Angiogenesis in a transgenic mouse model of prostate cancer

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Prostate cancer is the most common cancer among Canadian adult males.\(^1\)

In 2006, an estimated 20,700 men were diagnosed with prostate cancer and 4,200 died of it.\(^1\)

One in 7 men will develop prostate cancer during his lifetime, mostly after age 60.\(^1\)

The risk of prostate cancer increases with age by approx. 3-4% each year.

It is the second leading cause of cancer-related death.

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Angiogenesis

- Tumor growth limited in size without development of new blood vessels
- Maximum tumor size without angiogenesis is 2–3mm in diameter
- Release of soluble angiogenic factors induce neovascularization
- Termed ‘angiogenic switch’

Prostate Cancer Model and Imaging Modality

Mouse Model:

- The TransGenic Mouse Adenocarcinoma of the Prostate (TGMAP) was developed.
- PSP-94 promoter region with SV40 Tag oncogene.
- Correlation between tumorigenesis with puberty/age.
- Presence of tumor confirmed by histology.
- Progression: Prostatic hyperplasia followed by prostatic intraepithelial neoplasia (PIN) and eventually high grade carcinoma.

CT Perfusion:

- Fast rotation speed flat panel volumetric small animal CT scanner (GE Healthcare).
- CT perfusion software.
- Minimally invasive imaging method.
- Measures hemodynamic changes in tissues.

Hypothesis

- In the development of tumor there is an angiogenic phase at which blood flow and blood volume are maximal
Objective

- To study the development of angiogenesis in the TGMAP model by measurement of blood flow and blood volume with dynamic CT scanning over a period of 9 weeks.
Prior to CT perfusion scans mice were screened using Ultrasound (Vevo 770, VisualSonics Inc.)

- Mice were anesthetized with isoflurane
- The hair on the lower abdomen was removed using Nair®
- Mice were scanned with a 40 MHz probe to identify small tumors (approx. 2 mm in diameter)
- Scans performed weekly to ensure increased chance of identifying small tumors
- Once likely candidates were identified, CT perfusion scans commenced
CT Perfusion Protocol

- Twelve mice were anesthetized with isoflurane
- 200 µl of an iodinated contrast agent (Hypaque 200 I mg/ml) was injected via the tail vein at an injection rate of 2.0 ml/min, 5 s after the start of the scan
- Scanned for 40 s at 80 kVp, 60 mA spatial resolution 175 µm (in-plane) and 40 x 0.9 mm thick slices/s
- CT PERFUSION software computes blood flow (BF), blood volume (BV) and permeability (PS) maps
- Scan periodically: 7-14 days
Perfusion Maps

Average Maps

Blood Flow Maps

Volume Plot

Day 0: Volume: 27.54 mm³
Day 42: Volume: 58.77 mm³
Day 62: Volume: 284.94 mm³

Day of scan

Volume (mm³)

Day 0, Day 14, Day 28, Day 42, Day 49, Day 56, Day 62

Volume Plot

Day 0
Day 14
Day 28
Day 42
Day 49
Day 56
Day 62
Evaluation of Mean Blood Flow

Mean Blood Flow vs. Tumour Radius

- Significant if $p < 0.05$
Evaluation of Mean Blood Volume

Mean Blood Volume vs. Tumour Radius

- Significant if p < 0.05
Discussion

- Determination of peak blood flow and blood volume during tumor development is possible using CT perfusion
- Mean radius of tumor at maximal was found to be 2.48 ± 0.32 mm
- Similar trend found between blood flow and blood volume
- Peak phase in BF and BV may indicate a point where tumor is very well nourished
- This phase possibly results in an increase in the growth rate
- This may lead to an increased risk of metastases
Future Work

- Obtain a larger sample size to determine statistical significance
- Look at possibility of using Lipiodol as an embolizing agent
- Lipiodol contains ethyl esters of iodised fatty acids of poppy seed oil
- Main purpose: contrast agent
- Has been shown to produce embolizing effect
- Locally administer Lipiodol and see effects on tumor size, blood flow and blood volume

Arterial Curve Selection
Arterial Curve Selection

Absolute Units

Relative Units

Shape Comparison
Arterial Curve Selection

Blood Flow Map

Blood Volume Map

Blood Flow Map

Blood Volume Map