Prognostic factors and patterns of treatment failure in dogs with unresectable differentiated thyroid carcinomas treated with megavoltage irradiation

Alain P. Théon, Dr Med Vet, MS, DACVR; Stanley L. Marks, BVSc, PhD, DACVIM; Edward S. Feldman, DVM, DACVIM; Steven Griffey, DVM, PhD

**Objective**—To determine quality and duration of progression-free survival (PFS) time in dogs with unresectable thyroid carcinomas treated with definitive megavoltage irradiation and analyze prognostic factors of PFS and patterns of failure (local recurrence vs metastasis).

**Design**—Prospective clinical trial.

**Animals**—25 dogs with locally advanced thyroid carcinomas and no evidence of metastasis.

**Procedure**—Dogs were treated with 48 Gy during 4 weeks on an alternate-day schedule of 4 Gy/fraction.

**Results**—Irradiation was safe and effective for treatment of large unresectable thyroid carcinomas. Progression-free survival rates were 80% at 1 year and 72% at 3 years. Time to maximum tumor size reduction ranged from 8 to 22 months. Factors affecting PFS were not found. Twenty-eight percent (7/25) of dogs developed metastasis. Dogs with bilateral tumors had 16 times the risk of developing metastases, compared with dogs with a single tumor. Dogs with no evidence of tumor progression had 15 times less risk of developing metastases. Radiation-induced hypothyroidism was suspected in 2 dogs 13 and 29 months after irradiation.

**Conclusions and Clinical Relevance**—Irradiation is effective for local control of thyroid tumors, despite their slow regression rate. Results provided evidence that local tumor control affects metastatic outcome in dogs with thyroid carcinomas and is a strong basis for the development of new approaches that include irradiation in the management of dogs with advanced thyroid carcinomas. Improvements in local tumor control alone may be insufficient to improve survival times because of the high risk of metastatic spread before an initial diagnosis is made, which warrants initiation of early systemic treatment. (J Am Vet Med Assoc 2000;216: 1775–1779)

Thyroid tumors constitute 1.2 to 3.8% of all tumors in dogs.1–3 Most tumors are malignant and nonfunctional.4 Carcinoma is the most common tumor type, representing more than half of all tumors.1,3,4 Incidence of metastasis has been reported to be directly related to tumor size.6

Treatment options for large and invasive thyroid carcinomas are limited. Complete resection of thyroid tumors is impossible without removing important structures such as the larynx, trachea, esophagus, recurrent laryngeal nerve, and the carotid sheath.7 Treatment with radioiodine is not effective for control of large tumors, even when the tumor is hyperfunctional and appears to concentrate the radionuclide. Treatment of advanced functional thyroid carcinomas with large doses of radioiodine (> 2.22 x 109 Bq) is palliative. In one study,7 progression-free survival (PFS) time in 4 dogs that were treated 1 to 2 times with radioiodine (131I) ranged from 3 to 29 months (median, 8 months); in another study,7 PFS time was 17 months in 1 dog treated 3 times with 131I.

In humans, external-beam irradiation is used for extensive (ie, extraglandular) or invasive tumors, for gross postoperative residual cancer, and when the tumor is unresectable.10 In dogs, the slow regression rate of thyroid carcinoma after irradiation, as well as the high metastatic risk of this type of tumor, has led to the misconception that external irradiation does not have a curative role in the management of large unresectable thyroid carcinomas.

The purpose of the study reported here was to evaluate efficacy and toxicity of megavoltage irradiation in dogs with localized but unresectable thyroid carcinomas. Treatment efficacy was analyzed in terms of patterns of failure and time from irradiation until tumor progression.

**Materials and Methods**

Dogs—Twenty-five dogs with histologically confirmed differentiated thyroid carcinomas that were treated with megavoltage irradiation, which was administered with curative intent, were included in the study. Dogs with histologic, cytologic, or radiographic evidence of regional or distant metastases, or in which the tumor had recurred, were not entered in the study. Tumors were categorized histologically according to a previously reported classification scheme.1,11 Tumors included compact-cellular (n = 9), follicular (8), and follicular-compact-cellular adenocarcinomas (8). Dogs ranged from 3 to 18 years old (mean, 9.4 years; median, 10 years). Thirteen dogs were male, and 12 were female; 4 dogs were mixed-breeds, and 21 were purebred. The most commonly represented breeds were Labrador Retriever (n = 3) and Sheltie (3). Dogs were referred for irradiation, because their tumors were unresectable on the basis of clinical findings (n = 11) or after unsuccessful attempts at resection (14). On physical examination, 16 dogs had bilateral enlargement and 9 dogs had unilateral enlargement of the thyroid gland. Six dogs that had a diagnosis of hypothyroidism (T4 < 1 g/dl) were treated with thyroid supplementation (levothyroxine).
roxine sodium). All other dogs' serum T<sub>4</sub> concentrations were within reference range. Tumors were staged by use of the World Health Organization TNM scheme: in which "T" is used to indicate maximum diameter of the tumor (T2, 2 to 5 cm; T3, > 5 cm), and "b" is used to designate fixed tumors. Tumors were categorized as T2b (n = 14) or T3b (11).

Radionuclide imaging—Imaging studies with sodium pertechnetate Tc 99m ("TcO<sub>4</sub>") were performed in 20 dogs. On the basis of technetium scan findings, 7 dogs had unilateral laryngeal lobe involvement, and 8 dogs had bilateral thyroid lobe involvement. Five dogs had a large ventral laryngeal mass. In these 5 dogs, radiographic studies revealed invasion of laryngeal cartilages. The patterns of "TcO<sub>4</sub>" uptake in the tumor were evaluated according to a reported classification scheme. A well-circumscribed area of homogenous uptake was observed in 7 dogs. A poorly circumscribed area of uptake was observed in 13 dogs, with diffuse uptake in 9 dogs and areas of no uptake in 4 dogs. In these 4 dogs, an ultrasonographic examination was performed to assess tumor size. No dogs had evidence of mediastinal or pulmonary uptake of radionuclide. Imaging with "TcO<sub>4</sub>", scans prior to treatment were not available for 5 dogs, because resection had already been attempted. Radionuclide imaging with "TcO<sub>4</sub>", was performed in 3 dogs for evaluation of function of the thyroid gland and determination of "TcO<sub>4</sub>", uptake. Scintigraphic images were processed to determine peak radioiodine uptake (PRIU) and effective half-life (T<sub>eff</sub>) of "TcO<sub>4</sub>", in the thyroid gland as described. Each PRIU and T<sub>eff</sub> were 6% and 3.2 days in 1 dog, 10% and 1 day in another dog, and 10% and 0.9 day in a third dog, respectively. The values obtained in these 3 dogs did not warrant "TcO<sub>4</sub>", treatment.

Irradiation procedure—Each dog was anesthetized, and irradiation was performed with a telecobalt-60 unit, using an 80-cm source-skin distance. In dogs that had surgery performed previously, the time interval between surgery and radiation therapy ranged from 15 to 23 days (median, 21 days). Planned radiation dose was 48 Gy (minimum tumor dose) administered in 12 fractions of 4 Gy/fraction during 4 weeks on an alternate day schedule (ie, Monday, Wednesday, Friday). Computerized treatment planning was done on the basis of radiographic findings and neck contour, using a manual contour device (n = 21) as well as results of contrast-enhanced computed tomography (CT); magnetic resonance imaging (MRI); and ultrasonography obtained prior to irradiation. The treatment target volume included thyroid bed and adjacent lymph nodes. Radiation portal size ranged from 55 to 200 cm<sup>2</sup> (median, 136 cm<sup>2</sup>). Irradiation was performed by use of an opposing pair of bilateral fields. Depending on target volume conformation, bilateral open field technique (n = 19) or bilateral wedge field technique (6) was used. The dose was specified to the midline. Treatment fields extended from the level of the hyoid bone (including retropharyngeal lymph nodes) to the root of the neck (including superficial cervical and caudal deep cervical lymph nodes) and were limited dorsally by the spinal cord. Median coefficient of heterogeneity of the radiation dose in the target volume was 2%. In 2 dogs, however, target volume conformation resulted in a high coefficient of variation of 10% and 16%. All dogs were evaluated at our institution 2 weeks and 1, 3, 6, and 12 months after completion of the irradiation protocol and approximately every year thereafter. Additional follow-up information was obtained via telephone conversation with referring veterinarians and owners. Two dogs that had been in remission at the time of last contact were lost to follow-up after 9 and 24 months, respectively.

Data analyses—Progression-free survival time and acute and chronic radiation toxicoses were evaluated. Progression-free survival time was defined as the time between completion of the irradiation protocol and detection of measurable local tumor recurrence or death from causes unrelated to tumor progression, whichever came first. Local tumor progression was confirmed histologically. Regional or systemic metastasis was confirmed histologically, cytologically, and radiographically. Differences were analyzed, using Pearson square statistic or the Fisher exact test for categorical variables and t-test for continuous variables. Variables examined as indicators of prognosis included age, sex, tumor subtype, gland involvement (unilateral vs bilateral vs ventral mass), clinical stage (T2 vs T3), plasma thyroxine (T<sub>4</sub>) concentration, and pattern of "TcO<sub>4</sub>" uptake. Progression-free survival rates were computed by use of the product-limit method. The Cox proportional hazards regression model was used to determine significant prognostic factors of PFS time. Relative risk of tumor progression and metastasis were estimated by the hazard rate ratio. Computations were performed with a statistical software program. Differences were considered significant at P < 0.05. Acute and chronic radiation toxicoses for soft tissues that were included in the treatment volume (skin, trachea, and esophagus) were also analyzed.

Results

Analysis of survival—Significant correlations between age, sex, tumor subtype, tumor stage, gland involvement, and patterns of uptake were not found. Mean (±SE) PFS time was 45 ± 6 months; median survival time had not been reached. The product-limit estimates of the 1-year and 3-year PFS rates (±SE) were 80 (±8) and 72% (±11). Age, sex, tumor subtype, tumor stage, gland involvement, T<sub>4</sub> concentration, and pattern of "TcO<sub>4</sub>" uptake were not found to affect PFS time. Time to maximum tumor size reduction ranged from 8 to 22 months.

Patterns of failure—In 3 dogs, local tumor progression was the first cause of failure. In 3 dogs, concurrent local tumor progression and distant metastasis was the first cause of failure. In 4 dogs with no clinical evidence of tumor progression, metastasis was the first cause of failure. Pulmonary metastases were detected in 5 dogs, and 1 of these dogs also had bone metastasis. In 2 dogs, metastases were found in abdominal viscera. Rate of metastasis was significantly affected by the extent of thyroid gland involvement and local...
tumor progression. Dogs with bilateral tumors had 16 times the risk (P = 0.04) of developing metastasis, compared with dogs with a single tumor mass. Dogs with no evidence of tumor progression had 14.9 times (P = 0.033) lower risk of developing metastases. Tumor histologic type, tumor stage, and resection of tumors were not found to affect development of metastasis.

In dogs that developed metastasis, the time to metastasis was shorter in dogs with no evidence of local tumor progression; however, the difference was not significant (P = 0.08). In dogs with no evidence of tumor progression, mean time to metastasis was 5 months (median, 4.5); in dogs with concurrent local tumor progression, mean time to metastasis was 24 months (median, 15).

**Toxicoses**—Acute radiation reactions including esophageal, tracheal, or laryngeal mucositis resulted in mild dysphagia (n = 8), hoarseness, and cough (12); these reactions were well tolerated and self-limiting in most dogs. Treatment was interrupted for 4 to 7 days in 3 dogs after a cumulative dose of 40 Gy had been administered because of acute radiation reactions (including severe dysphagia that resulted in weight loss). These reactions were associated with treatment fields 160 cm² (P < 0.001). Treatment was resumed with no adjustment in radiation dose. Chronic radiation reactions that were evaluated in dogs with no tumor progression, and for a follow-up period of at least 1 year, included skin fibrosis and permanent alopecia (n = 6) and chronic tracheitis resulting in dry cough (4). Of the dogs that were euthyroid prior to treatment, hypothyroidism developed in 2 dogs 13 and 29 months after irradiation, respectively; hypoparathyroidism was also diagnosed in 1 of these dogs. A relationship between chronic radiation reactions and treatment field size was not found.

**Discussion**

Megavoltage irradiation was found to be effective for treatment of locally advanced thyroid carcinoma in dogs. However, when treatment was successful, there was little change in tumor size for months after treatment. Tumor disappearance or maximum tumor regression was not observed until 8 to 22 months after irradiation. These findings emphasize the need for long periods of evaluation after treatment to determine the therapeutic benefit of irradiation. The slow tumor regression after irradiation may lead to the misconception that these tumors are radioresistant.

Results of this study indicated that irradiation enhances survival time of dogs with unresectable differentiated thyroid carcinomas when there is no evidence of metastasis at the onset of treatment. Progression-free survival rate 3 years after irradiation was 72%. In dogs with comparable diseases, survival without treatment ranges from 2 to 38 weeks after diagnosis, and antineoplastic chemotherapy (using cisplatin, doxorubicin, or mitoxantrone) provides short-term palliation.

In humans, the most significant prognostic factors for differentiated thyroid malignancies are tumor histologic type, extent of local involvement, and age at diagnosis. In dogs with operable thyroid tumors, prognostic factors have not been identified. Breed, sex, age, histologic type, and tumor size do not appear to affect prognosis after resection. In the present study, prognostic factors for dogs with inoperable tumors were not found. Humans with papillary thyroid carcinomas have a better prognosis than those with follicular thyroid carcinomas after treatment with external beam irradiation. In the present study, tumor histologic type was not found to have prognostic value or influence the type of failure (local recurrence vs distant metastasis). More subtle distinctions in the responses of specific histologic types to irradiation may be revealed if diagnoses were made earlier in the evolution of these tumors. The lack of association between T stage and PFS time may indicate that once a tumor has invaded adjacent structures, the prognostic value of tumor volume in the efficacy of irradiation may be lost. Age was not found to affect prognosis; however, this needs to be interpreted cautiously, because there were only 2 young dogs (3 and 4 years old) in our study.

External-beam irradiation is not commonly offered as a treatment option for advanced thyroid carcinomas, because metastasis is often present at the time of diagnosis and is considered the principal cause of death. Rates of metastases at the time of diagnosis range from 35% to 62.5%. In dogs with no evidence of metastasis and operable tumors, tumor resection results in long-term local control and no development of metastasis. In these dogs, the low incidence of metastases after treatment (2/20) may provide preliminary evidence that local tumor control had an impact on subsequent development of metastases. Our findings support this assumption. The proportion of dogs with local failure and distant metastasis was higher than the proportion of dogs with local control and no evidence of metastases. In addition, effective local treatment with irradiation was found to affect late (>12 months), but not early (<6 months), development of metastasis. Early metastasis, which was observed in dogs with local tumor control, had most likely developed prior to diagnosis of thyroid carcinoma and were not affected by local irradiation. Alternatively, late development of metastases in dogs with tumor progression were assumed to reflect the development of distant metastases from the persistent or recurring primary tumors.

Acute radiation reactions were severe in 3 dogs. Although specific risk factors for these complications were not discerned from our data, they developed after use of the largest irradiation fields. Irradiation did not result in any life-threatening complications. This is in contrast with performing tumor resection, which is associated with a substantial risk of complications. In a study of 20 dogs with large mobile thyroid carcinomas, 5 (25%) dogs died because of treatment-related complications.

Radiation-induced hypothyroidism was suspected in 2 dogs after a latent period of 13 and 29 months without clinical or biochemical evidence of preexisting disease. This latent period for induction of hypothyroidism was longer than that previously reported for 1 dog with thyroid carcinoma that had been treated with...
external-beam megavoltage irradiation and surgery.26 Compared with irradiation alone, the shorter latent period may have been the result of the combined use of surgery and irradiation. In this study, the relative contribution to alterations in thyroid function by radiation effects and damage caused by the tumor could not be determined. In humans, hypothyroidism is a common complication following irradiation of the head and neck regions when the thyroid gland is in the radiation field. Subclinical hypothyroidism is the most common complication, with increases in serum thyroid-stimulating hormone (TSH) concentrations and normal serum T3 concentrations. Increases in serum TSH concentrations are usually detected within 6 months after irradiation.29 In this study, clinically and biochemically overt hypothyroidism was evaluated. Use of sensitive serum TSH assays may help detect the early effects of radiation on thyroid function in dogs.

There are no guidelines for the use of external-beam irradiation or radiiodine therapy either alone or in combination for well-differentiated thyroid carcinoma in dogs. In humans, external irradiation is indicated for extensive inoperable disease, for gross residual disease in the operative field or if connective tissue is invaded, or if there is extensive infiltration of the cervical lymph nodes. Treatment with 131I is preferred in the postoperative management of differentiated thyroid carcinoma for diagnosis and treatment of residual functioning thyroid gland tissue and functioning residual, recurrent, or metastatic thyroid tumor.30 Results of our study suggest that megavoltage irradiation can play a role in the management of dogs with differentiated thyroid tumors that are inoperable and when there is no evidence of systemic metastases. These findings are similar to those in humans where inoperable disease is approached with curative intent. Postoperative irradiation for humans with differentiated thyroid carcinoma after incomplete resection resulted in a 5-year survival rate of 78%.31 Efficacy of irradiation for treatment of gross disease, as evidenced in this study, provides a rationale for postoperative treatment of incompletely resected differentiated thyroid tumors in dogs. In dogs in which surgical inoperable disease cannot be attempted because of the advanced nature of the disease, external-beam irradiation should also be considered as a cytoreductive treatment, with reassessment of the tumor for resectability at a later time.

Radioiodine treatment of unresectable or inoperable primary thyroid tumors in dogs does not result in appreciable tumor regression, nor does it appear to prolong survival time unless treatments are repeated.32 Results of our study confirm those of another report,26 which states that most dogs with differentiated thyroid tumors are euthyroid or hypothyroid and are unlikely candidates for radiiodine therapy. Candidates for radioiodine treatment must have a functional thyroid tumor defined by a high differential absorption over a long period, as assessed by an 131I uptake tracer study. In our study, 3 dogs with large and intense 99mTcO4− uptakes were not candidates for treatment with 131I, because their tumors did not adequately concentrate 131I on tracer kinetic studies.

"The favorable results obtained with surgery alone for operable tumors emphasizes the need for early diagnosis and treatment of thyroid carcinomas.33 Further improvement in long-term prognosis of dogs with differentiated thyroid tumors will require development of chemotherapy regimens to treat metastasis. Although results of our study suggested that irradiation may decrease the risk of metastasis, the long-term benefit of local treatment for dogs with advanced thyroid carcinomas will be limited if undetected metastasis has already developed before treatment is initiated."

References


