

Cross-Sectional Imaging Characteristics of Pituitary Adenomas, Invasive Adenomas and Adenocarcinomas in Dogs: 33 Cases (1988–2006)

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Background: Pituitary tumors in dogs can be adenomas, invasive adenomas, or adenocarcinomas. In people, invasive adenomas and pituitary adenocarcinomas carry a worse prognosis than adenomas.

Hypothesis/Objective: To identify differentiating features on cross-sectional imaging in dogs with pituitary adenomas, invasive adenomas, and adenocarcinomas.

Animals: Thirty-three dogs that had computed tomography (CT) or magnetic resonance imaging (MRI) performed and a necropsy diagnosis of pituitary adenoma ($n = 20$), invasive adenoma ($n = 11$), or adenocarcinoma ($n = 2$).

Methods: Medical records were retrospectively reviewed for signalment, history, and diagnosis. CT and MR images were reviewed for characteristics of pituitary tumors.

Results: Mean (\pm standard deviation) age for dogs with pituitary adenomas (10.6 ± 2.9 years) was greater than that of those with invasive adenomas (8.3 ± 2.7 years, $P = .04$). Eighteen out of 20 (90%) dogs with adenomas had contrast-enhancing masses. Thirteen out of 20 (65%) had homogeneous enhancement. Mean adenoma height was 1.2 ± 0.7 cm. Eight out of 20 (40%) adenomas were round and 8/20 (40%) compressed surrounding brain. Eleven out of 11 dogs (100%) with invasive adenomas had contrast-enhancing masses. Seven out of 11 (64%) masses were homogeneous. Mean invasive adenoma height was 1.8 ± 0.7 cm, which was significantly greater than adenomas ($P = .03$). Mass shape varied from round to oval to irregular. Six out of 11 (55%) masses compressed surrounding brain. Clinical and imaging features were variable for 2 dogs with adenocarcinomas.

Conclusions and Clinical Relevance: Invasive adenoma should be suspected if a dog with a pituitary tumor is <7.7 years of age and has a mass >1.9 cm in vertical height. Adenocarcinomas are uncommon and metastatic lesions were not seen with imaging.

Key words: CT; Endocrinology; MRI; Pathology.

Imaging of the brain may be indicated as a part of the diagnostic plan in a variety of clinical situations including but not limited to the evaluation of seizures, cranial nerve dysfunction, behavior changes, pituitary-dependent Cushing's syndrome (hypercortisolism [HC]), and diabetes insipidus. Computed tomography (CT) and magnetic resonance imaging (MRI) are the cross-sectional modalities used to image the brain in dogs.^{1,2} Both modalities have the potential to provide high-resolution images of the brain and, with the administration of IV contrast material, result in a great degree of accuracy for mass detection. High-field MRI generally is considered to be superior to CT for the detection of small intracranial masses because of its exceptional contrast resolution. However, CT has advantages when it comes to defining bone erosion or regional mineralization. In people, in-

Abbreviations:

| | |
|------|--------------------------------------|
| CT | computed tomography |
| HC | hypercortisolism |
| LDDS | low-dose dexamethasone suppression |
| MRI | magnetic resonance imaging |
| PDH | pituitary dependent hypercortisolism |
| UCCR | urine cortisol:creatinine ratio |

tracranial lesion detection is similar comparing these 2 imaging modalities.³

Naturally occurring HC is one of the most common endocrine disorders of dogs. HC is pituitary dependent (pituitary dependent hypercortisolism [PDH]) in 80–85% of affected dogs and is caused by an autonomously functioning ACTH-secreting neoplasm within the pituitary gland.⁴ The diagnosis of HC usually is confirmed by results of endocrine screening tests such as the low-dose dexamethasone suppression (LDDS) test, ACTH stimulation test, or urine cortisol:creatinine ratio (UCCR). PDH may be differentiated from adrenal-dependent HC using more selective biochemical testing such as the LDDS test, high-dose dexamethasone suppression test, or endogenous plasma ACTH concentration. Visualization of 2 relatively equal-sized adrenal glands on abdominal ultrasound examination or identification of a pituitary mass by cross-sectional imaging techniques also supports the diagnosis of PDH.⁴ Pituitary tumors may be either benign adenomas or malignant adenocarcinomas.⁵ In people, pituitary adenomas are further divided into invasive and noninvasive types whereas the

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term adenocarcinoma is reserved for pituitary tumors with definitive evidence of metastatic behavior.⁶ Invasive adenomas are more likely than adenomas to result in severe clinical signs and are at higher risk of recurring after therapy.⁶ Adenocarcinomas carry a worse prognosis than adenomas, with 66% of affected people dying within the 1st year after diagnosis.^{7,8}

The purpose of our study was to determine if there are contrast-enhanced cross-sectional imaging characteristics, utilizing either CT or MRI scanning, that could be used to discriminate pituitary adenoma, invasive adenoma, and adenocarcinoma in dogs. It was hypothesized that, on cross-sectional imaging examination, invasive adenomas would be larger, more heterogeneously contrast enhancing, irregularly margined, and more compressive or invasive of surrounding tissues than adenomas, and that adenocarcinomas would be uncommon.

Methods

Medical records of dogs examined between 1988 and 2006 at the UC Davis Veterinary Medical Teaching Hospital were reviewed by the electronic database. Dogs were included in this study if they had undergone contrast-enhanced cross-sectional imaging of the pituitary region of the brain using either CT^{a,b} or high-field MRI^{c,d} before death or euthanasia. Furthermore, included dogs must have had a histologic diagnosis of pituitary adenoma, invasive adenoma or adenocarcinoma based on tissue obtained during necropsy. Slides were reviewed and tumors classified by a single pathologist (C.M.R.). Criteria for histopathologic diagnosis were adapted from criteria used in humans, as is generally accepted in the veterinary literature.⁹ Masses that were well delineated from adjacent parenchyma were classified as adenomas. Masses exhibiting local invasion of brain parenchyma or adjacent structures (eg, sella turcica, ventricles, meninges) were classified as invasive adenomas. Only tumors with distant intra- or extracranial metastasis, distinct from the main pituitary mass, were classified as adenocarcinomas.

CT studies consisted of 1–5 mm contiguous images through the pituitary region before and after IV contrast administration. Pre-contrast MR images consisted of sagittal T1-weighted and transverse T1-weighted, T2-weighted, and proton density sequences. Fluid attenuated inversion recovery images were reviewed if available. Postcontrast MR images consisted of sagittal and transverse T1-weighted sequences. If a dog underwent both CT and MRI examinations, the results of the MRI examination were preferentially evaluated because of superior image quality.

Information regarding age, body weight, and the presence or absence of HC was obtained from each medical record. The preliminary diagnosis of HC was based on history, physical examination results consistent with HC along with at least 1 clinicopathologic abnormality suggestive of HC detected on serum biochemical analysis (eg, decreased to low-normal BUN, increased alkaline phosphatase and alanine aminotransferase activities, hypercholesterolemia) in conjunction with urinalysis or microbial culture of urine (ie, urine specific gravity <1.020 or microbial growth on urine culture). The diagnosis of HC in these dogs was further supported by abnormal results on at least 1 of the 3 commonly used screening tests (LDDS, ACTH stimulation test, or UCCR). The ACTH stimulation test was included because of its high specificity despite relatively low sensitivity as assessed elsewhere.¹⁰ Finally, the type of treatment (if any) and time from imaging diagnosis of a pituitary mass to death or euthanasia was recorded.

Digital versions of MRI and CT examinations were reviewed by a board-certified veterinary radiologist (R.E.P.) who was unaware

of the histologic diagnosis. When digital images were not available, film versions of the studies were reviewed. Images were assessed for the presence of a visible mass. If a mass was visible, it was evaluated for the presence of contrast enhancement, character of the contrast enhancement (homogeneous/uniform or heterogeneous/patchy), shape of the mass (round, oval, or irregular), size of the mass (greatest vertical height on transverse images), and the presence of compression or invasion of surrounding structures (increase in the 3rd ventricle, compression of the hypothalamus, obstructive hydrocephalus, peritumoral edema, invasion of the sphenoidal bone). The maximal height of the mass was determined. Although an alternative method for assessing pituitary tumor height to brain area has been described,¹¹ this method was not used in the current study because many of the film studies did not have the brain area recorded and estimates would likely have resulted in substantial error.

Statistical Analysis

All statistical comparisons were performed by commercially available software.^e The age, body weight, and mass size were represented as mean (\pm standard deviation) and compared between groups by a Student's 2 sample *t*-test assuming equal variances. Time from imaging to death was expressed as mean (\pm standard deviation), median and range. A Pearson's Chi-squared goodness of fit test was used to determine if brain compression or type of contrast (homogenous versus heterogenous) enhancement were supportive of adenoma or invasive adenoma. A Fisher's exact test was used to determine if the presence of contrast enhancement or mass shape distinguished between adenoma or invasive adenoma. A *P*-value <.05 was considered significant.

Results

Thirty-three dogs met the inclusion criteria for this study and had a histological diagnosis of pituitary tumor. Twenty dogs were diagnosed with pituitary adenoma; 7 of those dogs underwent CT, and 13 underwent MRI. Eleven dogs were diagnosed with invasive adenomas; 4 of those dogs underwent CT, and 7 underwent MRI. Of invasive adenomas, all exhibited parenchymal invasion, 3 exhibited meningeal invasion, and 1 with meningeal invasion also had 3rd ventricle and infundibular cavity invasion (Fig 1). No cases had bony invasion. Two dogs were diagnosed with pituitary carcinoma, both of which underwent MRI. At necropsy, metastatic lesions were found in the cerebellar and brainstem meninges of 1 dog and the ventral diencephalon caudal to the pituitary of the other although no metastatic lesions were seen with imaging. In the former case, the metastatic lesions were regionally widespread, but formed only microscopic masses, and in the latter case, the metastatic lesions were in the general vicinity, but histologically distinct, from the main pituitary mass.

The mean age for dogs diagnosed with pituitary adenoma was 10.6 ± 2.9 years and was significantly greater than that of dogs with invasive adenomas (8.3 ± 2.7 years; *P* = .04). The dogs with pituitary carcinoma were 5 and 11 years old, respectively. The mean body weight of the dogs with adenomas (21 ± 10.2 kg) was not significantly different from that of dogs with invasive adenomas (25 ± 12 kg; *P* = .29). The dogs with pituitary carcinoma weighed 25 and 43.2 kg. Sixteen out of 20 (80%) dogs with an adenoma were diagnosed with HC

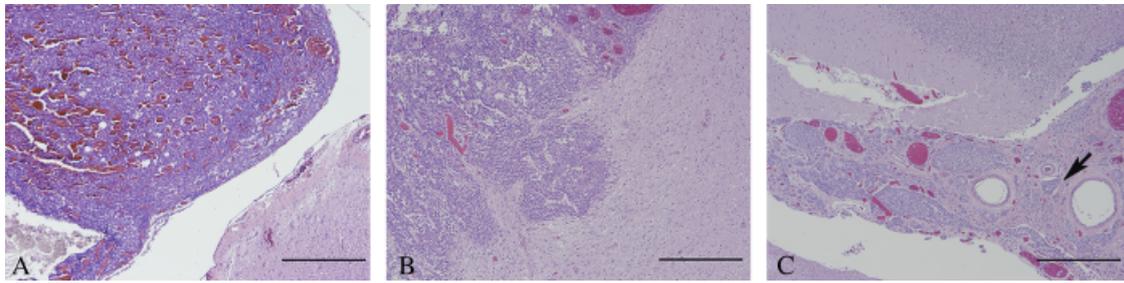


Fig 1. Histologic appearance of pituitary tumors. (A) Pituitary adenoma. Note well-delineated tumor margins and compression of adjacent parenchyma. Subgross, scale bar = 1 cm. (B) Invasive adenoma. Note irregular tumor margins and invasion of adjacent parenchyma. Scale bar = 500 μ m. (C) Pituitary carcinoma, with meningeal metastasis. Note intravascular tumor nests (arrow) and meningeal location. Cerebellum at top. Scale bar = 500 μ m.

whereas 4 (20%) did not meet the criteria for a definitive diagnosis of HC. Five out of 11 (45%) dogs with invasive adenomas were diagnosed with HC whereas 6 (55%) did not meet the criteria for a definitive diagnosis of HC. Both dogs with adenocarcinomas met the criteria for HC. Each dog that did not have a definitive diagnosis of HC was examined and underwent brain imaging because of signs attributable to central nervous system disease. Neurologic signs exhibited included conscious proprioceptive deficits, ($n = 7$), cranial nerve deficits ($n = 7$), obtundation ($n = 4$), lethargy ($n = 3$), seizures ($n = 2$), circling ($n = 2$), aggression ($n = 1$), and disorientation ($n = 1$).

Two dogs with adenomas did not have masses visible with imaging (1 each undergoing CT and MRI). Mean greatest vertical height for the visible pituitary adenomas was 1.2 ± 0.71 cm and for the invasive adenomas was 1.8 ± 0.70 cm. The adenomas were significantly smaller than the invasive adenomas ($P = .03$). The 2 adenocarcinomas measured 0.9 and 1.9 cm. Four out of 11 (36%) invasive adenomas had evidence of mineralization within the mass whereas none of the adenomas or adenocarcinomas did. Presence of contrast enhancement, type of contrast enhancement, tumor shape and brain compression were not significantly different between adenomas and invasive adenomas ($P = .54, .33, .10, .44$, respectively) (Table 1). One adenocarcinoma was homogeneously contrast enhancing whereas the other was

heterogeneous. Both adenocarcinomas were irregularly shaped but neither was considered compressive. Example images of an adenoma, invasive adenoma, and adenocarcinoma are shown in Figure 2.

Of the 20 dogs with adenomas, 8 received no treatment, 5 were treated with mitotane, 3 underwent radiation therapy, 1 received mitotane and radiation therapy, and 1 each received prednisone, ketoconazole, and pergolide mesylate. Eight of these dogs died or were euthanized because of unrelated illnesses and 12 were euthanized because of persistent or progressive clinical signs attributable to their intracranial masses. The mean time from diagnosis of a pituitary mass to death was 11.3 ± 18.7 months (median, 1.5; range, 0–72). Of the 11 dogs with invasive adenomas, 8 received no therapy, 2 underwent radiation therapy, and 1 received radiation therapy and prednisone. Ten dogs were euthanized because of poor prognosis or because of persistent and progressive clinical signs attributable to their intracranial mass. One dog was euthanized for an unrelated illness. In this group of dogs, the mean time from pituitary mass diagnosis to death was 4.2 ± 6.9 months (median, 1.25; range, 0–18). One dog with a pituitary adenocarcinoma underwent radiation therapy and lived 22 months. The other dog received prednisone and was euthanized after 1 week. Both dogs were euthanized because of recurrent or progressive clinical signs attributable to their intracranial masses.

Table 1. The number and percentage of dogs with each individual imaging finding are listed for pituitary adenomas, invasive adenomas, and adenocarcinomas.

| Imaging Finding | Adenomas ($n = 20$) | | Invasive Adenomas ($n = 11$) | | Adenocarcinomas ($n = 2$) | |
|----------------------|-----------------------|--------------------|--------------------------------|--------------------|-----------------------------|--------------------|
| | Number of Dogs | Percentage of Dogs | Number of Dogs | Percentage of Dogs | Number of Dogs | Percentage of Dogs |
| Visible mass | 18 | 90 | 11 | 100 | 2 | 100 |
| Contrast enhancement | | | | | | |
| None | 2 | 10 | 0 | 0 | 0 | 0 |
| Heterogenous | 5 | 25 | 4 | 36 | 1 | 50 |
| Homogenous | 13 | 65 | 7 | 64 | 1 | 50 |
| Compression/invasion | 8 | 40 | 6 | 55 | 0 | 0 |
| Shape | | | | | | |
| Round | 8 | 40 | 1 | 9 | 0 | 0 |
| Oval | 4 | 20 | 4 | 36 | 0 | 0 |
| Irregular | 6 | 30 | 6 | 55 | 2 | 100 |

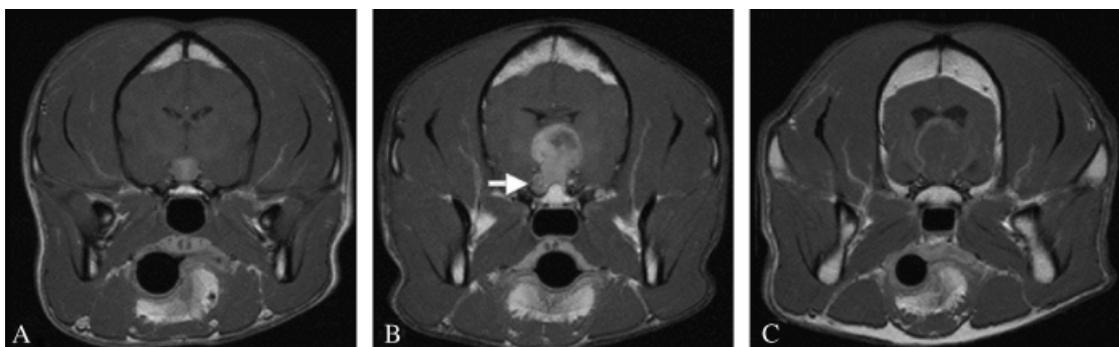


Fig 2. (A) A T1-weighted postcontrast magnetic resonance (MR) image of the pituitary gland demonstrates homogenous contrast enhancement of this adenoma. (B) A T1-weighted postcontrast MR image of the pituitary gland demonstrates the irregular shape of this invasive adenoma. Notice the invasion of tumor laterally outside the sella turcica (arrow). (C) A T1-weighted postcontrast MR image of the pituitary gland demonstrates the heterogeneous contrast enhancement and irregular shape of this adenocarcinoma.

Discussion

In people, pituitary tumors are classified as adenomas, invasive adenomas, and adenocarcinomas.^{8,12} Adenomas often are functional but typically slow growing and non-invasive.⁷ Invasive adenomas in people resemble adenocarcinomas in that they usually are functional, locally invasive, and can grow rapidly resulting in compression of regional brain structures.⁸ Pituitary adenocarcinomas are rare in people, making up only 0.2% of operated pituitary tumors.^{7,8} The differentiation of pituitary adenocarcinomas from regular or invasive adenomas is dependent upon the presence of systemic or intracranial metastatic disease. Furthermore, it is widely believed that adenocarcinomas arise from the malignant transformation of pre-existing adenomas with a variable latency period of approximately 6 years.¹³ Therefore, imaging tests such as MRI and CT cannot differentiate between adenomas and adenocarcinomas in people unless metastatic lesions are identified.¹³ Only a few reports describe pituitary tumors with high mitotic indices and without metastatic lesions in people. These tumors are difficult to classify but are felt to represent a subset of pituitary tumors that have undergone malignant transformation but have not yet metastasized.

In dogs, pituitary tumors are reportedly common, but there is little information describing differences between adenomas and invasive adenomas. Moreover, it is unusual to find case reports that describe pituitary adenocarcinomas. Therefore, the frequency of invasive adenomas is unknown and it is assumed that the frequency of pituitary adenocarcinoma is low. In 1 study, 2 of 7 pituitary macrotumors (tumors > 1 cm in height) were adenocarcinomas although the histologic criteria in that paper were not extensively defined.⁵ The results of our study indicate that pituitary adenocarcinomas represent a small percentage (6%) of pituitary masses whereas adenomas make up 61% and invasive adenomas make up 33%.

The results of this study suggest that signalment and imaging findings may give some indication of tumor type. Dogs with pituitary masses should be suspected to have an invasive adenoma if the dog is <7.7 years of age

or has a mass > 1.9 cm in greatest vertical height. The age and height cut-offs were calculated by taking 1 standard deviation beyond the mean. It seems logical that the larger masses are more likely to be invasive. However, the reason for invasive adenomas to predominate in younger dogs is unclear. These invasive adenomas may represent a subset of pituitary adenomas with more malignant pathobiological behavior. These tumors may arise at a similar age but grow much faster thereby resulting in clinical signs at an earlier time. Although age does not appear to relate to tumor type in people, invasive adenomas are a premetastatic malignancy implying more aggressive behavior.⁶

Histologically, invasive adenomas in dogs appear to invade the surrounding brain parenchyma but less commonly the meninges and 3rd ventricle. None of the cases in our study group had definitive evidence of invasion of the cavernous sinus or regional bone. This is unlike invasive adenomas in people in which infiltration of the dura is a common feature occurring in 45.5% of cases.¹⁴ Invasion of the cavernous sinus and bone also are common features of invasive adenomas in people¹⁵ whereas invasion of surrounding brain parenchyma is not described as a feature of invasive adenomas. None of the imaging variables other than tumor size proved useful for determining underlying tumor type. There is substantial overlap among the imaging findings of adenomas, invasive adenomas, and adenocarcinomas in dogs. The small size of individual meningeal metastatic foci and the proximity of metastatic lesions to the main pituitary mass in the other dog with adenocarcinoma may have precluded detection by imaging.

Mineralization of the pituitary mass identified with imaging was only seen in dogs with invasive adenomas. This is not a feature that has been reported previously in people, dogs or other species. The cause and association with tumor type is unknown. However, mineralization may prove to be an indicator of an invasive adenoma in dogs with pituitary masses.

Clinical signs associated with pituitary tumors are variable with most dogs presenting for clinical signs of HC or neurologic deficits. Neurologic signs often are vague and may or may not have a direct association with the pres-

ence of a visible pituitary tumor.¹⁶ Pituitary adenocarcinomas are thought to be more often nonfunctional. In this study, both dogs with adenocarcinomas showed clinical and laboratory evidence of HC, indicating the tumor likely was functional. Although a higher percentage of dogs with adenomas than with invasive adenomas had HC, there was substantial variability in these 2 groups. This suggests that tumor functionality does not predict tumor type. However, the majority of the dogs in this case series were examined because of clinical signs attributable to HC. Thus, these results may characterize a skewed population and may not represent the true population of dogs with pituitary tumors.

In veterinary medicine, PDH is often treated medically using mitotane or trilostane, which act to reduce serum cortisol concentrations.⁴ Although these therapies are effective at relieving the clinical signs associated with the disease, neither actually affects the pituitary tumor. Surgical therapy, using a transsphenoidal approach, is the therapy of choice for Cushing's disease in humans, and canine transsphenoidal hypophysectomy has gained support and success in Europe.¹⁷ Dogs with larger tumors as defined by imaging have been shown to respond less favorably to transsphenoidal hypophysectomy.¹⁸ Radiation therapy also is commonly used to treat these tumors.¹⁹ It may be used primarily or postoperatively in humans, and it is the treatment of choice in dogs with macrotumors, or those dogs that have neurologic signs attributed to their pituitary tumor. Success rates are greater in dogs with smaller tumors and less severe CNS signs.¹⁹ Radiation therapy substantially increases survival times in dogs with pituitary tumors.²⁰

There is a paucity of information in the veterinary literature regarding prognosis relative to the histology of pituitary tumors. Dogs with small masses have better overall survival regardless of treatment method, but histologic assessment of the masses in that study was not performed.²⁰ The treatments used for the dogs in our study varied widely. Some animals were treated medically for Cushing's disease with mitotane or ketoconazole. Dogs exhibiting neurologic signs may have received prednisone, radiation therapy, or both but many died or were euthanized without receiving any treatment. Only 3/11 dogs with invasive adenomas received some form of treatment. The other 8 dogs received no treatment, most dying or being euthanized because of the severity of their clinical signs or poor prognosis attributed to the size of the pituitary masses. This suggests that there may be a worse prognosis for dogs with invasive adenomas, but that radiation therapy can be successful in controlling the clinical signs associated with these larger, more aggressive tumors. The dog with a pituitary adenocarcinoma that received radiation therapy survived 22 months indicating that either this dogs' tumor had not undergone neoplastic transformation at the time of imaging or that radiation is a viable treatment option for dogs with this tumor type. Additional studies with standardized treatment protocols would be warranted for further investigation.

In conclusion, the results of this study indicate that an invasive pituitary adenoma should be suspected if the

affected dog is <7.7 years old and has a mass that is >1.9 cm in greatest vertical height. Mineralization was only seen in invasive adenomas. However, there is substantial overlap between the imaging findings for pituitary adenomas, invasive adenomas and adenocarcinomas. The presence of HC is compatible with either pituitary adenoma or carcinoma. Our results suggest that invasive adenoma may have a poorer prognosis in dogs but additional studies are necessary to confirm this impression.

Footnotes

- ^a 8800 whole body CT scanner or x/i Helical Scanner, General Electric, Medical Systems Divisions, Milwaukee, WI
^b Conray 400, Mallinckrodt Imaging, Tyco International Inc, Princeton, NJ
^c Signa 1.5 T, General Electric, Medical Systems Divisions
^d Magnevist, Berlex Laboratories Inc, Wayne, NJ
^e STATA 10.0, StataCorp LP, College Station, TX
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