Prostate cancer is the most common cancer and the second leading cause of cancer death among American men and accounts for about 11% of male cancer-related deaths (1). Approximately 85% of cases are diagnosed as localized disease (1). Radical prostatectomy, the current standard of treatment for localized disease, offers the potential for tumor eradication but also causes significant complications, including impotence in 80% of cases, incontinence in ~29%, bowel urgency in 20% (2), and tumor recurrence in 18% of patients (3). Finding additional treatment options for localized disease is likely to increase in urgency as detection methods continue to improve and diagnosis in younger patients increases (4, 5).

Systemic chemotherapy with cytotoxic drugs, such as mitoxantrone, taxanes, and estramustine, is used primarily to treat hormone-refractory advanced disease and rarely for localized disease (6–9). Regional chemotherapy, which has been used clinically to treat other types of cancer including bladder, skin, ovarian, colon, brain, and pancreatic cancer (10–16), represents an alternative to deliver high drug concentrations to the prostate.

Several properties of the prostate make it an ideal candidate for regional therapy. It is a small and encapsulated organ, enabling the achievement of high local drug concentrations whereas limiting toxicity to the extracapsular tissues. The blood perfusion rate to the prostate is relatively slow (i.e., 16 mL per minute per 100 g) compared with major organs, such as liver and kidney (17, 18). The drug removal via the perfusing blood is therefore minimal. Furthermore, the prostate is readily accessible; relatively noninvasive techniques, such as transurethral resection, brachytherapy placement of radioactive beads, and transrectal biopsies are commonly used. In spite of these factors favoring regional drug treatment of prostatic disease, the few attempts at developing this treatment modality have not met with success. For example, intraprostatic administration of cancer chemotherapy (19, 20), IFN (21), and antibiotics (22) showed limited activity. None of these earlier studies evaluated the intraprostatic drug distribution and transport, which are likely to play a role in determining the treatment activity.

The first goal of the present study was to determine the prostate tissue pharmacokinetics and spatial drug distribution after intraprostatic and i.v. administrations and to gain insight in the mechanisms of intraprostatic drug transport. The second goal was to evaluate intraprostatic drug delivery as a potential treatment option for localized prostate cancer. Doxorubicin...
was used as the model drug because its fluorescent property enables the study of spatial drug distribution in the prostate, and because it has been successfully used in another form of regional therapy (i.e., intravesical treatment of superficial bladder cancer; refs. 23–25). The selection of normal healthy dogs (i.e., not tumor bearing) as the animal model was based on the following considerations. First, in early prostate cancer, tumors represent only a small fraction of the tissue. Hence, drug distribution and transport within the normal tissue is expected to play an important role in the drug delivery to the multiple tumor foci. Second, there are anatomic similarities between dog and human prostates and both species show an age-related tendency to develop both benign hyperplasia and adenocarcinoma of the prostate (26). Third, the tissue should be of sufficient size to enable the study of drug distribution.

### Materials and Methods

**Chemicals and supplies.** Doxorubicin and epirubicin were gifts from Pharmacia-Upjohn (Milan, Italy) or purchased from Sigma Chemical Co. (St. Louis, MO). Tissue-embedding matrix was obtained from Miles, Inc. (Elkhart, IN); rubber cement from Elmer’s Products, Inc. (Columbus, OH); Krazy Glue from Borden, Inc. (Columbus, OH); and bovine serum albumin from Sigma Chemical. Cryosectioning was done using a Microm 300 cryostat (Carl Zeiss, Inc., Thornwood, NY).

**Dog protocol: intraprostatic infusion.** Animal protocols were approved by The Ohio State University Institutional Animal Care and Use Committee and followed the guidelines set by the Institute of Laboratory Animal Resources (27). Male beagle dogs, 9.0 ± 1.6 kg, were generously provided by Springfield Laboratory (Spencerville, OH) and Battelle Memorial Institute (Columbus, OH). A dog was anesthetized with a combination of pentobarbital and acepromazine, and the prostate exposed by abdominal incision. A 30-gauge needle was bent at a 90-degree angle at 2 mm from the tip, and the bent part was inserted in the lateral right side of the prostate and glued to the surface of the prostate with Krazy Glue. Doxorubicin (0.2 mg in 100 μL normal saline) was infused at the rate of 1 or 1.4 μL/min for 150 minutes, using a Harvard Apparatus Infusion/Withdrawal pump. The duration of infusion was selected to allow for the establishment of a steady state (steady-state plasma concentrations were reached between 90 and 120 minutes after both i.v. and intraprostatic injections; see Results) and for detailed study of the pharmacokinetics in lymphatic drainage, whereas limiting the secondary effects of anesthesia such as lowering of body temperature. To study the contribution of lymphatic flow to drug removal from the prostate, the lymphatic drainage was first identified in two dogs by following the movement of a trypsin blue dye solution injected into the prostate (100 μL, 4% w/v); the drainage was into the internal iliac lymph nodes with subsequent flow into the cisterna chylci. In two additional animals, a catheter was inserted in the cisterna chyli to collect the lymph fluid during and after intraprostatic doxorubicin infusion.

In all animals, blood samples were obtained from a jugular vein via a 5-inch venocatheter, and the urine was collected through a urethral 8 French Foley catheter. At the end of the infusion, the prostate was excised, placed on ice and/or frozen in liquid nitrogen, and stored at −70°C. In some animals, the internal iliac lymph nodes were also collected. The dog was then immediately euthanized by pentobarbital overdose.

**Dog protocol: i.v. infusion.** The prostate tissue pharmacokinetics of doxorubicin after i.v. injection was evaluated in two studies. In both cases, animals were sedated with 1 mg/kg of acepromazine, given i.s.c.

The first study evaluated the drug concentrations in plasma and prostate, using high-performance liquid chromatography (HPLC).

The dose was 2 mg/kg doxorubicin infused over 240 minutes. This dose was chosen to achieve tissue concentrations within the range observed after the intraprostatic infusion. A dog was catheterized in the right jugular vein. The drug solution was infused through the jugular vein catheter using a portable infusion pump (CADD-PLUS pump, SIMS Deltec, St. Paul, MN) placed in an animal jacket. A cephalic vein was catheterized for blood sampling. The prostates were harvested at the end of the infusions. The second study evaluated the spatial drug distribution by confocal microscopy. For this purpose, a dog was given an i.v. bolus dose of 16 mg/kg doxorubicin through a cephalic catheter and the prostate harvested 15 minutes later. In all studies, animals were euthanized immediately after harvesting the prostate.

**Drug distribution within the prostate after intraprostatic administration.** This was evaluated in three studies. The first study evaluated the drug distribution with respect to prostate geometry and the second study evaluated changes in the average tissue concentrations as a function of distance from the injection site. Both studies used HPLC to analyze drug concentrations, and the results indicated that the drug was localized in discrete zones (i.e., glandular lobule and urethra). Hence, the third study used confocal fluorescence microscopy to visualize the profile of drug concentration decline within these structures. The methodologies are as follows.

For the first study, the harvested prostate was placed on ice and sectioned into 36 pieces, as shown in Fig. 1A. The sections were frozen at −70°C until HPLC analysis. The time between removing the prostate from an anesthetized animal to completing the sectioning was <5 minutes.

**Fluorescence microscopy.** For fluorescence microscopy, excitation was at a wavelength of 514 nm using a 2-mW argon ion laser. The emission at 575 ± 12.5 nm was recorded by a photomultiplier tube and digitized by a 12-bit microcomputer to produce pseudocolor images of the fluorescence distribution. The images were obtained with an Olympus 10× dry lens with a numerical aperture of 0.25, using a 20-μm scanning step and a pinhole setting of 1,600 μm. The fluorescence intensity was obtained after subtracting the background fluorescence established from blank tissue pieces. Confocal scanning provided a cumulative fluorescence reading and an average intensity for the area of interest (presented as a rectangle). The fluorescence intensity inside a prostatic lobule was determined based on the signal in a rectangular area that included at least one half of the surface area of the cross section inside the lobule. A preliminary evaluation showed <15% variability in fluorescence intensity between different parts of the same lobular cross section. A phase contrast image was generated with the same microscope settings as used for fluorescence scanning and overlaid with the fluorescence image to visualize the location of the drug in the tissue. The standard curve samples for fluorescence microscopy were prepared by applying
known amounts of doxorubicin in solution to microscopic sections of blank prostate tissue. The standard doxorubicin solutions (2 μL) were pipetted on 5-μm-thick blank tissue sections and carefully spread over a surface area of ~2 cm². The standard slides were scanned using the same conditions as the samples. The mean fluorescence intensities were plotted against the applied drug concentrations. Linear standard curves were obtained for a concentration range of 2 to 200 μg/g ($r^2 = 0.997$) and 200 to 750 μg/g ($r^2 = 0.958$). The use of a standard curve enabled the correction of the quenching of fluorescence due to DNA binding.

To ascertain the quantitative measurements of the fluorescence microscopic results, the total drug concentrations in 12 cross-sections determined using this method were compared with the concentrations in adjacent tissue sections determined by HPLC analysis. The comparison showed good agreement between the two methods (average deviation was 15 ± 11%).

**Estimation of acinar volume.** The acinar volume was needed to calculate the acini flow rate. Hence, we used image analysis to determine the area fraction of a glandular lobule occupied by acini. Frozen prostate tissue sections were stained with H&E and analyzed using the Optimas image analysis program (Media Cybernetics, Silver Spring, MD). The glandular area of the lobule was outlined using a computer mouse, and the corresponding total pixel number was determined. The acinar area was electronically selected using a slower pixel intensity. The acinar volume, as a fraction of the glandular lobule, equaled (pixel number of low intensity area) divided by (total pixel number of lobule).

**Prostate targeting advantage by intraprostatic therapy.** The targeting advantage of regional therapy indicates the increase in tissue concentrations after regional delivery compared with systemic delivery and is expressed as enhancement in the tissue concentration adjusted for equivalent plasma concentrations. The advantage was calculated from the tissue and plasma concentrations at the end of 150 minutes regional and systemic infusions according to Eq. A.:

$$K_{\text{advantage}} = \frac{C_{\text{prostate, regional}} \cdot C_{\text{plasma, i.v.}}}{C_{\text{plasma, regional}} \cdot C_{\text{plasma, i.v.}}} \quad (A)$$

where $C_{\text{prostate, regional}}$ and $C_{\text{prostate, i.v.}}$ are the respectively prostate tissue concentrations and $C_{\text{plasma, regional}}$ and $C_{\text{plasma, i.v.}}$ are the plasma concentrations, after intraprostatic and i.v. administration.

**Results**

**Spatial drug distribution in the prostate after intraprostatic infusions.** Three studies were conducted. The first study evaluated the drug distribution with respect to prostate geometry. Figure 1B shows the HPLC results of the intraprostatic injection, presented as a three-dimensional composite in a prostate. The results indicate highly localized drug concentrations dispersed in discrete zones. Drug concentration did not decline gradually from the site of injection, as would be expected if the drug was distributed via a continuous process such as diffusion in an isotropic tissue. Instead, drug concentrations declined abruptly and were highly localized. For example, the drug concentration decline towards the urethra seemed less steep than the decline towards the bladder, and tissue concentrations were several folds higher in some segments compared with immediately adjacent segments. The average drug concentration in the right side of the prostate, which was the infusion site, was ~10 times the concentration in the left side. Compared with the plasma concentration at 150 minutes, the drug concentration was 12,300 ± 4,400-fold (mean ± SD) higher at the injection site and 242 ± 167-fold higher in the contralateral half that was not infused.

The second study evaluated the drug distribution as a function of distance from the injection site. Figure 2B shows the HPLC results on the changes in the average tissue concentrations. Tissue concentrations near the injection site reached 74.3 ± 14.4 μg/g, declined with increasing distance...
to about 1.58 ± 0.57 µg/g at 8 mm from the injection site, and increased to 11.5 ± 8.6 µg/g at the urethra followed by a decline to the lowest concentrations of 0.28 ± 0.34 µg/g found in the contralateral half of the prostate.

The results of the above two studies indicated that the drug was localized in discrete zones (i.e., glandular lobule and urethra). Hence, the third study used confocal fluorescence microscopy to visualize the spatial distribution and the profile of drug concentration decline within these structures. Figure 3A shows the fluorescence images overlaid on the transmission microscopic images. Prostate tissues of untreated control animals did not show appreciable fluorescence (data not shown), indicating no or minimal autofluorescence. On the other hand, tissues from doxorubicin-treated animals showed high fluorescence intensity. The fluorescence intensity did not gradually decline over distance but instead was localized in a well-defined area with much lower intensity in the remaining parts of tissue sections. Further examination of sequential sections away from the injection site showed high drug concentrations contained in a funnel-shaped structure, which was widest near the prostatic capsule and narrowed as it coursed towards the urethra. This structure is consistent with a glandular lobule (29). Morphologic examination showed a fibromuscular layer as its boundary. Within the lobule, the highest fluorescence was observed in the glandular cells lining the acini.

The fluorescence intensity readings were converted to doxorubicin concentrations using image analysis and the results were plotted as average concentrations against distance (Fig. 3B). Interestingly, the drug concentrations within the injection site glandular lobule were relatively constant with a decrease of <40 % over 7 mm. Based on this data, we estimated the half width to be 9.5 mm. Comparing the fluorescence intensity between the injection site and adjacent glandular lobules, the intensity in the adjacent lobules was substantially lower, ranging from 26.2 ± 10.6-fold lower near the prostate capsule to 6.1 ± 6.5-fold lower near the urethra. Low fluorescence intensity was found in the fibromuscular layer separating the lobules. Microscopic examination of the sections near the urethra indicated localization of fluorescence in the epithelial cells lining the prostatic ducts and the urethral wall.

The distribution of doxorubicin-derived fluorescence agreed with the drug concentration results obtained with HPLC. Both methods showed highly localized and heterogeneous drug distribution within the prostate, as well as elevated concentrations near the urethra. Fluorescence microscopy showed that the elevated fluorescence was associated with the urethral lining.

**Spatial drug distribution in the prostate after i.v. infusion.** Figure 3C and D shows the differences in the intraprostatic doxorubicin distribution after different treatment routes. In contrast to the highly heterogeneous drug distribution after intraprostatic injection, the i.v. injection yielded relatively homogeneous fluorescence intensity in all glandular areas of the prostate, with lower intensity in fibromuscular stroma tissue. Within the fibromuscular stroma, cells immediately surrounding blood vessels showed a strong fluorescence, suggesting drug localization in this area, which is consistent with earlier findings in breast cancer patients (30). Furthermore, i.v. injection did not result in elevated fluorescence intensity near the urethra as was observed for intraprostatic infusion.

**Drug concentrations in lymph nodes after intraprostatic infusion.** Figure 4 compares the doxorubicin concentration-time profile in the draining lymph fluid and plasma in the same animals (n = 2). In the lymph fluid, drug concentration increased with time during infusion and for 30 minutes after the infusion was ended. The peak lymph-to-plasma concentration ratio was 2.5 ± 0.3 (mean ± range), and the lymph-to-plasma AUC<sub>0-5hr</sub> ratio was 1.8 ± 0.2 (mean ± range). The lymphatic flow rate measured based on the volume collected
from the cisterna chyli was 0.17 mL/min. At the end of 5 hours, the doxorubicin collected from the draining lymphatic fluid represented 0.14% of the dose.

The doxorubicin concentration in lymph nodes at the end of 150 minutes infusion of 0.3 mg was $0.240 \pm 0.180 \, \mu g/g$ (mean $\pm$ SD, $n = 4$), which is 15% lower than the lowest concentrations in the prostate. The concentration in lymph nodes is ~3% of the average concentration in the prostate. Note that lymph node concentration represents the total of the free, extracellular protein-bound and tissue-bound drug concentrations and hence may be different from the concentration in the lymph fluid that represents only the first two drug moieties.

A comparison of the drug concentrations in the lymph nodes located at the same and contralateral sides of the injection site indicated no significant differences ($0.256 \pm 0.192$ versus $0.225 \pm 0.200 \, \mu g/g$; $P > 0.05$).

**Plasma pharmacokinetics of doxorubicin after i.v. or intraprostatic infusion.** Figure 5 shows the plasma concentration-time profiles of doxorubicin after the i.v. and intraprostatic infusions. In both cases, plasma concentrations increase rapidly during the first hours followed by slower increases to reach relatively constant levels of ~150 ng/mL for i.v. infusion and ~6.5 ng/mL for intraprostatic infusion. The intraprostatic-to-i.v. plasma concentration ratio was about 1:23, or about 4%.

**Calculation of prostate targeting advantage of intraprostatic therapy.** The results are summarized in Table 1. The average targeting advantage for intraprostatic infusion, calculated according to Eq. A, was 107-fold. Further analysis indicated highly variable targeting advantage in different separate areas in the prostate (i.e., a 963-fold advantage for the area near the site of injection), declining to a 19-fold advantage in the other one half of the prostate opposite from the site of injection.

**Calculation of acinar volume.** Results of image analysis indicate that the area fraction of a glandular lobule occupied by acini was $17 \pm 2\%$ ($n = 3$). A dog prostate typically consists of 15 glandular lobules (31), whereas the glandular tissue constitutes 62% of the organ (32). Hence, the weight of a

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**Fig. 3.** Spatial doxorubicin distribution: confocal fluorescence microscopic results. Animals were treated with doxorubicin and the prostates were harvested, frozen, and cryosectioned as described in Fig. 2A. Fluorescence image of each microscope section was overlaid with the transmission image of the same slides. Representative dog images. The distance from the urethra is indicated for each section, with negative numbers indicating the sections (right), where the injection took place. Fluorescence intensity is represented by pseudocolors. B, confocal fluorescence images were analyzed for concentrations in the injected lobule ($\bullet$), and in neighboring lobules ($\bigcirc$). The drug concentration within the injected glandular lobule was relatively constant, with a 26-fold drop across the fibromuscular layer near the capsule, declining to a 6-fold drop near the urethra. Distance is relative to the urethra (0 mm). Points, mean (n = 4); bars, ± SE. C, prostatic cross-section of an animal receiving an intraprostatic doxorubicin infusion shows a heterogeneous distribution with a steep fluorescence intensity gradient across the fibromuscular stroma. D, doxorubicin, 16 mg/kg, was injected by i.v. bolus administration in a dog. Fifteen minutes later, the prostate was harvested and subsequently cryosectioned for fluorescent microscopy. Note the even distribution in the adjacent glandular tubules after the i.v. infusion. A blood vessel in the fibromuscular stroma, surrounded by cells exhibiting high fluorescent intensity (inset, arrow). Original magnification 100×. Exposure time, 30-fold longer than for panel (C).
lobule can be calculated as follows. For an average dog prostate weight of 8 g, the weight of the glandular tissue is 4.96 g, which is divided in 15 lobules. At a tissue density of ~1, the volume per lobule equals 330 μL. Accordingly, the acinar volume was calculated to be 56 μL per lobule.

Discussion

The goals of the present study were to provide a better understanding of the mechanisms of drug transport in the prostate after an intraprostatic infusion and to determine the tissue targeting advantage of this administration route. The key findings are discussed below, with reference to the prostate anatomy and blood perfusion.

Prostate anatomy and perfusion. The prostate gland of dogs is composed of 15 glandular lobules, each surrounded by a layer of fibromuscular stroma. Each lobule contains multiple acini, which are duct-like structures lined with glandular and basal cell layers (31). This anatomy is very similar to that found in the human prostate, which is comprised of ~20 to 70 tubuloalveolar glands that converge into 16 to 32 ducts that connect to the prostatic urethra (33, 34). The amount of stromal tissue in normal human prostates (45-55%) is 20% to 40% higher than in the dog (38%; ref. 32). The prostate is perfused by two groups of blood vessels, the capsular and urethral groups. The urethral group perfuses from the bladder to the base of the prostate and reaches the central and transition zones. The capsular group tortuously enters the lateral surface of the prostate, perfusing the peripheral zone of the prostate and returning to the outer portion of the prostate. In our study, doxorubicin was injected into lobules in the peripheral zone.

Spatial drug distribution in the prostate after intraprostatic infusion. Evaluation by HPLC and confocal microscopy of the distribution of doxorubicin in the prostate showed that doxorubicin remained confined to the injection site lobule bound by the surrounding fibromuscular stroma, with a drastic drug concentration decline of 6- to 26-fold across the thin stromal structure. To our knowledge, this is the first experimental evidence that fibromuscular stroma is a barrier to drug transport. Other studies from our laboratory showed that tightly packed cells, such as densely packed epithelial cells and muscle bundles are formidable barriers to drug penetration, whereas penetration is less impeded by loosely packed interstitial tissue (35). This led to the inference that in the prostate, the interlobular septum, rather than other stromal materials, is the more likely barrier to drug transport.

Another interesting finding from the confocal microscopy results is the slow drug concentration decline within the injection site lobule, from the point of injection near the prostatic capsule toward the urethra (<40% decrease of fluorescence intensity over 7 mm). Saturable tissue binding, whereas it may lead to relatively constant tissue concentrations, can be ruled out as a major cause because the doxorubicin concentration in the injection site lobules (74 μg/g) far exceeded the maximal binding capacity of the major doxorubicin-binding macromolecules (i.e., DNA [0.02 μg/g doxorubicin] and cardiolipin [14 μg/g doxorubicin] in the glandular tissue; ref. 36). In consideration of diffusion and convection (due to the flow of infused and intraprostatic fluid in the acini) as the potential drug transport mechanisms within a prostatic glandular lobule, our results suggests acinar flow as an important intraprostatic drug transport mechanism, for the following reasons.

Diffusion of a solute in an aqueous environment is governed by Fick’s laws. In a tissue, a solute can also be removed by the perfusing blood. The distributed model describes the combined effects of diffusion and blood perfusion on the concentration decline of the solute with distance (37). The distance corresponding to a decline in concentration by 50%, or half width, is described by Eq. B (for blood flow rate-limited removal).

\[
W_{1/2} = 0.693 \times \left( \frac{\psi \times D}{\pi \times q} \right)^{1/2}
\]  

where \( D \) is the diffusion coefficient and can be calculated based on the molecular weight (3.49 × 10^{-4} cm²/min for...
doxorubicin), $\psi$ is the effective volume fraction occupied by interstitial space, $\tau$ is the tortuosity factor, and $q$ is the blood flow rate. With literature values of 0.04 for $\psi/\tau$ (38, 39), and 55 mL/min/100 g for $q$ (40), the half width for doxorubicin in the prostate was calculated to be 0.15 mm. This value is within 4-fold of the experimentally determined value of 0.53 mm in the bladder wall (28).

In contrast to diffusion-mediated transport, convection-mediated transport typically shows flatter concentration-depth profiles, as reviewed by Morrison et al. (41). For example, a $<10\%$ concentration decline over 10-mm distance was observed for 180-kDa macromolecules in brain tissues at flow rates between 0.0008 and 3 $\mu$L/min. Our results indicate a half width of about 9.5 mm for doxorubicin in the prostate tissue, which is much closer to the value for flow-mediated transport than for diffusion-mediated transport. The steeper concentration decline than would be expected for convection may be due to the dilution of drug concentration by the prostatic fluid secreted in the acini. In dogs, the secretion rate of prostatic fluid ranges from 1.7 to 33 $\mu$L/min (42). This translates to a secretion rate of 0.11 to 2.2 $\mu$L per minute per lobule for a prostate consisting of 15 lobules. This secretion rate is significant compared with the infusion rate of 1 or 1.4 $\mu$L/min in our study, accounting for up to 60% of the total bulk flow rate (i.e., sum of prostatic fluid secretion rate and intraprostatic drug infusion rate) and would account for the concentration decline over the length of a glandular lobule. Note that at this bulk flow rate, the fluid in the acini (56 $\mu$L per lobule) would be replaced every 15 to 50 minutes. This data suggests an important role of the convective flow in the acini for intraprostatic doxorubicin transport.

Targeting advantage of intraprostatic therapy. Comparison of tissue and plasma concentrations after intraprostatic and i.v. injections indicates a 107-fold prostate tissue targeting advantage by regional injection. Because the experiments used different dose rates for intraprostatic and i.v. injections (respective dose rate of 0.3 mg/kg over 150 minutes versus 2 mg/kg over 240 minutes), we also calculated the amount of doxorubicin presented to the prostate by the two administration routes at the same dose rate for comparison. Because doxorubicin elimination is considered independent of the dose at concentrations below 500 ng/mL (43), we used the total body clearance of 25.4 mL/kg min in beagle dogs obtained for an i.v. 2 mg/kg dose found in a separate study to calculate the plasma AUC for a 0.3 mg i.v. dose. The calculated AUC equaled 0.109 $\mu$g hour/mL. At a blood flow rate of 264 mL/h to an 8 g dog prostate (40), the amount of doxorubicin presented to the prostate equaled the product of (plasma AUC) and (prostate blood flow rate) or 4.09 $\mu$g. This value is about 73-fold lower compared with the dose and in general agreement with the 107-fold targeting advantage.

Lymphatic drainage. The low lymphatic fluid and lymph node concentrations observed after intraprostatic drug administration indicate a minimal contribution of the lymphatic system to drug removal or transport. The finding of comparable concentrations in lymph nodes at the side of the injection site and the contralateral side further argues against lymph fluid drainage as an important route of delivery of doxorubicin to the lymph nodes.

Summary. The present study represents the first in a series of studies to evaluate the merits of the intraprostatic delivery approach. The results indicate that intraprostatic chemotherapy provides a significant tissue targeting advantage over systemic chemotherapy and may be used to achieve the maximal tissue concentrations, and/or limit the systemic concentrations and toxicity. Our findings further suggest acinar flow as an important mechanism of intraprostatic drug transport and indicate the important role of suborgan structure in drug transport in regional therapy, with the fibromuscular stroma as a formidable barrier to intraprostatic drug distribution. In view of the frequently multifocal nature of prostate cancers, further refinements to overcome the drug distribution barriers and/or ascertain relatively homogeneous drug distribution in different parts of the prostate are needed. Finally, future studies should be directed to address the differences in drug transport in normal and tumor-bearing prostate as well as the antitumor efficacy of intraprostatic chemotherapy in preclinical models.

### Table 1. Prostate concentrations and targeting advantages

<table>
<thead>
<tr>
<th>Administration</th>
<th>Plasma at end of infusion (ng/mL)</th>
<th>Location</th>
<th>Tissue Concentration (µg/g)</th>
<th>Tissue/plasma ratio</th>
<th>Targeting advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.v.</td>
<td>155 ± 9</td>
<td>Whole prostate</td>
<td>1.98 ± 0.46</td>
<td>12.8 ± 2.60</td>
<td>1</td>
</tr>
<tr>
<td>Intraprostatic</td>
<td>6.47 ± 1.83</td>
<td>Whole prostate</td>
<td>7.93 ± 1.43</td>
<td>1,360 ± 650</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Point of injection</td>
<td>74.3 ± 14.4</td>
<td>12,300 ± 4,400</td>
<td>963</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contralateral half</td>
<td>1.60 ± 1.09</td>
<td>242 ± 167</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowest concentration</td>
<td>0.282 ± 0.344</td>
<td>44 ± 52</td>
<td>3.44</td>
</tr>
</tbody>
</table>

NOTE: Dogs were given intraprostatic infusions of 0.3 mg doxorubicin over 150 minutes ($n = 6$) or i.v. infusions of 2 mg/kg over 240 minutes ($n = 2$). Prostates were harvested at the end of infusions and tissue concentrations were determined by HPLC. Concentration ratios were calculated using a tissue density of 1.0. The targeting advantage in various regions of the prostate was calculated using Eq. A. Point of injection represents the tissue specimens nearest to the injection site. Contralateral half represents the one half of the prostate opposite to the site of infusion. Lowest concentration represents the concentrations at $\sim$12 mm left of the urethra (see Fig. 2). Mean ± SD.
References
