face of recurrent tumor within months of finishing treatment. Improvements in survival times might make these side effects more acceptable to owners, and minimizing side effects while increasing expected survival duration would induce more owners to treat nasal tumors.

Modern imaging techniques, including CT and MRI, have dramatically increased the accuracy of radiation therapy treatment planning for both human and veterinary patients. Before the routine use of CT and MRI for diagnosis and treatment planning, clinicians grossly underestimated the extent of disease present in nasal tumor cases. It has been demonstrated that using external landmarks without the benefit of CT scans for radiation planning would result in geographic misses in 90% of veterinary patients [11,13]. Although the information gained from using these imaging modalities usually increases the amount of tissue included in the treatment field, in general, the use of computerized treatment planning allows for a decrease in the amount of normal tissue irradiated. Advanced imaging also allows for more accurate evaluation of responses and their duration. The greatest extent of regression seen on CT scans seems to occur 3 to 6 months after the completion of treatment [14].

For external beam treatments, three-dimensional conformal radiation and stereotactic radiotherapy are particularly exciting new areas. The development of multileaf collimators and on-line portal imaging techniques should make the delivery of three-dimensional radiation therapy more efficient. Intensity-modulated radiation is also being developed. All these improvements decrease the amount of normal tissues irradiated and improve the distribution of dose across tumor tissue. This should decrease side effects, but it remains to be seen whether these advances in radiation planning and delivery translate into increased survival times with radiation used as a single treatment modality. All these improvements have been instituted in the treatment of most human patients. Unfortunately, only small increases in tumor control have been noted, without a concomitant positive impact on survival. Not until multimodality approaches were instituted in human oncology were increases in survival documented [15]. It is important to note that only by improving the therapeutic ratio of

radiation therapy with the technologic improvements listed previously were radiation oncologists able to decrease morbidity sufficiently that the addition of other treatment modalities could be considered.

Most canine nasal tumor patients relapse in the mid- to caudal nasal cavity. Boosting the dose there with conventional external beam radiotherapy via shrinking fields added to morbidity but not to increased tumor control in a previous study [16]. Although numbers were small in this study, it is unlikely, given the human experience, that a significant difference would have been detected regardless of cohort size. Implementation of improvements in treatment planning should allow for increased dose intensity to the tumor and safe administration of multimodality approaches, including the addition of surgery, radioprotectors, radiosensitizers, concurrent chemotherapy, immunotherapy, and targeted biologic therapies. The challenge remains to find a multimodality approach that successfully increases survival times with acceptable morbidity. The radioprotector amifostine has been shown to reduce the incidence of acute and chronic side effects in human head and neck cancer patients treated with radiation and to allow more patients to complete treatment without interruption [17]. The use of radioprotectors, such as amifostine, has yet to be fully explored in veterinary patients. Although surgery performed before megavoltage external beam radiation therapy does not seem to influence outcome, the impact of surgery after radiation therapy has not yet been assessed. Brachytherapy techniques have also been successful in treating human head and neck tumors [15,84]. Because of the noncompliant nature of our patients, these techniques can be difficult to apply to veterinary head and neck cases. Several brachytherapy techniques have been developed and successfully applied, however [18,19].

Rationale for chemoradiation therapy

The purpose of administering chemotherapy and radiotherapy together is to take advantage of the radiosensitizing capability of many active chemotherapeutic drugs for various tumor types and thereby increase regional control rates as well as survival. Protracted radiation therapy as a single modality treatment results in decreased local control rates, presumably because of accelerated repopulation of tumor cells surviving the initial treatment [20]. The failure of induction chemotherapy to provide any survival benefit when compared with surgery or radiation alone in randomized trials may have a similar cause. Significant benefits were not demonstrated until chemotherapy was administered concurrently with the radiation therapy. Administering cytotoxic drugs concurrent with radiation has the potential to increase toxicity substantially, however, and necessitates frequent interruptions in radiotherapy.

Mechanisms behind the synergy of chemoradiation therapy have been postulated to include interference with sublethal damage repair, tumor cell cycle synchronization, and prevention of the emergence of radioresistant or

drug-resistant cells [21]. Cisplatin, carboplatin, paclitaxel, docetaxel, and gemcitabine all have radiation-enhancing properties [15,22–24]. Cisplatin is perhaps the most important chemotherapeutic agent for treating squamous cell carcinoma of the head and neck in human patients [25] and is also the only chemotherapeutic drug with significant activity documented against canine nasal carcinomas [26]. Carboplatin has significantly less toxicity but also lower response rates [27]. In human patients, fluorouracil (5-FU) has demonstrated synergy with cisplatin, leading to the establishment of the now standard human treatment combination regimen of cisplatin plus 5-FU [28]. This combination has not been evaluated in canine patients. The optimal schedule for radiosensitization has not been determined in human or veterinary clinical trials. Nevertheless, the greatest survival benefit observed in most human studies is seen in the patient group receiving concurrent cisplatin chemoradiation [29,30]. Because these trials have resulted in an improvement in regional control that is profound enough to affect survival by 20% to 30% on average, concurrent chemoradiation with cisplatin is now considered the standard of care in human medicine [15]. Other treatment modifications, such as altered fractionation with concomitant boost or hyperfractionation with or without the addition of pre- or post-radiation chemotherapy, only provided modest increases in regional control. Interestingly, the longest survival times reported to date have resulted from treating canine nasal tumors with external beam megavoltage radiotherapy combined with the use of cisplatin as a slow-release formulation likely to result in radiosensitizing doses [31]. This study yielded 1-year survival rates of 81%, and the 2-year survival rate was 39%. These results have not been duplicated using carboplatin as a radiosensitizer [32]. Concurrent chemotherapy with 5-FU/cyclophosphamide or mitoxantrone or preoperative surgery has not affected outcome in previous veterinary series, but none of these compounds are documented to be good radiosensitizers [6,7,9,33]. Phase I and II studies are in progress using radiation combined with gemcitabine chemotherapy [35,36], but response rates are not yet available.

It is important to note that increased toxicity, especially to mucous membranes, was also documented in all these multimodality studies. Aggressive support in the form of analgesics, oral care, and, on occasion, gastrostomy tube placement is required, ideally at a treatment center familiar with the expected severity of toxicity and potential complications. Until we make improvements in limiting the morbidity associated with chemoradiation, the biggest advantage is to patients with excellent performance status and minimal tumor burden. Durable complete responses and prolonged survival are probably possible in this small subset of patients, based on the information gathered in human clinical trials [15]. In the interim, new treatment modalities, such as immunotherapy, gene therapy and biologically targeted compounds, should continue to be evaluated for dogs with nasal sinus tumors.

Oral tumors

Aggressive surgical techniques are well described in the literature and allow for complete resection of a significant percentage of oral tumors [37,85,86]. The most common oral tumors in veterinary medicine include dental tumors, fibrosarcomas, melanomas, and squamous cell carcinomas.

Dental tumors

Common dental tumors in veterinary patients include epulides, ameloblastoma, and other odontogenic tumors. Most dental tumors are well controlled with surgery or radiation therapy even if they achieve fairly large dimensions. Median survival times of 2 to 3 years are reported for both surgery and radiation used as single modalities [38–43]. Except in the case of extremely large tumors, single modality therapy is usually adequate. Combination therapy should be reserved for large ameloblastomas that are incompletely resected. These tumors should also be treated with radiation therapy to minimize risk of recurrence.

Fibrosarcomas

Because of the low metastatic potential of oral fibrosarcomas, most are best treated by surgery wherever possible. Unresectable or incompletely resected fibrosarcomas require the application of multiple treatment modalities. Unfortunately, this situation occurs in a significant percentage of oral fibrosarcoma cases.

In a summary of various papers on mandibulectomy or maxillectomy, fibrosarcomas were found to recur in greater than half of the cases, with median survival times of approximately 11 months and 35% of the patients alive at 1 year [37]. The administration of radiation therapy to those patients with microscopic disease after resection seems to improve outcome, providing a median survival time of 540 days [44]. This is in contrast to radiation alone, where control rates without surgical cytoreduction are approximately 50% at 1 year [45]. Oral fibrosarcomas had a statistically significant lower median survival time (540 days) when compared with fibrosarcomas located in other tumor sites (2270 days), indicating the difficulty of effectively treating large portions of the oral cavity with high doses of radiation therapy while avoiding unacceptable normal tissue complications [44].

Radiation is usually delivered after surgery to dogs with oral fibrosarcoma. There is evidence of a dose response. The human literature indicates that patients who began radiation more than 6 weeks after surgery and whose total therapy time extended beyond 12 to 13 weeks have worse outcomes [15].

Melanomas

Two important prognostic factors have been identified repeatedly in studies of canine malignant melanoma: the size of the primary tumor and the ability of the first treatment intervention to control the disease effectively. Thus, any melanoma with a diameter larger than 2 cm is considered to have significant metastatic potential, and recurrence after surgery is inevitably associated with aggressive behavior. These findings should be interpreted as a caveat to treat aggressively the first time. Patients with small lesions (< 2 cm in diameter) that are completely resected have a median survival time of 511 days in comparison to median survival times of only 164 days for those patients with a tumor greater than 2 cm in diameter or positive lymph node status [46,47].

Melanomas are also responsive to coarsely fractionated radiation therapy [48–51]. Complete response rates ranging from 53% to 69% have been reported, with overall median survival times ranging from 5 to 9.5 months. Again, the size of the primary tumor is found to influence the survival time. Dogs with less than stage II disease (primary tumor <2 cm in diameter) have reported survival times ranging from 14.9 to 20 months in comparison to 5 to 6 months for cases with higher stage disease. Distant disease is the usual cause of death in malignant melanoma, particularly when large tumors or early metastasis is present. This highlights the need for multimodality treatment in melanoma. Early studies with hyperthermia added to radiation therapy demonstrated extremely high response rates; however, these response rates did not translate into increased survival times, and hyperthermia is not routinely available [52,53]. The addition of radiation therapy to surgery for malignant melanomas is unlikely to increase overall survival times, because distant disease is the most common cause of death in these cases [49,50].

Based on early studies indicating objective responses in measurable melanomas, carboplatin has been added to the treatment regimen of malignant melanomas at many institutions across the country [54]. Results from those studies are just beginning to be presented and must be cautiously interpreted, because the data are not yet mature and there is substantial variability in the protocols employed. One early study indicates that survival time increased for all stages of malignant melanoma when chemotherapy was added to the treatment regimen but only achieved statistical significance for dogs with stage III disease [50]. Large multi-institutional trials are required to elucidate fully any benefit gained through the addition of chemotherapy to the treatment of canine oral melanoma.

Immunotherapy also shows promise in the treatment of oral melanomas. A randomized study of 98 dogs treated surgically or by surgery in conjunction with liposome muramyl tripeptide immunotherapy (L-MTP) showed that those dogs with tumors less than 2 cm in diameter and lymph node positivity had an 80% survival rate 2 years later in comparison to only 25% in the surgery alone arm. Unfortunately, L-MTP did not positively

alter survival durations in those cases with larger tumors or metastatic disease [55]. In vivo transfections of established tumors with immunostimulatory genes can elicit antitumor activity and have been demonstrated to induce complete and sustained local regression of large tumor burdens in some canine melanoma patients [56]. Studies are currently underway to combine immunotherapy with surgical resection. Further indication of the role of immunotherapy in the manipulation of oral melanomas was provided by a phase I trial of human tyrosinase DNA vaccination [57]. As these studies mature, adjuvant immunotherapy may replace the use of chemotherapy in these tumors.

Osteosarcomas

Oral osteosarcoma is another tumor that challenges both local control and the control of distant disease. With the possible exception of mandibular osteosarcoma, where surgery alone may prove curative [58], oral osteosarcomas require both surgery to control the primary site and chemotherapy to address distant disease. In those animals in which complete resection is not possible, it is logical to add definitive radiation therapy to increase control rates. There are limited published data available to provide information on the impact of adding adjunctive radiation on local control rates or survival times other than evidence of activity in vertebral tumors, however [59]. As for dogs with melanoma, the survival of most of these animals is limited by the development of distant disease and would not be expected to improve unless systemic therapy is combined with effective local control.

Canine oral squamous cell carcinomas

The prognosis for these tumors seems to be quite site specific, with tumors in the rostral oral cavity curable by surgery [37,60] or radiation therapy alone [61]. Those of the caudal oral cavity, including the tonsil and base of the tongue, are highly metastatic, and a multimodality approach is indicated. A radiation dose response has been documented for these tumors, with 1-year control rates of 46% in those cases receiving greater than 40 Gy [61]. Median disease-free intervals of approximately 1 year are recorded in response to radiation alone, with doses ranging from 38.5 to 57 Gy in a variety of schema. Negative prognostic factors for survival include advanced age of the patient, caudal oral location, larger radiation portal size requirement, and recurrent disease [62,63]. The addition of hyperthermia increases control rates significantly, but this modality is not routinely available [53,64]. The addition of chemotherapy to treatment regimens for canine oral squamous cell carcinoma of the caudal mandible or maxilla, whether as an induction agent or concurrent radiosensitizer or in the

adjuvant setting, awaits further study. Tonsillar squamous cell carcinomas seem to be favorably affected by a multimodality approach. In a small series of eight cases treated with radiation alone, median survival times of 110 days were reported [65]. Local recurrence was noted in only two of the eight cases, but distant disease developed in five of the eight cases. When surgery, radiation therapy, and chemotherapy were applied to a similar patient population, the median survival time was increased to 270 days [66].

Feline oral squamous cell carcinomas have poor outcomes and remain a therapeutic challenge. Patients left untreated or treated with any single treatment modality have survival expectations of less than 3 months [67]. In those few cats with mandibular tumors that are amenable to surgical resection followed by radiation, a median disease-free interval of 11 months has been reported. Most of these cats suffered local recurrence [68]. The use of etanidazole as a radiosensitizer resulted in a median survival time of 116 days [69]. Clearly, treatment of feline oral squamous cell carcinoma is an area warranting further investigation.

Salivary gland tumors

Primary salivary gland neoplasias are rare in the cat and dog. Many patients present with extracapsular extension of tumor, and the numerous vital structures in close proximity to the salivary glands make aggressive surgical removal difficult. Incomplete removal invariably results in local recurrence [70]. The addition of radiation therapy to surgical excision seems to increase control rates and survival times [71,72]. Median survival times of 550 days for dogs and 516 days for cats have been reported with the addition of radiation therapy. Radiation significantly affected outcome in these cases, but the role of chemotherapy remains to be defined. Over half of the cats presented with more advanced stages of primary tumor had metastatic disease at the time of diagnosis [72].

Ear canal tumors

Many ceruminous gland adenocarcinomas and squamous cell carcinomas of the ear are amenable to surgical resection via total ear canal ablation with or without bulla osteotomy [73–75]. Most dogs live longer than 2 years when treated with surgery alone, and most cats live longer than 1 year when treated with surgery alone. In animals with incomplete tumor resection, the addition of adjuvant radiation therapy seems to be of potential benefit [76]. Because the metastatic potential of aural tumors is generally low, ranging from 5% to 15%, chemotherapy is unlikely to have a major role in the treatment of these cases [73].

Thyroid tumors

Eighty to ninety percent of canine thyroid tumors can be expected to be malignant. Although smaller and freely moveable tumors are amenable to long-term control by surgery alone [77], larger nonresectable tumors have been shown to be responsive to external beam radiation therapy [78]. Progression-free survival rates were 80% at 1 year and 72% at 3 years in one radiation study. It often took many months for responses to be evident. Twenty-eight percent of these dogs developed distant disease. Dogs with bilateral disease were found to be at increased risk for metastatic disease [78]. Responses to doxorubicin and cisplatin chemotherapy have been documented in canine thyroid carcinoma cases [79,80]. Thus, chemotherapy may also contribute to the multimodality treatment of canine thyroid carcinomas in combination with radiation therapy or surgery for those animals at increased risk of developing metastatic disease [81]. Multimodality approaches have been shown to benefit human anaplastic thyroid carcinoma patients [34].

Biologically targeted therapies

The molecular and cellular pathways involved in the unregulated cell growth that leads to head and neck tumors are complex. As clinical researchers learn more, we can expect the development of biologically targeted therapies. Three targeted therapies in human head and neck tumors show early promising results. These include treatment with epidermal growth factor receptor (EGFr) antagonists and cyclin-dependent kinase (cdk) inhibitors and the administration of replication competent adenoviruses. The EGFr is a transmembrane glycoprotein that is a member of the tyrosine kinase growth factor receptor family. Activation of this proto-oncogene results in overexpression of the receptor and has been demonstrated to occur in more than 90% of human squamous cell head and neck tumors. Several monoclonal antibodies directed against epitopes on the EGFr are in clinical development, including the chimeric antibody C225 [82]. Enhanced toxicity is noted when this chimeric antibody is combined with a number of chemotherapy agents, including cisplatin, as well as when it is combined with radiotherapy. Phase I clinical trials are underway in human squamous cell carcinoma patients [83].

Summary

The refinement of radiation therapy techniques should result in a decrease in morbidity in canine and feline nasal carcinoma patients and should further allow for the addition of adjuvant therapies. Patients with large oral tumors that are incompletely excised should have radiation therapy added to their treatment regimen. Tumors with significant metastatic potential,

such as melanoma, should be considered for addition of chemotherapy. Carboplatin has activity in melanomas and is being added at several institutions, but trial results are not yet available. Chemoradiation has become the treatment of choice for human head and neck squamous cell carcinomas but remains largely unexplored in veterinary medicine. Hopefully, development of chemoradiation will benefit feline squamous cell carcinoma patients, because current treatment regimens are largely ineffective. Immunotherapy agents and targeted biologic therapeutics seem to hold promise for the future.

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