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# Prostate artery chemoembolization in prostate cancer: A proof of concept study in spontaneous prostate cancer in a canine model

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ABSTRACT

*Purpose:* The purpose of this study was to assess the feasibility and efficacy of docetaxel-loaded bead chemoembolization in spontaneous prostate cancer in a canine model.
*Materials and methods:* Five pet dogs with histopathologically proven prostate cancer were referred for prostate artery chemoembolization (PACE). After PACE, all animals were followed, including pharmacokinetic study and clinical and biological evolution, until death. Pelvic contrast-enhanced computed tomography examination was performed at one and two months. Animals were subjected to pathological examination after death.
*Results:* Both prostate arteries were successfully chemoembolized in all dogs. A median dose of 18 mg (Q1, Q3; 11.8, 20 mg) docetaxel loaded in 3 mL of 50–100 $\mu$m super absorbent polymer beads was injected into each dog. At one month, four of the five dogs were still alive and the median prostate volume was 51% lower (prePACE median prostate volume, 18.4 mL [Q1, Q3; 12, 32.1 mL] *vs.* postPACE median prostate volume, 6.2 mL [Q1, Q3; 6.2, 11 mL]). At two months, three dogs died because of disease progression. The two remaining dogs showed a 70% median decrease in prostate volume. Prostate pathological examination showed 73% of necrosis. No worsening of urinary symptoms was observed. Pharmacokinetic analysis showed limited systemic passage of docetaxel. All dogs died of metastatic spread at nine months.
*Conclusion:* This study suggests that PACE is feasible and safe for the treatment of spontaneous prostate cancer in a canine model and may provide a new approach to treat selected patients with prostate cancer.


## 1. Introduction

Prostate cancer is the most frequently diagnosed cancer in developed countries and more than 1.2 million of prostate cancers are diagnosed each year [1]. Conventional treatments of localized prostate cancer include radiation therapy, with or without hormonal therapy, brachytherapy, and radical prostatectomy [2]. Active surveillance is an alternate option for the treatment of localized disease [2]. Prostate artery embolization has been introduced as a minimally invasive option for the treatment of prostate benign hyperplasia, with good results in terms of lower urinary tract syndrome and prostate volume reduction [3–5]. Arterial chemoembolization is a well-established option for the treatment of a variety of primary or secondary liver cancers [6]. It consists of the intra-arterial delivery of drug-eluting beads into the tumor arterial network, providing the cumulative benefit of super-selective arterial occlusion (embolization) and drug delivery by the embolic material itself. However, this approach has received little attention to date for the treatment of prostate cancer in humans [4]. However, the application of this concept to treat localized prostate cancer needs to be evaluated in preclinical animal models before it can be safely applied in humans.

The purpose of this study was to assess the feasibility, efficacy, and safety of prostate artery chemoembolization (PACE) for the treatment of spontaneous canine prostate carcinoma.

## 2. Materials and methods

### 2.1. Animal selection

This animal study was fully compliant with the European Community guidelines for the use of pets for clinical research purposes and

*Abbreviations:* Cmax, Maximum concentration; CT, Computed tomography; PACE, Prostate artery chemoembolization; SAP, Super absorbent polymer

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was approved by the ethics committee (#OCR Internal Ethics Committee 2017-021). Experimental procedures were conducted at the ONCOVET – Veterinary Cancer Center (Villeneuve d'Ascq, France).

This study included five consecutive dogs treated between June 2017 and August 2018. From the current clinical population of dogs referred to the clinic, the study was proposed for animals meeting the inclusion and exclusion criteria summarized in Table 1. All animals underwent a baseline clinical examination, quality of life evaluation, biological testing, and a whole-body triple phase computed tomography (CT) examination (Optima, GE Healthcare). CT images were acquired without and after intravenous administration of iodinated contrast material (iohexol, 300 mg I/mL, Omnipaque™ 300, GE Healthcare) at a dose of 1.5 mL/kg of body weight during the arterial and venous phases. CT data were obtained using a 0.625 mm slice thickness. The diagnosis of prostate cancer was histopathologically confirmed after analysis of tissue specimens obtained by systematic sextant biopsies of the prostate for the five dogs.

### 2.2. Prostate artery chemoembolization

PACE was performed under general anesthesia by an interventional radiologist (O.P.) with 15 years of experience. The bladder was drained using a 5-Fr Foley catheter. Super selective catheterization of both prostate arteries was performed under fluoroscopy guidance (CIOS alpha, Siemens Healthineers) through 4-Fr percutaneous common femoral artery access. A Terumo $\alpha$ 2.0-Fr. (Terumo) and 0.014-In Fathome® guide wire (Boston Scientific) was used for navigation and delivery of the chemoembolic agents. The endpoint of embolization was occlusion of both prostatic arteries. At the end of the procedure, the arterial access site was closed with a 7/0 resorbable suture strings. Animals were monitored under direct supervision of a veterinarian until they fully recovered from the anesthesia. Buprenorphine (0.02 mg/kg) was given for pain or distress every 6 to 8 hours during the first 12 hours.

### 2.3. Drug-eluting bead preparation and docetaxel dose

Super absorbent polymer (SAP) (HepaSpheres™ 50-100 $\mu$m, Merit Medical,) were loaded with 30 mg/m$^2$ docetaxel (Taxotere®, Sanofi-Aventis) to obtain a 3-mL solution. Docetaxel (30 mg/m$^2$) was retrieved from a vial containing a 20 mg/mL solution and mixed with (Omnipaque™ 300) to obtain 3 mL of solution [7]. Then the preparation was transferred to a vial containing 25 mg dry 50 - 100 $\mu$m SAP and agitated for 10 min, resulting in a gel with low viscosity.

**Table 1**
Study inclusion and exclusion criteria.

| |
|---|
| **Inclusion criteria** |
| Male dog of any breed and age |
| Histologically-proven prostate carcinoma |
| Life-expectancy > 1 month |
| Surgical treatment declined |
| Informed consent form signed by the pet owner |
| **Exclusion criteria** |
| Platelet count < 100,000/mm$^3$ |
| Neutrophil count < 1,500/mm$^3$ |
| Severe anemia (Hb < 8 g/dL) |
| Severe liver failure and/or renal failure |
| Previous bladder/prostate surgery |
| Allergy to iodinated contrast agent |
| Participation in a clinical trial within the last month |
| Anticancer treatment within 30 days before inclusion (chemotherapy or radiotherapy) |
| Altered performance status |
| Active bacterial infection |

### 2.4. Animal follow-up

Animals were monitored at discharge, at day 30, and day 60 by clinical examination including pain and vital signs. Quality of life score was studied using dedicated questionnaires filled by pet owners and veterinary doctors [8]. Blood sampling was performed at discharge, day 30, and day 60 and liver and renal function, total blood cell counts, and serum albumin levels were assessed. All adverse events were reported using the VCOG-CTCAE V1.1 classification [9].

### 2.5. Response to PACE

The morphological response to PACE was assessed at day 30 and day 60 by calculating the prostate volume in mL, assuming the volume to be estimated by the following formula: width $\times$ depth $\times$ height $\times$ 0.52 as generally done in estimating the volume by prostate imaging [10].

### 2.6. Docetaxel safety profile

The pharmacological safety profile of PACE was evaluated by assessing the systemic passage of docetaxel by measuring its concentration in plasma. All dogs underwent peripheral blood sampling at baseline and 20, 40, 60, 120, 180 and 24 hours after PACE. Plasma was separated immediately and stored at - 80°C. Docetaxel levels were measured by high-resolution mass spectrometry [11,12]. The pharmacokinetic parameters, including plasma concentration over time (AUC in ng $\times$ min/mL); maximum concentration (Cmax in ng/mL); docetaxel half-life ($t_{1/2}$, in min); k elimination rate constant (in min$^{-1}$) were calculated using a non-compartmental model and the trapezoidal rule.

### 2.7. Pathological evaluation

All dogs were followed as long as ethically possible and were euthanized when they presented with intractable pain and a major decline in the quality of life. Autopsy was performed on all animals and the prostate/bladder bloc harvested for histopathological analysis by a pathologist (F.L.) with 20 years of experience. All samples were fixed in formalin and embedded in paraffin with hematoxylin and eosin staining. The histopathological evaluation included an evaluation of tumor necrosis and changes in the tumor margin, including stromal reaction, lymphocytic infiltration, vascular proliferation, and stasis of the border vessels. Tumor boundaries were defined as the peripheral fibrous stromal reaction zone. The histological images of 5 to 10 regions of the tumor border were captured at magnifications of 40x and 100x for each tumor sample. The thickness of the tumor border was measured on the images at a magnification of 40x. The mean and median of the 5 to 10 regions were then recorded and assessed using a four-point scale as follows: +++: prominent, ++: moderate, + mild: and -, none. The tumor viability rate was estimated by using a whole-slide imaging device (NanoZoomer2.0-HT; Hamamatsu Photonics,) and was expressed as the percentage of viable tumor area for each slice.

### 2.8. Endpoints

The primary endpoint was feasibility of PACE, defined as the ability to catheterize both prostatic arteries and inject the full dose of chemoembolic agent loaded with docetaxel.

The secondary endpoints were efficacy and safety of PACE. These endpoints were assessed by the change in prostate volume observed at contrast enhanced CT after PACE, histopathological response, and reporting of toxicity using the VCOG-CTCAE V1.1 classification [9].

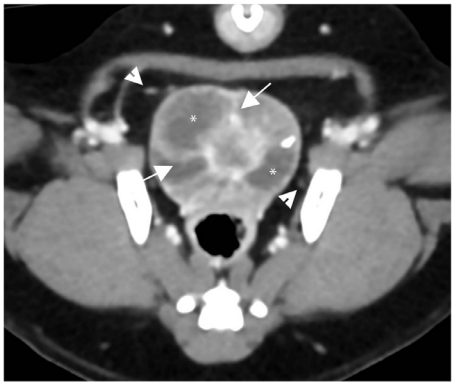

**Fig. 1.** Baseline contrast-enhanced CT image in the axial plane (dog # 1) shows enlargement of the prostate, with thin enhancing septa (arrows) surrounding central hypoattenuating areas (stars) with satellite lymph nodes (arrowheads).

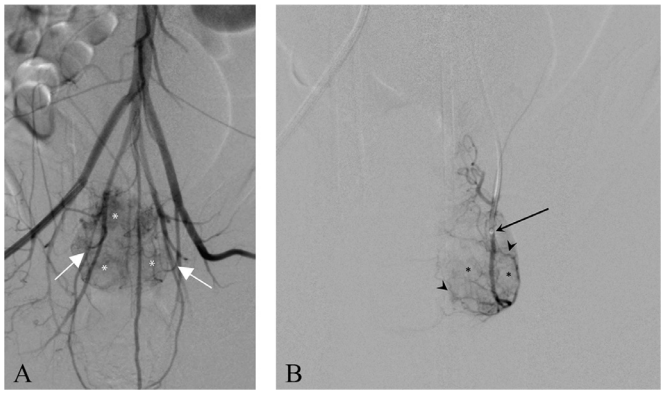


**Fig. 2.** 11-year-old dog (dog # 1) with prostate cancer treated with intra-arterial chemoembolization. A, Global angiogram in anterior-posterior projection of both internal iliac arteries shows contrast agent staining into prostate parenchyma (stars). Both prostate lobes are supplied by enlarged collaterals of the inferior vesical arteries (arrows). Successively both prostate arteries were catheterized and docetaxel eluted beads were injected.B, Selective angiogram of left prostate artery in anterior-posterior projection shows the microcatheter tip distally placed into the prostate artery (arrow). Angiogram reveals tortuous vessels (arrowheads) associated with marked prostate tissue blush (stars) before chemoembolization.

### 2.9. Statistical analysis

Data were reported as medians, 1st and 3rd quartiles. The percentage of prostate decrease was the ratio between the prostate volume before PACE and those after PACE at day 30 and day 60.

## 3. Results

### 3.1. Animal characteristics at baseline

Between June 2017 and August 2018, five dogs with a median age of 10 years (Q1, Q3; 9, 10 years) were included. At baseline, all dogs were referred to the veterinary clinic for urinary retention and reduced quality of life. Presence of prostate cancer was suspected on CT, when an enlargement of the prostate was associated to enhancement of thin septa surrounding a central hypoattenuating zone after intravenous administration of iodinated contrast material (Fig. 1). CT also showed metastatic spread as pelvic lymph nodes with or without small lung nodules in all dogs. Histopathological analysis demonstrated complete invasion of the gland in all dogs, with vascular and lymphatic involvement. No hematological nor biochemical abnormalities were observed. The baseline characteristics of the dogs are shown in Table 2.

### 3.2. Angiographic findings and PACE

Angiography of both internal iliac arteries showed staining of contrast material in the prostate, with mild hypervascularization, suggestive of prostate cancer. All prostatic arteries arising from the anterior branch of the internal iliac artery were enlarged (Fig. 2). Prostate arteries of all dogs were super-selectively catheterized on both sides. A median dose of 3 mL (Q1, Q3; 2.5, 3 mL) docetaxel-loaded SAP was injected in both prostate arteries, accounting for a median total amount of 18 mg (Q1, Q3; 11.8, 20 mg) docetaxel, representing 90 to 98% of the planned dose. All animals tolerated well the procedure and no immediate complications were observed.

### 3.3. One-month follow-up

All dogs were successfully discharged at day 2. Dog # 2 was euthanized at day 25 because of rapid worsening of general status. All four surviving dogs showed a decrease in their quality of life (median baseline score 23 *vs.* 45 at one month). Urinary retention (VCOG-CTCAE V1.1 grade III) occurred in three dogs during the first month. All were successfully managed with alfuzosine. One dog experienced grade I (VCOG-CTCAE V1.1 classification) urinary incontinence during the first month due to major prostate gland necrosis following PACE and spontaneously resolved (Fig. 3).

### 3.4. Midterm post-PACE follow-up

Two of the four dogs were euthanized before day 60 because of rapid disease progression with lung and bone metastases and major worsening of their performance status. The two remaining dogs were euthanized at day 91 and day 145 because of disease progression with bone and lung metastases and a decrease in their performance status. The clinical and morphological outcomes are summarized in Table 3.

### 3.5. CT findings and changes in prostate volume

At 30 days, contrast-enhanced CT showed a median prostate volume of 6.2 $cm^3$ (Q1, Q3; 6.2, 11 $cm^3$) with a median decrease

**Table 2**
Baseline characteristics of the dogs.

| Dog number | Breed | Gender | Age (years) | Weight (Kg) | Quality of life score* | Prostate volume** (mL) | Gleason score | Metastatic spread |
|---|---|---|---|---|---|---|---|---|
| 1 | Cross breed | Neutered male | 11 | 7.8 | 20 | 18.41 | 5 + 5 = 10 | 2 < 10 mm lung nodules + Pelvic lymph nodes |
| 2 | Beagle | Neutered male | 9 | 15.5 | 35 | 32.1 | 5+ 5 = 10 | Pelvic lymph nodes |
| 3 | French Pointer | Neutered male | 9 | 31.2 | 27 | 37.98 | 5 + 4 = 9 | Pelvic lymph nodes |
| 4 | Cross breed | Neutered male | 12 | 17.3 | 28 | 10.97 | 5 + 5 = 10 | 2 < 10 mm lung nodules + Pelvic lymph nodes |
| 5 | Jack Russel Terrier | Neutered male | 10 | 7.7 | 27 | 12.04 | 5 + 5 = 10 | Pelvic lymph nodes |

* Quality of life score: from 13 for the best to 65 for the worst quality of life.
** Assessed on contrast-enhanced computed tomography.

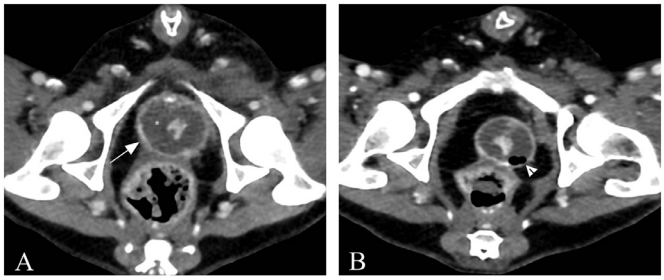


**Fig. 3.** 11-year-old dog (dog # 1) with prostate cancer treated with intra-arterial chemoembolization. The prostate volume decreased by 66% at day 30 and 77% at day 60 following intra-arterial chemoembolization. A, Pelvic CT image in the axial plane obtained at day 30 following intra-arterial chemoembolization of prostate arteries shows a broad necrotic area (star) with only the capsule (arrow) remaining. B, Pelvic CT image in the axial plane obtained at day 60 following intra-arterial chemoembolization of prostate arteries shows a large hypoattenuating prostate containing internal gas (arrowhead) suggestive for extensive necrosis.

of 47 =%. Dog # 4 showed extensive necrosis of the prostate that led to grade I urinary incontinence. At day 60, CT showed a 78% and 65% decrease in prostate volume for the two dogs that were still alive.

### 3.6. Docetaxel safety profile

The plasma levels of docetaxel over the entire blood-sampling period are report in Fig. 4. The highest docetaxel plasma concentration levels were recorded at 40 minutes after PACE with a Cmax of 83.28 ng (Q1, Q3; 51, 98 ng). The AUC of docetaxel was 29333.42 ng × min/mL (Q1, Q3; 12304, 41551 ng × min/mL). The median half time was 388 min-1 (Q1, Q3; 349, 447 $min^{-1}$) and the elimination rate constant was k = 0.0017 $min^{-1}$ (Q1, Q3; 0.0015, 0.0020 $min^{-1}$).

### 3.7. Pathological findings

Only four of the five dogs had a pathological examination after death after PACE. The organ harvest of Dog # 2 was not performed at the request of the dog's owner. Pathological examination showed necrosis involving a median of 88% (Q1, Q3; 73, 95%) of the prostate volume. Histopathological examination revealed 1 to 30% of the remaining viable tumor, with a low rate of mitosis. Inflammatory reaction and fibrosis were limited in all dogs (Table 4). No rectal or bladder wall ischemic/necrotic damage related to PACE were observed. Beads were found in the intra-prostatic arteries and tumors (Fig. 5). Intravascular beads were surrounded by fibro-muscular stroma, with a thick rim of epithelioid macrophages, lymphocytes, and multinucleated giant cells. Intratumor beads were found in a fibrinous transformation tissue containing epithelioid macrophages and multinucleated giant cells (Fig. 5). No beads were found in the bladder wall.

## 4. Discussion

Herein, we report that PACE using docetaxel-eluting beads is able to induce a significant reduction in prostate volume and necrosis of most of the gland, with no major complications in canine prostate cancer.

The canine prostate gland shares many morphological and functional similarities to that of humans [13]. Canine prostatic tumors are derived from urothelial or ductal cells, and their growth is most often androgen-independent [14–16]. Comparative pathogenic studies have shown canine prostate cancer to be similar to hormone-resistant human prostate cancer [17,18].

Three previous studies (two on humans, one on pet dogs) have tested the treatment of prostate cancer using an intra-arterial approach [19–21]. Pisco et al. tested chemotherapy and embolization using a mixture of *chelidonium majus* mother tincture and docetaxel followed by bead embolization in 16 patients with localized prostate cancer as an alternative to conventional treatment [15]. They were able to show a short-term biological response but the biological relapse rate at 12 months was 37.5% [19]. In addition, no histopathological analysis was performed to confirm the biological response. These results are not sufficient to support this approach in clinical application. Mordasini et al. performed bland embolization before radical prostatectomy for localized prostate cancer in 12 patients [20]. The goal of this trial was to reduce metachronous tumor recurrence, allowing safer and margin-free surgery. Despite two patients with complete target lesion necrosis, all 12 patients had secondary cancerous foci or remaining viable target lesion cancer in the remaining gland. They failed to achieve complete eradication of prostate cancer [20].

Intra-arterial chemotherapy has already been tested in canine prostate cancer. Culp et al. reported an increase in local tumor

**Table 3**
Follow-up and change in prostate volume.

| | | | | Day 30 | | |
|---|---|---|---|---|---|---|
| Dog # | Quality of life score‡ | Urinary complication grade‡‡ | General status | Prostate volume (mL) | Decrease in prostate volume (%) | Note |
| 1 | 32 | 3* | Stable disease | 6.27 | 65.9 | |
| 2 | N.D. | N.D. | N.D. | N.D. | N.D. | Euthanized at Day 25 |
| 3 | 50 | 0 | Disease Progression | 25.03 | 34.1 | Progression of lymph node metastases |
| 4 | 44 | 1** | Stable disease | 6.09 | 44.5 | Prostate necrosis |
| 5 | 49 | 3* | Disease Progression | 6.17 | 48.8 | Progression of lymph node and lung metastases |

| | | | | Day 60 | | |
|---|---|---|---|---|---|---|
| Dog # | Quality of life score‡ | Urinary complication grade‡‡ | General status | Prostate volume (mL) | Decrease in prostate volume (%) | Note |
| 1 | 37 | 0 | Disease Progression | 4.1 | 77.6 | Euthanized at Day 91 |
| 2 | N.D. | N.D. | N.D. | N.D. | N.D. | Euthanized at Day 25 |
| 3 | N.D. | N.D. | Disease Progression | N.D. | N.D. | Euthanized at Day 41 |
| 4 | 50 | 1** | Disease Progression | 3.8 | 65.0 | Euthanized at Day 145 |
| 5 | N.D. | N.D. | Disease Progression | N.D. | N.D. | Euthanized at Day 46 |

‡ Quality of life score: from 13 for the best to 65 for the worst quality of life.
‡‡ VCOG-CTCAE.V1.1 Urinary Grade.
* Urinary retention.
** Urinary incontinence; N.D.: not done.

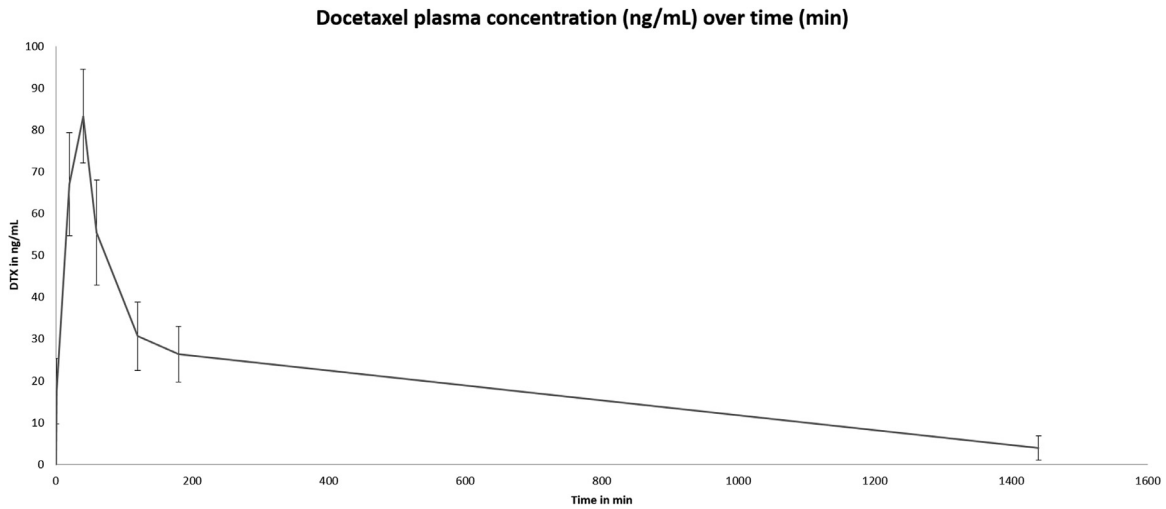


**Fig. 4.** Pharmacokinetic analyze curve. Peak concentration of docetaxel was obtained 40 min after injection, with a median maximal concentration of 83.28 ng (Q1, Q3; 51, 98 ng) with limited systemic passage over time (AUC, 29333.42 ng × min/mL; Q1, Q3: 12304, 41551 ng × min/mL).

response in a comparative study aiming to compare intra-arterial carboplatin infusions and intravenous injection, in accordance with the study results [21]. They showed that dogs treated with the intra-arterial injection exhibited fewer hematological complications.

The oncological challenge of prostate cancer treatment is to achieve complete eradication with the lowest possible morbidity (preservation of urinary continence and sexual function). The risk of leaving metachronous lesions is one of the limitations of focal treatment. Focal therapy (high-intensity focused ultrasound, irreversible electroporation, cryotherapy, and laser) has been proposed to ablate prostate cancer tissue with limited side effects [22]. However the major limitation of these approaches is the risk of metachronous tumor recurrence in the remaining prostatic tissue [23]. The aggressive nature of docetaxel-eluting bead chemoembolization paves the way for a new application in the treatment of prostate cancer.

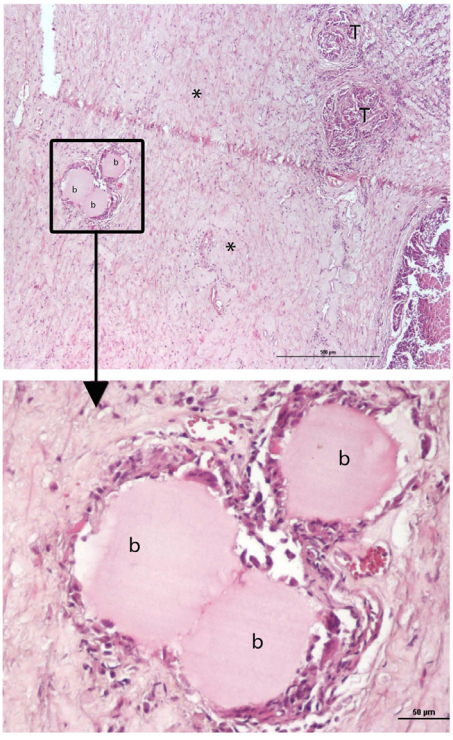


**Fig. 5.** Histopathological analysis after hematoxylin and eosin staining at a magnification of 4 × and 20 × . The prostate is massively necrotic after chemoembolization, containing a residual tumor islet. Three microspheres (b) located in a necrotic fibrinous exudate (star), near viable tumor nodules (T), are shown (Scale bar = 500 $\mu$m). The image at a magnification of 20 × (Scale bar = 50 $\mu$m) shows beads surrounded by epithelioid macrophages and multinucleated giant cells.

In our study, no major complications, such as non-target embolization or hematological events, were observed [24]. Furthermore, the study shows that this approach has an excellent pharmacological safety profile, exhibiting very low systemic passage of docetaxel. These findings suggest low rates of hematological and myocardial toxicity in future application in human.

Docetaxel was chosen as the drug for PACE because it is a standard of care for first-line treatment of metastatic hormone-resistant prostate cancer and it has shown superior efficacy compared to other chemotherapies [25]. The combination of docetaxel with drug-eluting beads is not completely obvious, as docetaxel is alcohol soluble, as opposed to other chemotherapeutics, which are mostly water-soluble. Super absorbent polymers are characterized by a spherical shape, calibration, biocompatibility, and ease of fluid absorption due to its superabsorbent property. Docetaxel can be loaded onto SAP when it is dissolved in a nonionic contrast agent [7]. The combination of both products has been already tested in the context of compassionate care for locally advanced breast carcinoma and ovarian carcinoma/breast cancer liver metastases [26–29]. The size of 50 to 100-$\mu$m dry SAP to obtain 200 to 400-$\mu$m microspheres after docetaxel loading was chosen to avoid non-target embolization, as previously proposed [30,31]. When prepared as described, this results in a gel that is easy to inject into the microcatheter. The viscous nature of the docetaxel-SAP allows for safe injection into the prostate arteries, with deep penetration of the eluted beads (observed by histopathology), with a limited risk of non-target embolization. Furthermore, this approach makes it possible to achieve a high intratumor drug concentration and long-lasting delivery. This is associated with low systemic docetaxel release. Given the 2 to 30% of residual tumor remaining, sequential treatment using 1, 2, or 3 PACE sessions four weeks apart could be proposed.

Docetaxel-PACE has several potential advantages for prostate cancer treatment. For patients under active surveillance whose disease requires better management, docetaxel-PACE can be proposed first, without precluding later therapy such as surgery or radiation therapy. Patients eligible for focal treatment (high-intensity focused ultrasound, irreversible electroporation, or cryoablation) can benefit from docetaxel-PACE to overcome the high rate of metachronous

**Table 4**
Histopathological analyses of the animals after death.

| Dog # | Prostate | | | | | | | Bladder | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | necrosis | Tumor cells | No. of tumor cell mitoses / 10 fields | Inflammatory reaction* | Fibrosis* | Vascular and lymphatic tumor emboli* | Presence of beads* | Invasion by the prostate tumor* | Wall Necrosis* | Presence of beads* |
| 1 | 95% | 2% | 1 | + | + | - | +++ | - | - | - |
| 2 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| 3 | 50% | 25% | 3 | ++ | ++ | +++ | ++ | ++ | - | - |
| 4 | 95% | 3% | 1 | + | + | + | +++ | - | - | - |
| 5 | 80% | 12% | 2 | + | + | +++ | ++ | ++ | - | - |

* Indicates +++ prominent, ++ moderate, + mild, and - none. ND: not done.

tumor recurrence [32]. Relapse after radiation therapy suggests that only radical and extensive prostatectomy can be managed safely.

This study had several limitations. First, the late diagnosis of prostate cancer at a metastatic stage, associated with the high degree of aggressiveness of canine prostate cancer, did not allow to study survival after PACE. Second, a larger sample of animals would allow an accurate description of PACE efficacy and toxicity. Human trials should consider the need for repeat PACE to achieve complete eradication of the tumor.

In conclusion, this animal study shows that PACE with docetaxel-eluting beads is feasible and allows achieving up to 70% decrease in prostate volume with acceptable safety profile.

## Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

## Animal rights

This animal study was fully compliant with the European Community guidelines for the use of pets for clinical research purposes and was approved by the ethics committee (#OCR Internal Ethics Committee 2017-021).

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## CRediT authorship contribution statement

**Olivier Pellerin:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Carole Déan:** Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – review & editing, Project administration. **Philippe Reb:** Conceptualization, Resources, Writing – review & editing. **Celine Chaix:** Resources, Writing – review & editing. **Franck Floch:** Investigation, Resources, Writing – review & editing. **Dominique Tierny:** Conceptualization, Validation, Writing – review & editing, Project administration. **Marc Sapoval:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – review & editing, Funding acquisition.

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## References

[1] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[2] Mottet N, van den Bergh RC, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[3] Cadour F, Tradi F, Habert P, Scemama U, Vidal V, Jacquier A, et al. Prostatic artery embolization using three-dimensional cone-beam computed tomography. Diagn Interv Imaging 2020;101:721–5.
[4] Pisco J, Campos Pinheiro L, Bilhim T, Duarte M, Rio Tinto H, Fernandes L, et al. Prostatic arterial embolization for benign prostatic hyperplasia: short- and intermediate-term results. Radiology 2013;266:668–77.
[5] Boeken T, Di Gaeta A, Moussa N, Del Giudice C, Dean C, Pellerin O, et al. Association between intravesical prostatic protrusion and clinical outcomes in prostatic artery embolization. Diagn Interv Imaging 2021;102:141–5.
[6] Gaba RC, Lokken RP, Hickey RM, Lipnik AJ, Lewandowski RJ, Salem R, et al. Quality improvement guidelines for transarterial chemoembolization and embolization of hepatic malignancy. J Vasc Interv Radiol 2017;28:1210–1223.e3.
[7] Seki A, Hori S. Transcatheter arterial chemoembolization with docetaxel-loaded microspheres controls heavily pretreated unresectable liver metastases from colorectal cancer: a case study. Int J Clin Oncol 2011;16:613–6.
[8] Iliopoulou MA, Kitchell BE, Yuzbasiyan-Gurkan V. Development of a survey instrument to assess health-related quality of life in small animal cancer patients treated with chemotherapy. J Am Vet Med Assoc 2013;242:1679–87.
[9] Veterinary cooperative oncology group. Common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol 2016;14:417–46.
[10] Marin L, Ezziane M, Comperat E, Mozer P, Cancel-Tassin G, Coté J-F, et al. Comparison of semi-automated and manual methods to measure the volume of prostate cancer on magnetic resonance imaging. Diagn Interv Imaging 2017;98:423–8.
[11] Mortier KA, Lambert WE. Determination of unbound docetaxel and paclitaxel in plasma by ultrafiltration and liquid chromatography-tandem mass spectrometry. J Chromatogr A 2006;1108:195–201.
[12] Alexander MS, Kiser MM, Culley T, Kern JR, Dolan JW, McChesney JD, et al. Measurement of paclitaxel in biological matrices: high-throughput liquid chromatographic-tandem mass spectrometric quantification of paclitaxel and metabolites in human and dog plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2003;785:253–61.
[13] Leroy BE, Northrup N. Prostate cancer in dogs: comparative and clinical aspects. Vet J Lond Engl 2009;180:149–62 1997.
[14] Winkler S, Reimann-Berg N, Murua Escobar H, Loeschke S, Eberle N, Höinghaus R, et al. Polysomy 13 in a canine prostate carcinoma underlining its significance in the development of prostate cancer. Cancer Genet Cytogenet 2006;169:154–8.
[15] Huang Z, Chen Q, Luck D, Beckers J, Wilson BC, Trncic N, et al. Studies of a vascular-acting photosensitizer, Pd-bacteriopheophorbide (Tookad), in normal canine prostate and spontaneous canine prostate cancer. Lasers Surg Med 2005;36:390–7.
[16] Nau WH, Diederich CJ, Ross AB, Butts K, Rieke V, Bouley DM, et al. MRI-guided interstitial ultrasound thermal therapy of the prostate: a feasibility study in the canine model. Med Phys 2005;32:733–43.
[17] Leav I, Schelling KH, Adams JY, Merk FB, Alroy J. Role of canine basal cells in postnatal prostatic development, induction of hyperplasia, and sex hormone-stimulated growth; and the ductal origin of carcinoma. Prostate 2001;48:210–24.
[18] Sorenmo KU, Goldschmidt M, Shofer F, Goldkamp C, Ferracone J. Immunohistochemical characterization of canine prostatic carcinoma and correlation with castration status and castration time. Vet Comp Oncol 2003;1:48–56.
[19] Pisco J, Bilhim T, Costa NV, Ribeiro MP, Fernandes L, Oliveira AG. Safety and efficacy of prostatic artery chemoembolization for prostate cancer-initial experience. J Vasc Interv Radiol 2018;29:298–305.
[20] Mordasini L, Hechelhammer L, Diener P-A, Diebold J, Mattei A, Engeler D, et al. Prostatic artery embolization in the treatment of localized prostate cancer: a bicentric prospective proof-of-concept study of 12 patients. J Vasc Interv Radiol 2018;29:589–97.

[21] Culp WTN, Weisse C, Berent AC, Reetz JA, Krick EL, Jackson DE, et al. Early tumor response to intraarterial or intravenous administration of carboplatin to treat naturally occurring lower urinary tract carcinoma in dogs. J Vet Intern Med 2015;29:900–7.
[22] Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M. High intensity focused ultrasound: the fundamentals, clinical applications and research trends. Diagn Interv Imaging 2018;99:349–59.
[23] Pesapane F, Patella F, Fumarola EM, Zanchetta E, Floridi C, Carrafiello G, et al. The prostate cancer focal therapy. Gland Surg 2018;7:89–102.
[24] Cornelis FH, Barral M, Jenoudet H, Boutault JR, Zurlinden O. Successful conservative management of non-targeted embolization of the penile glans after prostate artery embolization. Diagn Interv Imaging 2020;101:617–8.
[25] Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[26] Yuki T, Hori S, Yamashiro K, Ohira R, Hori A. Transarterial chemoembolization for liver metastasis of ovarian malignant melanoma resulting in long-term survival. Gan To Kagaku Ryoho 2016;43:1757–60.
[27] Hori A, Yuki T, Yamashiro K, Ohira R, Hori S. Introduction of hyperthermia therapy with low dose systemic chemotherapy and hepatic transarterial chemo-embolization for a case of advanced prostatic cancer. Gan To Kagaku Ryoho 2016;43:2432–4.
[28] Kennoki N, Hori S, Hori A, Takeo Y, Oshiro H. Transcatheter arterial chemoembolization with spherical embolic material for locally advanced breast cancer: first report of HepaSphereTM treatment for primary breast cancer. BJR Case Rep 2016;2:20150417.
[29] Seki A, Hori S, Sueyoshi S, Hori A. Local control and prognostic significance of transarterial treatment for limited recurrence of ovarian cancer as third-line and beyond therapy. Int J Clin Oncol 2014;19:1065–73.
[30] Jeon GS, Won JH, Lee BM, Kim JH, Ahn HS, Lee EJ, et al. The effect of transarterial prostate embolization in hormone-induced benign prostatic hyperplasia in dogs: a pilot study. J Vasc Interv Radiol 2009;20:384–90.
[31] Sun F, Sánchez FM, Crisóstomo V, Díaz-Güemes I, López-Sánchez C, Usón J, et al. Transarterial prostatic embolization: initial experience in a canine model. AJR Am J Roentgenol 2011;197:495–501.
[32] Barat M, Colleter L, Mongiat-Artus P, Jolibois Z, Quero L, Hennequin C, et al. Salvage cryoablation for local recurrence of prostatic cancer after curative therapy. Diagn Interv Imaging 2019;100:679–87.