

MOTIVATION

1. Metastatic disease represents a major health problem and is largely the cause of high probability post-treatment recurrence in many cancers.
2. Colorectal cancer and other common cancers regularly metastasize to the liver.
3. Models of metastasis are an important means for evaluating metastasis-targeted therapeutics, but traditionally have been inefficient due to difficulty in determining staging times, the need serial sacrifice and inefficient and potentially inaccurate gross methods for measuring tumor burden.
4. Non-invasive, in vivo, high resolution imaging modalities, such as MRI, offer great potential for efficient and accurate measurement of metastatic tumor burden.

AIMS

1. To use serial passage of C26 (colorectal tumor) liver metastases in an intrasplenic injection mouse model to obtain a stable and reproducible liver metastasis model.
2. To use high field (7T) MRI to characterize tumor appearance and growth in the liver metastasis mouse model.
3. To compare T2-weighted MRI with gadolinium and iron-oxide contrast MRI for delineating metastases from normal tissue.
4. To correlate MRI-determined tumor burden with survival after a cyclophosphamide treatment.

BACKGROUND

METHODS

Colorectal Cancer & Metastasis Statistics

- There will be an estimated 150,484 new cases of colorectal cancer in 2004 [1], of which at least 38% will experience a recurrence within 5 years after treatment [1].
- In 40-80% of the recurrent cases, the liver is the site of the recurrence [1].

Traditional Metastasis Models

- While mouse models of metastatic liver disease have been used in the past [2], most commonly they have required serial sacrifice for evaluation of therapeutic effectiveness.
- Quantifying the extent of metastases in the excised liver is problematic, involving counting and/or weighing of metastatic nodules.

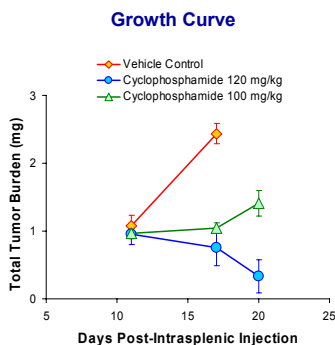
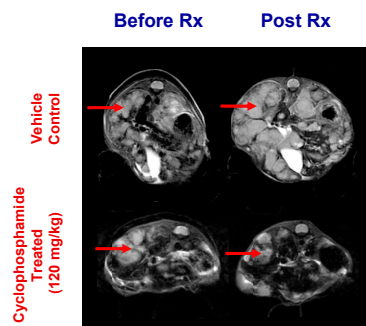
Motivation for an MRI Model of Liver Metastasis

- An **in vivo imaging model** of metastatic colon cancer would be valuable in the elucidation of the disease process and development of therapeutics at the preclinical level.
- Clearly, an **in vivo model** whereby MRI could be used for delineating metastases from normal tissue, and image processing software utilized for counting nodules and measuring the overall tumor burden would be a significant advantage.
- While research groups have worked with MRI in models like this in recent times [3], the availability, utility and validation of previously used models is lacking.

- Liver metastases were obtained in Balb/C mice after an intrasplenic injection of C26 colorectal tumor cells, without surgery.
- Repeated serial passage of the metastases was used to obtain an aggressive and reproducible liver metastasis model.
- Once the model was reproducible, MRI was used to image the appearance of liver metastases and to quantify overall tumor burden.
- T2-weighted (T2w) MRI (TR=2s, TE=25ms) was used to delineate the metastases, taking advantage of the high natural contrast between liver (containing iron with high T2 relaxivity) and tumor tissue (with lower T2 relaxivity).

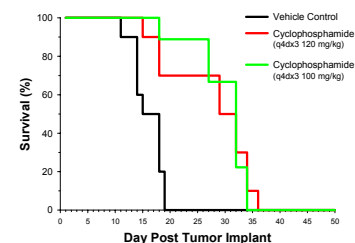
- Both Gadolinium- (Magnevist™) and Iron-oxide- (Feridex™) contrast MRI was compared with T2w MRI, in terms of ability to delineate metastases.
- MRI was used to quantify tumor burden after treatment with a standard chemotherapy (cyclophosphamide, q4d x3 @ 100 and 120 mg/kg)
- Metastases were generally well delineated from normal tissue on MRIs and were circled manually using a custom written Matlab-based interface.

Tumor Growth



RESULTS AND CONCLUSIONS

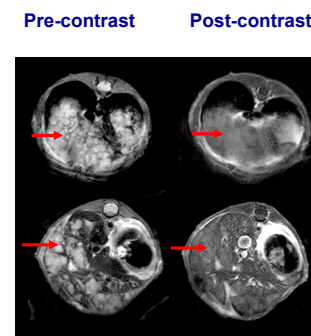
Survival



Conclusions

- ⇒ By serial passage, an efficient and reproducible model of liver metastasis was obtained.
- ⇒ Liver metastases were well delineated by simple, non-gated, T2-weighted MRI, even in the thoracic region.
- ⇒ Gadolinium and iron-oxide contrast MRI presented no great advantage over conventional T2-weighted MRI, as there is sufficient natural iron-induced contrast between liver and tumor tissue.
- ⇒ Using MRI, growth of metastatic tumors was readily quantified over time. MRI-determined growth inhibition following cyclophosphamide treatment as early as day 17, correlated with survival to 36 days.
- ⇒ MRI provides a rapid, non-invasive and highly efficient method for accurate determination of drug response in a mouse model of liver metastasis.

Gadolinium Contrast MRI



Iron-oxide Contrast MRI

