“Mutation stratification of desmoid-type fibromatosis using a radiomics approach – preliminary results”

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Disclosure

Non-profit organisation

STICHTING COOLSINGEL
The vast majority of desmoid tumors harbor a \textit{CTNNB1} mutation

- About 80-90\% of DTF tumors harbor a mutation in the \textit{CTNNB1} (\(\beta\)-catenin) gene\textsuperscript{1}
- Supportive diagnostic tool
- Prognostic value?
  - S45F \textit{CTNNB1} mutations have higher recurrence rates\textsuperscript{2-5}
The traditional diagnostic pathway of DTF

1. Symptoms
2. Doctors visit
3. Imaging
   - IHC β-catenin stain
   - Biopsy-histological diagnosis
   - Definite diagnosis
   - Treatment
4. CTNNB1 mutation
5. Sanger sequencing
6. Next generation sequencing
Radiomics – make use of conventional imaging methods

- Identification of imaging features that serve as molecular surrogates
- Non-invasive method
- Widely available (pre-treatment) images
- 3D (multiple planes)
Radiomics – previous studies

Non-small cell lung cancer\textsuperscript{6}

Gevaert et al. 2017
- Prediction of epidermal growth factor receptor (EGFR) mutation status
- \(n=186\), CT imaging
- 16 semantic features significantly correlated with presence of EGFR (e.g. emphysema, distribution, nodules)
- AUC value 0.89

Clear-cell renal cell carcinoma\textsuperscript{7}

Karlo et al. 2014
- CT features and mutation status (VHL, PBRM1, SETD2, KDM5C, BAP1 genes)
- \(n=233\), CT imaging
- VHL gene: well defined tumor margins \((p=0.013)\), nodular tumor enhancement \((p=0.021)\) and gross appearance of intratumoral vascularity \((p=0.018)\)
- KDM5C and BAP1: renal vein invasion \((p=0.022)\) and \((p=0.046)\) respectively
Can we use radiomics in the clinical practice in the context of DTF?

Can we predict DTF $CTNNB1$ mutation status?
Imaging – segmentation – feature extraction – prediction models

Online Multiparametric Database

<table>
<thead>
<tr>
<th>Lung PET</th>
<th>Liver CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Desmoid T1-weighted MR</td>
<td>Liver T2-weighted MR</td>
</tr>
<tr>
<td>Brain T1-Weighted MR</td>
<td>Mammogram</td>
</tr>
</tbody>
</table>
Imaging – segmentation – feature extraction – prediction models

Online Multiparametric Database
- Lung PET
- Liver CT
- Head Desmoid T1-weighted MR
- Liver T2-weighted MR
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Radiomics Platform
- Segmentation
- Classification
- Registration
- Feature Extraction
  - Shape
  - Intensity
  - Advanced
Imaging – segmentation – feature extraction – prediction models

Online Multiparametric Database
- Lung PET
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Radiomics Platform
- Segmentation
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- Feature Extraction
  - Shape
  - Intensity
  - Advanced

Predictions
- Genetic Mutations
- Tumor Phenotype
- Therapy Response
- Patient Prognosis
- Dementia Diagnosis
- Quantitative maps

Erasmus MC Cancer Institute
Using +/- 400 imaging features

Semantic features
e.g. age, gender, tumor location, pregnancy

Computational features
e.g. texture, shape, intensity and orientation
Can we predict DTF $CTNNB1$ mutation status?

- Treatment naive extra-abdominal / abdominal wall DTF
- Known $CTNNB1$ mutation or available formalin fixed parafin embedded samples
- T1 weighted MR imaging (spin-echo (SE) or gradient- echo (GRE))
- Between 2004 and 2017
Cross-validation model

Total: 49 Patients

Training: 80 %

Test: 20 %

Train Model

Repeat 100x

Evaluation
Can we predict DTF *CTNNB1* mutation status?

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>35</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Abdominal wall</th>
<th>Extra-abdominal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>37</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CTNNB1 mutation</th>
<th>T41A</th>
<th>S45F</th>
<th>Wild-type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21</td>
<td>11</td>
<td>17</td>
<td>49</td>
</tr>
</tbody>
</table>
The radiomics technique has a promising role for differentiating WT tumors from tumors with a *CTNNB1* mutation

<table>
<thead>
<tr>
<th></th>
<th>T41A</th>
<th>S45F</th>
<th>WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity [95% CI]</td>
<td>0.26 [0.06 – 0.41]</td>
<td>0.11 [-0.05 – 0.11]</td>
<td>0.42 [0.20 – 0.64]</td>
</tr>
<tr>
<td>Specificity [95% CI]</td>
<td>0.78 [0.61 – 0.94]</td>
<td>0.93 [0.83 – 1.02]</td>
<td>0.87 [0.75 – 0.99]</td>
</tr>
<tr>
<td>Area under the curve [95% CI]</td>
<td>0.58 [0.28 – 0.61]</td>
<td>0.58 [0.43 – 0.73]</td>
<td>0.75 [0.61 – 0.88]</td>
</tr>
</tbody>
</table>
Which features are relevant?

T-test

No single significant features after correction for multiple testing

Combination of features?
Conclusion from the preliminary results

- Promising role for differentiating WT tumors
Use of radiomics in clinical practice

- Prediction the \textit{CTNNB1} mutation status does not change the diagnostic routine
- Biopsy is still needed to confirm the diagnosis

Can we differentiate DTF tumors from other soft tissue tumors?
Can we differentiate DTF tumors from other soft tissue tumors?

- Treatment naive fibromyxosarcoma, myxoid liposarcoma and leiomyosarcoma of the **extremities**
- T1 weighted MR imaging
- 2004 and 2017

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyxosarcoma</td>
<td>29</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>29</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>29</td>
</tr>
</tbody>
</table>
Challenges using radiomics in the clinical practice of DTF

Discovery phase study, no validation of findings

**Imaging**
Differences in imaging protocols, different scanning methods
T1W MR images, extrapolate to other sequences

**DTF**
Small sample size, create a bigger cohort
Poor DNA quality not able to obtain CTNNB1 mutations
Challenges using radiomics in the clinical practice of DTF

Radiomics

Learning curve in segmentation

Currently, semi-automatic segmentation → time consuming → automatic segmentation?

Inter- and intra observer differences
Inter and intra-observer variability
Inter and intra-observer variability

Original    Obs. 1, att. 1
Inter and intra-observer variability

Original  Obs. 1, att. 1  Obs. 1, att. 2
Inter and intra-observer variability

Original  Obs. 1, att. 1  Obs. 1, att. 2  Observer 2  Observer 3
Radiomics is a promising new technique

Future perspectives
Large cohort (multiple institutes)
Inclusion of multiple sequences
Imaging of DTF using a standard imaging protocol

Optimizing the radiomics platform and analysis (include more imaging features)
Using radiomics to quantify tumor progression / regression (e.g. tumor enhancement) over time
https://github.com/MStarmans91/WORC

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