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Original Research Article

Investigating the role of functional imaging in the management of soft-tissue sarcomas of the extremities

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ABSTRACT

Background and purpose: In this work, we validate a texture-based model computed from positron emission tomography (PET) and magnetic resonance imaging (MRI) for the prediction of lung metastases in soft-tissue sarcomas (STS). We explore functional imaging at different treatment time points and evaluate the feasibility of radiotherapy dose painting as a potential treatment strategy for patients with higher metastatic risk.

Materials and methods: We acquired fluorodeoxyglucose (FDG)-PET, fluoromisonidazole (FMISO)-PET, diffusion weighting (DW)-MRI and dynamic contrast enhanced (DCE)-MRI data for 18 patients with extremity STS before, during, and after pre-operative radiotherapy. We tested the lung metastases prediction model using pre-treatment images. We evaluated the feasibility of dose painting using volumetric arc therapy (VMAT) via treatment re-planning with a prescription of 50 Gy to the planning target volume (PTV_{50Gy}) and boost doses of 60 Gy to the FDG hypermetabolic gross tumour volume (GTV_{60Gy}) and 65 Gy to the low-perfusion DCE-MRI hypoxic GTV contained within the GTV_{60Gy} (GTV_{65Gy}).

Results: The texture-based model for lung metastases prediction reached an area under the curve (AUC), sensitivity, specificity and accuracy of 0.71, 0.75, 0.85 and 0.82, respectively. Dose painting resulted in adequate coverage and homogeneity in the re-planned treatments: $D_{95\%}$ to the PTV_{50Gy}, GTV_{60Gy} and GTV_{65Gy} were 50.0 Gy, 60.3 Gy and 65.4 Gy, respectively.

Conclusions: Textural biomarkers extracted from FDG-PET and MRI could be useful to identify STS patients that might benefit from dose escalation. The feasibility of treatment planning with double boost levels to intratumoural GTV functional sub-volumes was established.

1. Introduction

Soft-tissue sarcomas (STS) comprise a heterogeneous group of tumours arising from mesenchymal tissues. Standard-of-care treatment consists of surgery combined in many cases with radiotherapy. Pre-operative radiotherapy is now generally favored for the treatment of STS because of the smaller treated volume and lower dose that results in better long-term function as compared with postoperative radiotherapy [1,2]. With such treatment, local control is over 85%. However, about 50% of patients with high grade tumours will develop metastatic disease [3], with the lungs being the main site of metastases (≃80% of cases) [4]. The prognosis of patients who develop lung metastases is poor with a 3-year survival rate of approximately 50% [5]. To date, additional treatment such as chemotherapy has not been shown to prevent the development of metastases or improve survival.

High grade STS are often very large and heterogeneous, often with areas of necrosis. Our hypothesis is that a higher radiotherapy dose given preoperatively to radioresistant/hypoxic components of the tumour could be an effective strategy to improve the outcome for patients at high risk of metastatic disease. Greater tumour cell killing from higher radiotherapy doses would reduce the risk of dissemination of viable tumour cells at surgery as well as the risk of persistent intratumoural hypoxia that can drive the metastatic phenotype [6,7].

Several studies have demonstrated that positron emission tomography (PET) could be used in STS for evaluating prognosis, staging the disease and assessing response to therapy [8–10]. Some studies also observed that glucose demands in hypoxic portions of large tumours may be significantly higher than in normoxic cancer cells [11] and that

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the degree of fluorodeoxyglucose (FDG) uptake may indirectly reflect the level of hypoxia [12]. Evidence in this regard is however not clearly established and the most widely used tracer for non-invasive assessment of hypoxia in solid tumours remains fluoromisonidazole (FMISO). Overall, both FDG-PET and FMISO-PET functional characteristics could be of interest in STS treatment management to identify potential radioresistant regions [13].

The imaging modality of choice for STS is, however, magnetic resonance imaging (MRI) [14–16]. Diffusion-weighted magnetic resonance imaging (DW-MRI) can provide information about cellular density, and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) about vascular characteristics [17]. In STS, an increase in apparent diffusion coefficients (ADC) obtained from DW-MRI scans is positively correlated with response to therapy [18] and with a decrease in tumour cellularity [19]. Furthermore, it has been suggested that low-perfusion DCE-MRI information could be used as a surrogate of hypoxia [20,21], and that heterogeneity in DCE-MRI pharmacokinetic maps holds potential as imaging biomarkers of STS response to therapy [22,23].

Tumours exhibiting higher intratumoural heterogeneity are associated with worse prognosis [24–26]. Recently, a model quantifying the heterogeneity of STS tumour sub-regions in terms of size and intensity variations from textural characteristics of fused FDG-PET/MRI pre-treatment images was proposed [27]. This model was developed to assess the likelihood of future development of lung metastases in STS. This information could be useful to identify patients that would benefit the most from dose escalation to hypermetabolic and hypoxic tumour sub-volumes.

In this work, we provide a description of the results derived from a prospective study carried out at our institution. FDG-PET, FMISO-PET, DW-MRI and DCE-MRI data for extremity STS patients were acquired before, during, and after pre-operative radiotherapy (RT). Our main objectives were: i) to validate the texture-based model previously developed for the prediction of lung metastases; ii) to evaluate the complementarity and evolution of PET and MRI functional information over the course of radiotherapy; and iii) to evaluate the feasibility of radiotherapy planning with dose escalation to sub-regions of the gross tumour volume (GTV). We hypothesize that the integration of these three processes into STS management could lead to a novel treatment strategy for patients at higher risk of developing metastatic disease, for which at this time other options (e.g., systemic chemotherapy) are limited.

2. Material and methods

2.1. Patients

Eligible patients were those with age ≥18 years with histologically confirmed primary STS of the extremities without lymph node or distant metastases at presentation and who were deemed suitable for limb preservation surgery. Patients with rhabdomyosarcoma, Ewing sarcoma, osteosarcoma or Kaposi sarcoma, or those with contraindications for MRI (e.g., MRI unsafe because of metallic foreign body in the brain or eye, cochlear implant, some types of pacemakers etc.) were not eligible. The study was approved by the Research Ethics Board of our institution and all patients provided signed informed consent prior to study entry.

Clinical characteristics of the 18 patients accrued to the study between 2013 and 2016 are given in Supplementary Table 2. There were ten males and eight females with a median age of 57.5 years (range: 27–80 years). Nine of the 18 patients had tumours in the thigh, four in the shoulder girdle, three in the arm, and two in the leg. Eleven tumours were > 10 cm in size, six were 5–10 cm, and one was < 5 cm. Thirteen of the 18 patients had high-grade tumours. One patient developed local recurrence, and this patient and six others developed metastatic disease (lung: 5, lymph nodes: 2, bone: 3, liver: 1, soft tissue: 1, adrenal: 1). Four patients have died including two of disease. Twelve patients remained free of disease at a median follow-up of 24 months (range 13–35 months). The median follow-up of the whole cohort was 22 months (range 10–37 months).

2.2. Standard-of-care radiotherapy planning and treatment delivery

Image-guided intensity modulated radiotherapy was applied per our standard practice for all patients. The GTV was delineated on the MRI co-registered to the planning computed tomography (CT) scan. The clinical target volume (CTV) margin was +3 cm proximal and distal and +1.5 cm radially, anatomically confined, i.e., not extending into bone or beyond an intact facial barrier or the skin surface. The planning target volume (PTV) margin was +5 mm, cropped at 5 mm from the skin. Dose prescription was as follows: minimum 50 Gy in 25 fractions to cover 95% of the PTV, > 99% of the PTV to receive > 97% of the prescribed dose, and < 2% of the PTV to receive > 110% of the prescribed dose.

2.3. Study design

FDG-PET, FMISO-PET, DW-MRI and DCE-MRI images were to be collected at pre-radiotherapy (pre-RT), mid-radiotherapy (mid-RT) and post-radiotherapy (post-RT) time points (see details in Supplementary Fig. 1). Image acquisition, interpretation, and registration protocols are given in the Supplementary Material. Standard-of-care MRI data acquired for anatomical tumour definition were also collected including T1-weighted (T1), T2-weighted fat-saturated (T2FS) and T1-weighted post-injection of a gadolinium contrast agent (T1 post-gado) images. We planned a maximum accrual of 20 patients in order to comply with the allowed timeframe of the study protocol, with the expectation that at least 15 patients would complete all required imaging studies as planned.

Overall, complete imaging data comprising FDG-PET, FMISO-PET, DW-MRI and DCE-MRI were obtained at pre-RT for only 14 of the 18 patients. This was due to technical issues with DW-MRI in three patients, and with FMISO-PET in one of these and one additional patient. Only 7 of the 18 patients completed all planned imaging studies, mainly due to patient-related factors (practical difficulties with scheduling, claustrophobia and refusal for other reasons).

2.4. Image analysis

We applied the prediction model fully developed and described in previous work [27] to the new patient cohort of this study. This model linearly combines four texture features extracted from fused FDG-PET/MRI scans: i) small zone emphasis on FDG-PET/T2FS; ii) zone size variance on FDG-PET/T1; iii) high gray-level zone emphasis on FDG-PET/T1; and iv) high gray-level run emphasis on FDG-PET/T2FS. The performance of the complete multivariable model response (defined by the linear coefficients of the model as previously determined in [27]) for predicting the future development of lung metastases in the new cohort of this study was assessed using receiver-operating characteristic (ROC) curve metrics.

FDG-PET and FMISO-PET data were converted into standard uptake value (SUV) maps using injected tracer dose and patient body weight. Apparent diffusion coefficient (ADC) maps were calculated from three DW-MRI series acquired with *b*-values of 100, 500 and 800 s/mm^2, assuming a standard mono-exponential signal decay model and using a linear fit to the natural logarithm of the pixel data. DCE-MRI data were processed using the Tofts model [28] with a population-based model for the arterial input function [29] to produce maps of the permeability constant K^{Trans}. Maps of the initial area under the signal enhancement curve (IAUC) from the injection to 60 s post-injection were also extracted from the DCE-MRI data [30].

Descriptive statistics were first extracted for each tumour at all