Classification of tumor sub-volumes based on Dynamic Contrast Enhanced MRI model hierarchy for Locally Advanced Cervical Cancer

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PURPOSE Heterogeneous uptake of contrast agent during Dynamic Contrast Enhanced – MRI experiments is often found in patients with locally advanced cervical cancer. Most recently, Halle et al.[1] identified that patients with a large volume of low enhancing regions were more likely to respond worse to chemo radiation treatment, while also linking this enhancement profile to a more hypoxic gene profile. This supports the dominating notion that hypoxia is a poor prognostic factor and may be identified by DCE-MRI. The information obtained from the heterogeneous enhancement within the tumor is likely to reflect distinct domains of different underlying tissue characteristics. Recently, Sourbron and Buckley[2] showed the hierarchical structure of a set of kinetic models based on the general 2-Compartment eXchange Model (2CXM). Under limiting condition this generic model may be simplified to the Tofts model (TM) (weakly vascularized), the Extended Tofts model (ETM) (highly perfused) and the Compartmental Tissue-Uptake model (C-TU) (uptake regime) as shown in Fig. 1. The aim of this study was to evaluate the ability of a set of nested kinetic models to classify sub-volumes within cervix cancer tumor tissue. The correlation of model selection to tumor stage was investigated.

MATERIALS AND METHODS In brief, 15 cervical cancer patients with advanced stages (FIGO: IIA/IIB/IIIB/IVA – 1/9/4/1) underwent DCE-MRI prior to radiotherapy. DCE-MRI was performed using a 3T Philips Achieva scanner and a three-dimensional (3D) saturation recovery spoiled gradient echo technique with 20–24 slices having a 5 mm slice thickness, TR/TE of 2.9/1.4 ms, Tsat of 25ms, flip angle (FA) of 10°, in-plane resolution 2.3 mm x 2.3 mm and 2.1 s time resolution. The bolus injected was 0.1 mmol/kg Dotarem at 4 ml/s, followed by a 50 ml saline flush. A total of 120 dynamic scans were obtained of which 18 time-points were scanned before the bolus arrived at the iliac arteries. A T1 relaxation map was constructed before contrast injection using a 3D gradient recalled echo sequence with five different FA scans (5°, 10°, 15°, 20°, 25°) with the same orientation and field of view as the dynamic scan. The nested set of kinetic models included 2CXM, C-TU, ETM and TM as described in the review by Sourbron and Buckley[2]. The model which described best the temporal contrast agent concentration profile (i.e. best fit) was identified using the corrected Akaike Information Criteria as previously described in Kallehauge et al.[3] (Fig. 2). For the kinetic analysis a population based input function using a similar injection profile was applied, described earlier by Parker et al.[4]. For statistical inference a one sided non-parametric Wilcoxon rank-sum test was employed with the significance level of p<0.05.

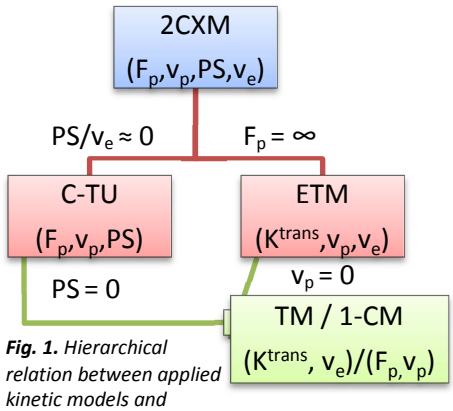

Fig. 1. *Hierarchical relation between applied kinetic models and limiting conditions.*

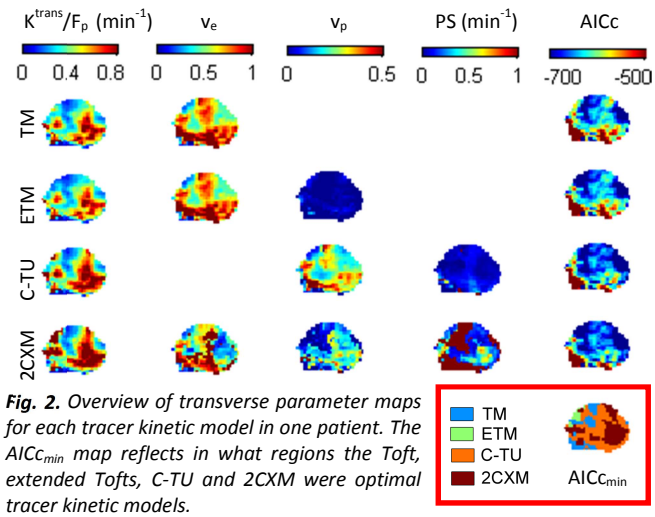

Fig. 2. *Overview of transverse parameter maps for each tracer kinetic model in one patient. The AICc$_{min}$ map reflects in what regions the Toft, extended Tofts, C-TU and 2CXM were optimal tracer kinetic models.*

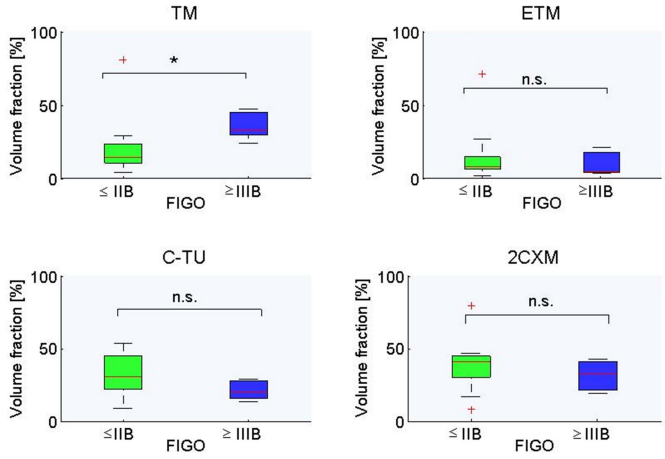

Fig. 3. *Significance of model presence to distinguish between low and high grade tumors in patients with advanced cervical cancer. '*' means significant while 'n.s.' is not significant.*

RESULTS The main observation was the ability of the hierarchical tracer kinetic model sub-volume classification to detect distinct contiguous regions within the tumor. The division of the tumors into the nested set of kinetic model, measured by median and interquartile range (IQR) of volume fraction were; TM: 23.4% (12.4% - 32.4%), ETM: 7. 4% (4.6% - 16.4%), C-TU: 27.9% (17.6% - 37.9%) and 2CXM: 40.5% (24.6% 43.0%) (See highlighted red box of patient example in Fig. 2). There was a significant difference (p=0.01) in the percentage volume best described by TM between patients with tumor stage ≤IIB (10 pts) and tumor stage ≥IIIB (5 pts) (Fig. 3.). The volume fractions described by the remaining models were not found to differ significantly between the stage groups.

DISCUSSION The model selection map (AICc$_{min}$) in all patients reflected heterogeneous pattern with contiguous regions in which one of the models outperformed the others (Fig. 2). The fact that it was contiguous regions suggests that this was not caused by noise but rather reflected different underlying properties of the tissue. The observation that tumor grade was linked to tumors exhibiting enhancement profile that most closely resemble TM, following the reasoning of Sourbron[2], may reflect at least two different physiological characteristics. Since TM is mathematically indestinguisable from the limiting case to C-TU where the permeability of the vessels is negligible (intravascular regime) (see Fig. 1), this indicates that regions with no permeable vessels or low vascularity, both limiting the supply of oxygen and nutrition to the malignant tissue, have higher resistance to intervention. This may be a plausable physiological explanation as to why advanced stage cervical cancers have poorer prognosis than low stages[5].

CONCLUSION Firstly, we found that the hierarchical kinetic classification approach was able to identify contiguous regions within tumor tissue in patients with locally advanced cervical cancer. Secondly, it was seen that patients with the most advanced stages (≥IIIB) tended to be overly expressing regions of TM DCE-MRI enhancement profiles.

REFERENCES [1] Halle et al., Cancer Res, 2012; 72: 5285–95. [2] Sourbron and Buckley, Phys. Med. Biol., 2012; 57: R1–R33. [3] Kallehauge et al. Acta Oncol, 2014; 53: 1064–1072. [4] Parker et al. MRM, 2006; 56: 993–1000. [5] Pötter et al. Radiother Oncol; 2011; 100: 116-123