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Image-guided doxorubicin delivery for pediatric tumors using MRI-guided HIFU hyperthermia and temperature-sensitive liposomes

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American Association of Physicists in Medicine

Acknowledgements

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Disclosures

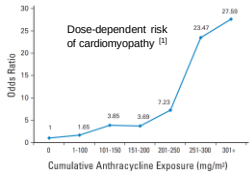
Profound Medical – manufacturer of clinical MR-HIFU system
FUS Instruments – manufacturer of preclinical MR-HIFU system
Celsion – provided Thermodox for all studies

Image-guided DOX delivery for pediatric sarcomas

Doxorubicin in pediatric sarcoma
Adjuvant for tumor debulking,
cumulative dose limited by cardiotoxicity

Therapeutic Ratio = [DOX] tumor / [DOX] heart

Goal: Improved local control without increasing systemic toxicity



1. **Does longer heating time increase DOX in tumor more than heart?**
2. **Does lower injected dose reduce DOX in heart more than tumor?**
3. **Does DOX release delay tumor growth in a rat pediatric sarcoma model?**
4. **Is it feasible to perform MR-HIFU hyperthermia in pediatric subjects?**

[1] Blanco, JCO 2012

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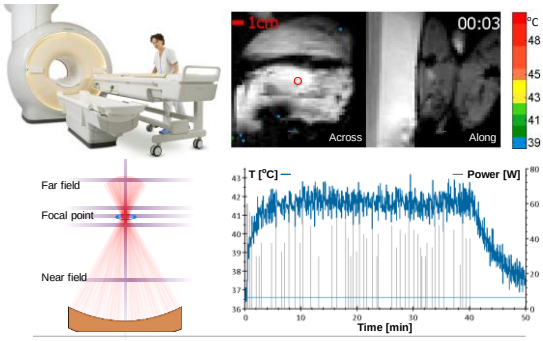
MR-HIFU hyperthermia + Thermodox in rabbit Vx2



[7] Tillander, Med Phys 2016. [8] Chu, IJROBP 2016.

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Image-guided DOX delivery for pediatric sarcomas

1. **Does longer heating time increase DOX in tumor more than heart?**
   - Rabbit bilateral Vx2 tumor model, base temperature 36-37°C
   - Thermodox: 2.5 mg DOX/kg infused over 5-6 minutes at start of heating
   - MR-HIFU 10 or 40 minutes of mild hyperthermia (42°C)
   - At 180 min post injection, saline perfusion and tissue harvesting
   - Tissue [DOX] extracted using AgNO3 and chloroform:isopropanol, measured using HPLC-MS
   - **Does therapeutic ratio (tumor DOX / heart DOX) increase with heating time?**
2. **Does lower injected dose reduce DOX in heart more than tumor?**
3. **Does DOX release delay tumor growth in a rat pediatric sarcoma model?**
4. **Is it feasible to perform MR-HIFU hyperthermia in pediatric subjects?**

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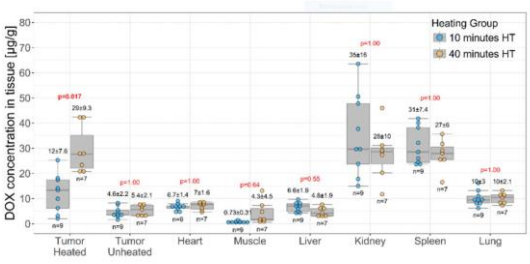
Aim 1: Exposure duration and therapeutic index



Bing et al, IJH 36(1): 2019

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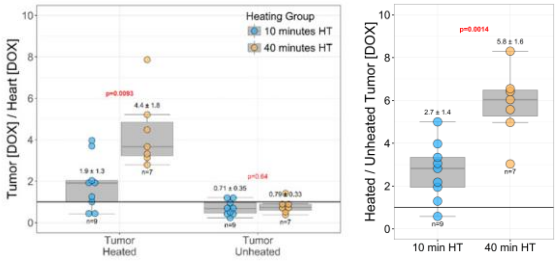
Tumor : Heart increases with heating duration
Heated Tumor : Unheated Tumor does too



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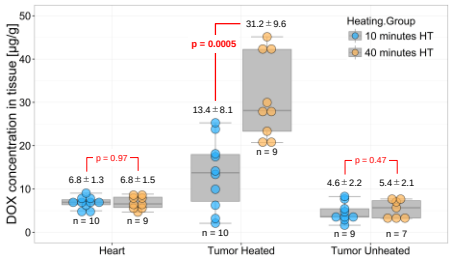
Prolonged heating increased tumor [DOX], Heart [DOX] unchanged



1 Longer heating time increases therapeutic ratio between tumor and heart

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Image-guided DOX delivery for pediatric sarcomas

1. **Does longer heating time increase DOX in tumor more than heart?**
2. **Does lower injected dose reduce DOX in heart more than tumor?**
   - Rabbit bilateral Vx2 tumor model, base temperature 36-37°C
   - Thermodox: 0.1, 0.5 or 2.5 mg/kg infused over 5-6 minutes at start of heating
   - MR-HIFU 40 minutes of mild hyperthermia (42°C)
   - At 180 min post injection, saline perfusion and tissue harvesting
   - Tissue [DOX] extracted using AgNO3 and chloroform:isopropanol, measured using HPLC-MS
   - **Does therapeutic ratio (tumor DOX/heart DOX) decrease with injected dose?**
3. **Does DOX release delay tumor growth in a rat pediatric sarcoma model?**
4. **Is it feasible to perform MR-HIFU hyperthermia in pediatric subjects?**

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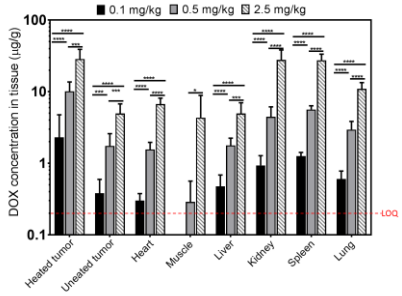
Aim 2: Effect of dose reduction on [DOX]

Expect 5x increases for unheated tissues, saturation in heated tumor



Bing et al, in preparation

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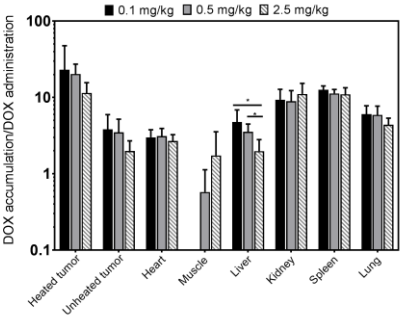
Effect of dose reduction on DOX accumulation efficiency



Bing et al, in preparation

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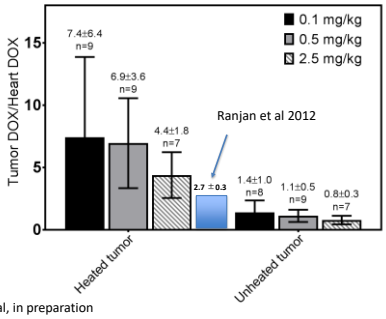
Effect of dose reduction on therapeutic index



Bing et al, in preparation

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Image-guided DOX delivery for pediatric sarcomas

1. **Does longer heating time increase DOX in tumor more than heart?**
2. **Does lower injected dose reduce DOX in heart more than tumor?**
3. **Does DOX release delay tumor growth in a rat pediatric sarcoma model?**
   - Rat unilateral ES-1 Ewing's sarcoma tumor model
   - Thermodox:2.5 mg/kg, 40 minutes of mild hyperthermia (42°C)
   - Single treatment 11 days after tumor implantation
   - Tumor growth monitored for up to 60 days post HIFU with MRI
   - **Does MR-HIFU+Thermodox provide an enhanced treatment effect in this tumor model?**
4. **Is it feasible to perform MR-HIFU hyperthermia in pediatric subjects?**

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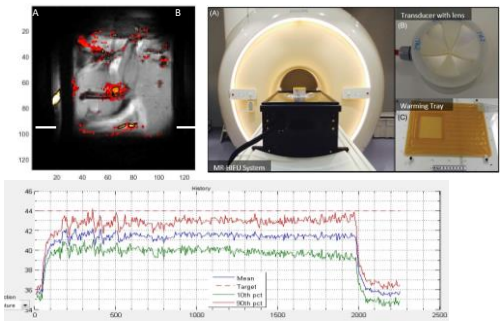
Aim 3: Therapeutic effect in pediatric tumor model



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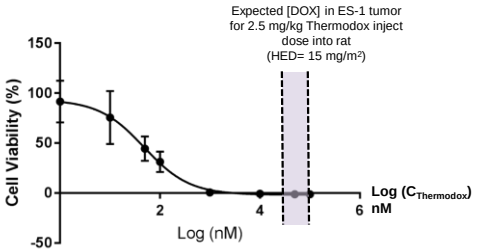
In vitro efficacy and dose determination



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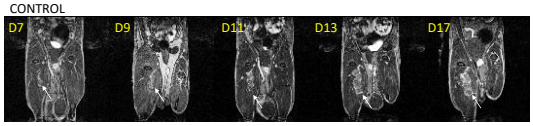
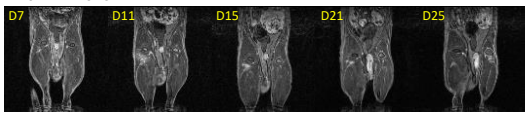
Imaging Results

CONTROL



HIFU+THERMODOX



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In vivo tumor growth curves

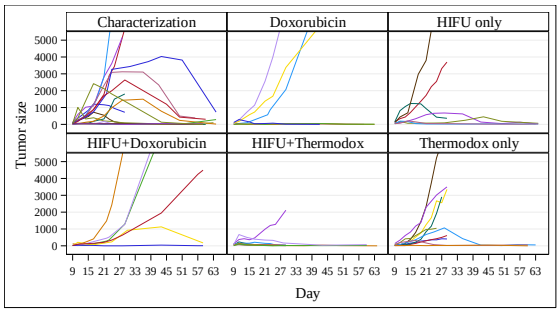

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Image-guided DOX delivery for pediatric sarcomas

1. Does longer heating time increase DOX in tumor more than heart?
2. Does lower injected dose reduce DOX in heart more than tumor?
3. Does DOX release delay tumor growth in a rat pediatric sarcoma model?
4. Is it feasible to perform MR-HIFU hyperthermia in pediatric subjects?

- Evaluated stability of MR thermometry in pediatric subjects, and the feasiblility fo breath-holds for hyperthermia
- Evaluated the targetability of pediatric tumors through a retrospective analysis

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Aim 4: Feasibility of MR-HIFU in pediatric sarcomas

- Retrospective imaging review of pediatric cancers at UT Southwestern

Shim et al, PB&C, 2016

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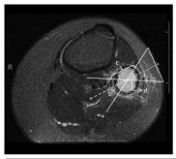
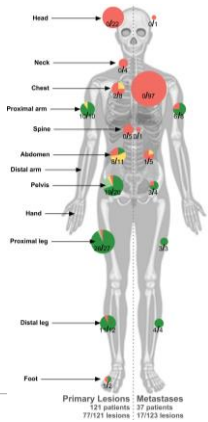
Aim 4: Feasibility of MR-HIFU in pediatric sarcomas

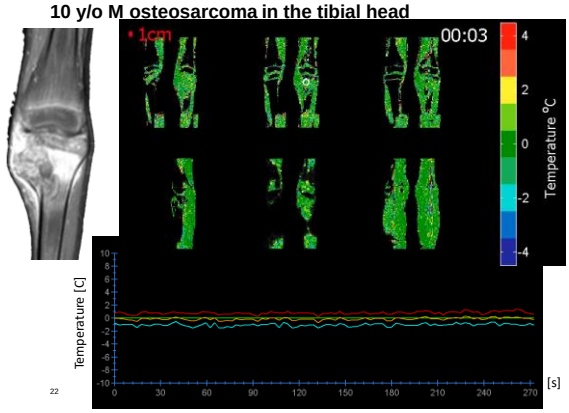
- Primary targetable regions are in the extremities (legs, arms)
- Pelvis is potentially targetable
- Metastatic disease in lungs is not targetable



Shim et al, PB&C, 2016



10 y/o M osteosarcoma in the tibial head



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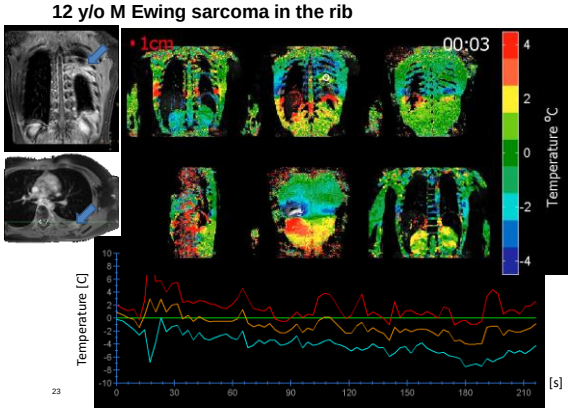
12 y/o M Ewing sarcoma in the rib



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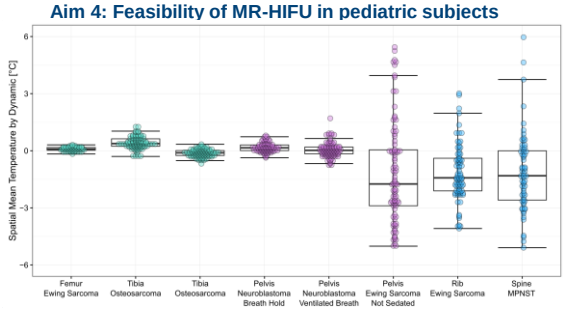
Aim 4: Feasibility of MR-HIFU in pediatric subjects



Scan Type	TR [ms]	TE [ms]	FOV [cm]	Voxel [mm]	Matrix	Slice [mm]	Flip [°]	Slices [#]	Dyn [s]	Dur [min]
T1 FFE-EPI	36	16	40 x 40	2.5 x 2.5	160 x 160	7	20	6	3.2	2 - 6

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Conclusions

- Local doxorubicin delivery in pediatric cancers could improve local control
  - MR-HIFU hyperthermia + temperature-sensitive liposomes is a potential strategy to achieve this goal
- For MR-HIFU hyperthermia + Thermodox®
  - Longer heating duration improves the therapeutic index
  - Increasing dose appears decreases the therapeutic index
  - Significant tumor control effect observed in Ewing's sarcoma model
- MR-thermometry is feasible in extremities and organs without motion
- MR-HIFU can be targeted to tumors primarily in the extremities and possibly pelvis