Technical Report

Robotic MRI/CT Guided Multiregional 'smart' Biopsy for Characterization of Tumor Heterogeneity: A Prospective Development Study

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Rationale and Objectives: Intratumoral heterogeneity means single site tumor biopsy might not be representative. Here we develop and optimize an MRI-informed robotic multiregional 'smart' biopsy technique in retroperitoneal and pelvic sarcomas (RPS). We also explore the relationship between imaging and histological biomarkers.

Materials and Methods: Participants with suspected RPS underwent multiparametric (mp)MRI within a week prior to biopsy. Three target regions with differing MRI characteristics were contoured. Robotic or freehand multiregional biopsy was performed, collecting samples from each target region in separate specimen pots. CT/MRI fusion extracted quantitative imaging biomarkers for correlation with histological biomarkers at precise biopsy sites. The primary endpoint was feasibility and safety. Spearman's correlation explored the relationship between imaging and histological biomarkers.

Results: Twelve participants (7 women), median age 58.6 years interquartile range [IQR]: 52 – 75 years underwent biopsy. All procedures were technically successful with same-day discharge. The within-tumor range of Apparent Diffusion Coefficeint correlated very strongly with the within-tumor range of Ki-67 proliferation index; Spearman's $\rho = 0.91$ (95% CI 0.68 to 0.98). Ranges represent intratumoral heterogeneity uniquely obtained by multiregional biopsy.

Conclusion: Multiregional robotic MRI-informed, CT-guided biopsy is feasible and safe in RPS. Sampling three distinct regions within tumors provides a more comprehensive and accurate representation of tumor biology than standard biopsy. The close relationship between imaging and histological heterogeneity biomarkers has broader implications for pancancer biopsy techniques, imaging characterization, and personalized treatment selection.

Key Words: Image-Guided Biopsy; Robotics; Sarcomas; Magnetic Resonance Imaging; Interventional.

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Abbreviations: ADC Apparent Diffusion Coefficient, **CI** confidence interval, **CTCAE** Common Terminology Criteria for Adverse Events, **EF** Enhancement Fraction, **FF** Fat Fraction, **Mp** Multiparametric, **RPS** retroperitoneal and pelvic sarcoma

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BACKGROUND

Image-guided biopsy usually involves sampling tumors in a single region for diagnostic purposes. Ultrasound and CT are ubiquitous due to widespread availability and low cost (1). However, more advanced techniques are needed to meet the challenges posed by the era of personalized cancer and digital medicine. For example, it is well recognized that tumors are heterogeneous and that a biopsy from a single, often semirandom region poorly represents the full genomic mutational and immune landscape (2–5) and can deleteriously inform treatment regimens (6). Biopsy of multiple subregions is a potential solution, although an important corollary is how to best choose and safely target them.

The superior contrast resolution offered by MRI can demonstrate intratumoral heterogeneity noninvasively, globally, and in vivo. Tumor subregions of given imaging signatures can be defined on multiparametric (mp-)MRI (7) and potentially targeted at biopsy for improved tumor characterization, and better decision making. While MRI techniques have recently been developed that explicitly measure histological properties noninvasively (8,9), they require validation (10) through accurate radiological/histological image registration if imaging-based, non-invasive 'digital biopsy' is to be realized (11).

While 'freehand' biopsy is standard, accurate targeting of small tumor subregions may be limited by operator variability, suboptimal technique and increased procedure time due to multiple needle adjustments. Rapid technological advances within interventional radiology might improve subregion targeting. For example, stereotactic and robotic devices can increase needle placement accuracy, reduce adjustments (i.e., less tissue trauma and patient distress), facilitate complex (e.g., double oblique) trajectories and reduce procedure time (12–15). Robot assistance may be particularly beneficial in the context of complex multiregional tumor sampling.

However, novel procedures require systematic development and optimization. In accordance with the Idea, Development, Exploration, Assessment, Long-term follow-up (IDEAL) recommendations for surgical and interventional innovations (16), we previously developed a technique for CT-guided robotic biopsy using MRI fusion in a phantom and concluded that it was suitable for clinical investigation (17).

The primary objective of this study is to develop a feasible and safe method for multiregional biopsy, guided by multiparametric (mp)-MRI (7) to sample distinct tumor subregions based on cellularity and vascularity, with the intention of representing whole tumor biology more comprehensively than single site biopsy. We chose patients with retroperitioneal and pelvic sarcoma (RPS) because of their relatively large size and immobility, ideal for multi-regional sampling. Futhermore, their significant imaging and histological heterogeneity poses substantial challenges in representative biopsy, including sampling errors (18–20) that can adversely affect treatment decisions (21), and, ultimately, outcomes (22).

We will explore the relationship between quantitative MRI biomarkers and histological biomarkers at precise biopsy sites to enhance our understanding of the biophysical basis of MRI signal. In the era of targeted therapy which recognizes tumor heterogeniety, this approach has applications in transational research studing tumor biology, and therapeutic implications by sampling the most tumor components.

METHODS

Ethics and Consent to Participate

An IDEAL compliant (23) phase I/IIa single arm prospective development study approved by the Royal Marsden Hospital Institutional Review Board (identifier 1102). Research was conducted according to the declaration of Helsinki. Informed written consent was obtained from all study participants.

Participants

This study was conducted between September 2021 and September 2022 at a specialist cancer center. Participants meeting the eligibility criteria were approached for participation, and none declined.

Inclusion criteria were: (i) adults (aged 18 years or above) with suspected RPS; (ii) biopsy required for clinical diagnostic purposes; (iii) capable and willing to undergo procedures; and (iv) prior diagnostic CT for planning procedures with tumor size $>$ 5 cm in minimum dimension, and safe accessibility of multiregional targeting. Exclusion criteria were (i) contraindication to biopsy, (ii) contraindication to MRI, (iii) acutely unwell patients, (iv) unable to tolerate study procedures and (v) unable to provide written informed consent.

Twenty-two patients were referred during the study period. Seven patients had tumors either too small or unsuitable for multiregional sampling, two patients were unlikely to tolerate study procedures due to comorbidities and another was unable to undergo MRI due to a pacemaker. Twelve participants, median age 58.6 years (interquartile range [IQR] 52 – 75 years, 7 women), were therefore included in the study (Fig 1).

MRI Acquisition

Participants underwent multiparametric (mp-)MRI of their whole tumor as defined on the prior CT within a week

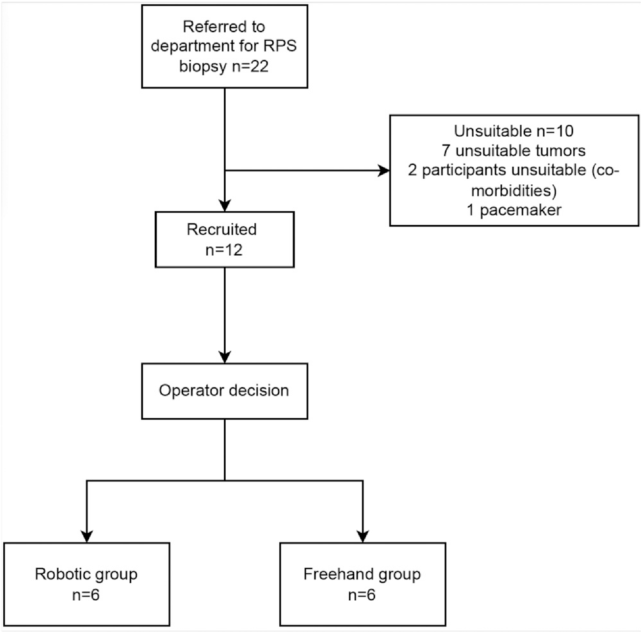

Figure 1. Participant recruitment flow diagram. RPS = retroperitoneal and pelvic sarcoma.

prior to, or on the same day as biopsy. Participants were scanned in the same position as intended for biopsy. The fifth participant onward (eight in total) was scanned in a whole-body vacuum immobilization mattress (Klarity Medical, OH, USA) to improve stabilization and MRI/CT registration at biopsy. Mp-MRI was performed using a 1.5 Tesla MRI scanner (MAGNETOM Sola, Siemens Healthineers, Erlangen, Germany). Acquistion comprised diffusion-weighted, Dixon, contrast-enhanced and cine MRI. Apparent diffusion coefficient (ADC), fat fraction (FF), and enhancement fraction (EF) maps were produced (7). Full acquisition parameters are provided in the supplemental materials.

Biopsy Region Selection and Contouring

Mp-MRI images were evaluated by a board-certified attending Interventional (XX, 12 years' experience) and Diagnostic Radiologist (XX, 13 years' experience) using a PACS workstation (Sectra IDS7, Linköping, SE). Joint interpretation allowed imaging characteristics and biopsy safety to be agreed. Three 'target regions' with heterogeneous imaging signatures were selected per participant. Chosen solid target regions were defined as: "Region A": strongly impeded diffusion and high enhancement reflecting high cellularity and vascularity; "Region B": discordant diffusion and enhancement characteristics and "Region C": less impeded diffusion and poor enhancement. A volume of interest was contoured for each region on the ADC map using image analysis software (Osirix MD 11.0, Bernex, SW). Typical images for target region selection and contouring are shown in Figure 2.

The MRI with contoured target regions displayed on a laptop computer during biopsy procedures. Biopsy was performed using CT guidance as informed by MRI signature using visual cues from both sets of images. A sample from each target region was placed in a separate pot for later radiological/pathological correlation. Full procedure technique with example images are fully detailed in the supplemental materials.

Outcome Measures

Participant characteristics comprised age, sex and estimated tumor volume using the prolate ellipsoid formula (24).

Outcomes were:

- Safety, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (25).
- Ability to perform procefure within a 60 min time window.
- Radiation dose, procedure duration and number of needle manipulations.
- Percentage of successfully sampled target regions (using CT/MRI fusion).
- Correlation between tumor proliferation as measured by %Ki67 on immunohistochemistry with tumor cellularity as measured by ADC at each of the sampled regions (median and within-tumor range).

Radiation dose length product (DLP) (mGy*cm) was recorded using the procedure dose report, and duration was

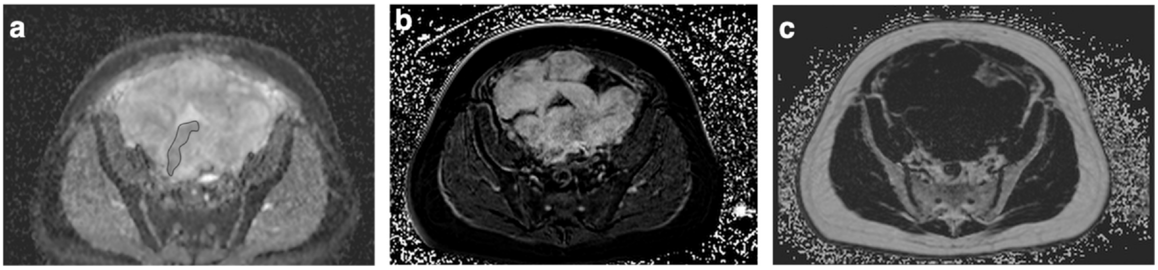

Figure 2. Selected axial plane images from multiparametric MRI of a 51-year-old man with a spindle cell neoplasm. (**a**) Apparent diffusion coefficient (ADC) map, with a contour of the selected region demonstrating a low ADC value compared to the global tumor average, (**b**) enhancement fraction map showing high enhancement relative to the global tumor average, (**c**) fat fraction map. Based on these findings, the contoured region was classified as "region A.".

defined as the time between the planning topogram and final scan. The number of needle manipulations (not including initial placement) for each region was summed to give a total number of manipulations per participant.

Extraction of Quantitative Imaging Metrics at Biopsy Sites

A point-based registration of CT images and mp-MRI maps was performed using suitable anatomical landmarks (Osirix MD). Mean values of ADC, FF and EF were extracted at each biopsy site. A rectangular region of interest was contoured over the biopsy notch and transferred to all coregistered maps. The mean signal intensity was recorded at the three biopsy sites. An example is provided in Figure 3.

Biopsy sample processing and analysis methods are described in the supplemetary materials, where Nuclear-to-stromal ratio (NSR) and Ki-67 proliferation index (%Ki-67) was extracted for each biopsy site. A flow diagram of study methods is also provided in the supplemental materials.

Statistical Analysis

Study Size

Since this was a phase I/IIa prospective development study, a formal sample size calculation was not appropriate. However, a sample size of twelve has been recommended for pilot studies(26) and was also chosen as a pragmatic number for our study considering the prevalence of the condition and to reduce the number of participants exposed to risk. Participants have not been reported upon previously.

Statistical Analysis

Statistical analysis was carried out by XX (9 years of experience of statistical analysis) using GraphPad Prism version 9 (GraphPad, San Diego, CA). Normality was checked for all data using the Shapiro–Wilk test. A P value of < 0.05 was considered to indicate statistical significance.

Freehand and robot-assisted procedures were compared in terms of procedure duration, radiation dose, and the number of manipulations using independent samples T-tests or nonparametric equivalent.

The relationship between quantitative imaging and histological biomarkers was explored for malignant tumors. Mean values of ADC, NSR and %Ki-67 were extracted from all biopsy sites (three per participant); ADC_{mean}, NSR_{mean} and $\%Ki\text{-}67_{mean}$. The range (highest minus lowest values from the three sites) of within-tumor ADC, NSR and %Ki-67 was calculated to give ADC_{range}, NSR_{range} and $\%Ki\text{-}67_{range}$. These metrics provide a single within-tumor statistical representation of imaging and tissue heterogeneity that can only be achieved using multiregional biopsy. Spearman's rank correlation coefficient (ρ) explored the relationship between $ADC_{range/mean}$ versus $NSR_{range/mean}$ and $\%Ki\text{-}67_{range/mean}$.

RESULTS

Participant Characteristics

Median estimated tumor volume was 1.7 litres (IQR 1.4 – 2.7 L). No participants received prior systemic therapy. Final histology was liposarcoma in nine (seven dedifferentiated) and

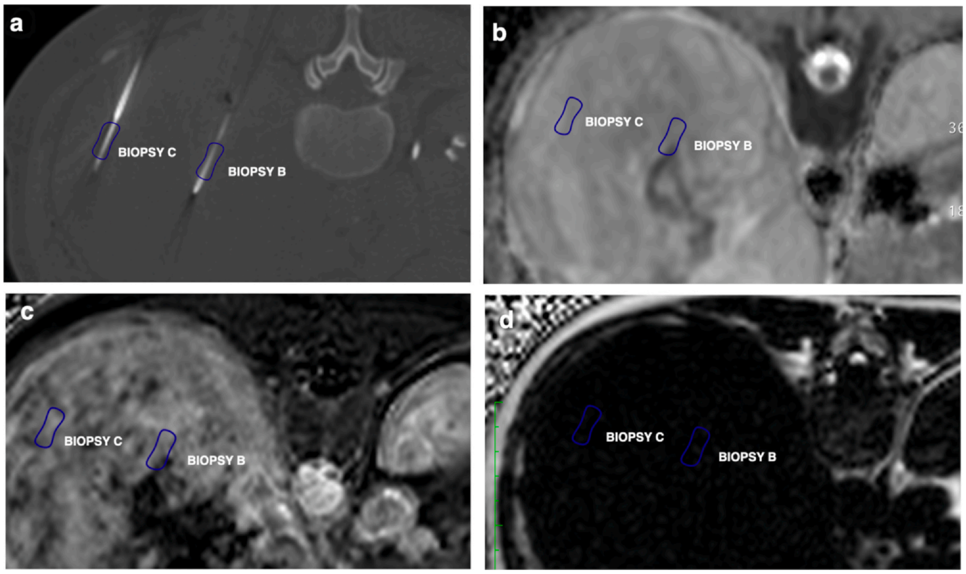

Figure 3. Extraction of quantitative imaging metrics from precise biopsy sites in a 57-year-old woman with dedifferentiated liposarcoma. (**a**) Unenhanced axial plane CT image previously registered with the MRI using point-based registration. Two regions of interest are contoured to overlie biopsy needle side notches (for target regions **b** and **c**). (**b**) Extraction of apparent diffusion coefficient (ADC) values at biopsy sites (mean ADC value 1568 x 10–6 mm2/s in region **b** and 1892 x 10–6mm2/s in region **c**). (**c**) Extraction of the enhancement fraction (EF) (42.5 in region B and 40.0 in region **c**). (**d**) Extraction of the fat fraction (FF) map (mean FF 2.1% in region **b** and 2.2% in region **c**).

TABLE 1. Clinicopathological Characteristics

Participant Number	Age	Sex	Tumor Volume (L)	Histopathological Subtype
1	51	M	2.7	Spindle cell tumor (benign)
2	53	F	0.6	Leiomyosarcoma
3	84	M	1.5	DDLPS
4	33	F	0.7	Solitary fibrous tumor (malignant)
5	66	F	2.7	WDLPS
6	55	M	2.1	DDLPS
7	49	F	6.8	WDLPS
8	68	F	1.6	DDLPS
9	59	F	1.8	DDLPS
10	76	M	3.1	WDLPS/DDLPS
11	57	F	1.6	DDLPS
12	85	M	1.3	DDLPS

leiomyosarcoma, solitary fibrous tumor and atypical spindle cell tumor in one participant each. A summary of clinicopathological characteristics is provided in Table 1. Twenty two patients were referred for the study of whom 12 were recruited (Fig 1).

Main Results

Safety and Tolerability

All (12/12, 100%) participants were discharged on the same day without complications. All (12/12, 100%) procedures were technically successful, defined as tissue obtained from three sites, without instance of all-cause withdrawal. Three CTCAE grade I adverse events, namely pain managed with simple analgesia, were recorded in 12 patients.The evolution of the biopsy technique is provided in the supplemental materials. Total radiation dose was median 639 (IQR 514 – 923) mGy*cm, and procedure duration was 48 min ± 15 mins.

Comparison of Freehand and Robot-assisted Procedures

All (6/6, 100%) robot-assisted procedures and 4/6 (67%) freehand procedures were carried out within one hour. Robot-assisted procedures were significantly quicker than freehand procedures (37 min ± 6.2 min vs. 59 min ± 13 min, $P = 0.003$). Radiation dose was lower for robot-assisted procedures, although statistical significance was not reached (623 ± 200 vs. 1041 ± 680 mGy.cm, $P = 0.18$). Robot-assited procedures also required fewer needle manipulations than freehand procedures; 0.8 ± 0.75 versus 8.0 ± 1.9, $P < 0.0001$.

Correlation of ADC Values versus Histopathological Metrics

A spindle cell tumor was excluded from the analysis due to benignity, confirmed after resection. The median region-of-interest size was 1.4 cm^2 (IQR 1.1–1.6cm^2). ADC_{mean} demonstrated negligable correlation with %Ki-67_{mean}; $\rho = -0.07$ (−0.42 to 0.29). ADC_{range} correlated very strongly with %Ki-67_{range}; $\rho = 0.91$ (0.68 to 0.98). A scatterplot of this relationship is shown in Figure 4. Figures 5 and 6 show typical examples of ADC and %Ki-67 imaging/histological homogeneity/heterogeneity. ADC_{range} correlated poorly with NSR_{range}; $\rho = -0.16$ (−0.71 to 0.50).

DISCUSSION

We report, for the first time, the feasibility of using MRI-informed, CT guided robotic biopsy to capture intratumoral heterogenetiy in proliferation and cellularity, such that all procedures were successfully completed without complications, and multiregional sampling was achieved in all participants. This translational research study provides proof-of-concept that functional imaging can represent tumor components that are proliferating at different rates, which could have strong applications for the study of tumor biology, cancer evolution, drug development and drug resistance.

While multiregional CT/MRI fusion biopsy has not previously been described in the literature to our knowledge, Beer et al. reported upon ultrasound-guided fusion biopsy of radiomic-based CT regions in six participants with high-grade serous ovarian cancer (27). They concluded feasibility and safety for radiomic-based region targeting. However, two participants had insufficient diagnostic material, and the median time between CT and biopsy was 21 days (range 7 – 30 days). In contrast, our technique allows biopsies to be performed on the same day as MRI, improving patient convenience and enhancing image registration due to consistent anatomy, augmented by vacuum mattress immobilization. While the authors used Dice similarity coefficients (0.37 – 0.79) to assess registration accuracy, an objective assessment of biopsy site was not possible due to the limitations of ultrasound.

Studying the relationship between imaging and histological/molecular/genomic heterogeneity requires accurate image co-registration, which presents considerable challenges when relying on surgical specimens due to shrinking, disorientation and loss of structural integrity (28). These challenges are mitigated by in-vivo image-guided biopsy, such that we extracted and compared quantitative MRI and histological biomarkers at precise biopsy sites. While absolute ADC values did not correlate with those of %Ki-67 ($\rho = -0.07$), the within-tumor ADC_{range} across three biopsy sites, uniquely provided by multiregional biopsy, demonstrated a remarkably strong correlation with %Ki-67_{range} ($\rho = 0.91$). This suggests a relationship between imaging and histological heterogeneity, and supports

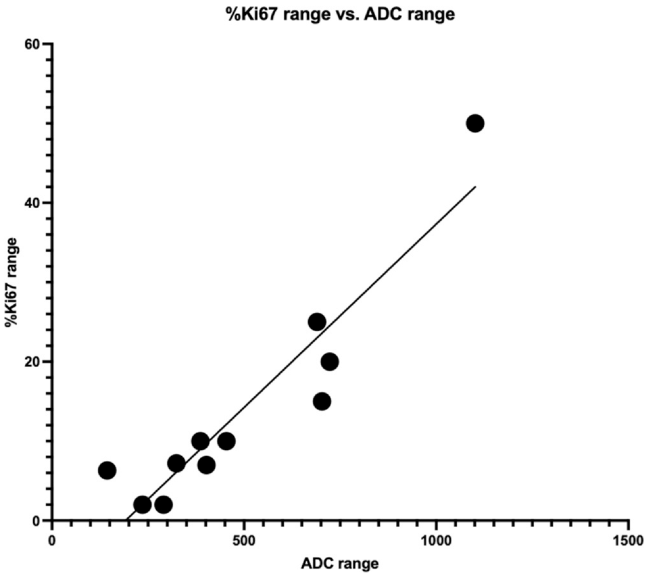

Figure 4. Scatterplot of %Ki67 range (a histological heterogeneity metric from the three biopsy sites) versus ADC range (an imaging heterogeneity metric from the three biopsy sites). Spearmans ρ = 0.91.

the hypothesis that multiregional biopsy offers a more comprehensive assessment of tumor biology than single-site biopsy. The prognostic value of Ki-67 heterogeneity is well recognized across cancers (29,30), and our observed correlation – despite differences in histological diagnoses among participants – suggests this relationship may extend across histologies. Our study makes a step toward noninvasive global assessment of tumor histology, i.e., 'digital biopsy', and we anticipate that multiregional biopsy techniques will become an important tool for assessing cancer heterogeneity, with the potential to influence clinical decision making.

Although biopsy was safely performed using both conventional freehand and robotic techniques without complications, robotic guidance demonstrated several advantages. *Post-hoc* analyses showed robotic procedures were faster (37 vs. 59 mins, $p = 0.003$), and required fewer needle manipulations (0.8 vs. 8.0, $p < 0.0001$), corroborating the findings of our phantom study (17).

Our study has several limitations. First, we we acknowledge that the access to multiparametric MRI, specialist equipment and expertize may limit practicability in general clinical settings. However, this is typical for early prospective development studies (23) and our intention was to develop and evaluate the feasibility of a method that could, in the long term, facilitate validation of imaging biomarkers and advancement of non-invasive 'digital biopsy' techniques. Secondly, we did not use direct image fusion due to concerns about additional unfamiliar steps and potential patient motion, although retrospective image fusion confirmed successful target region sampling. While our study supports using robotic guidance, it was not the main focus of this

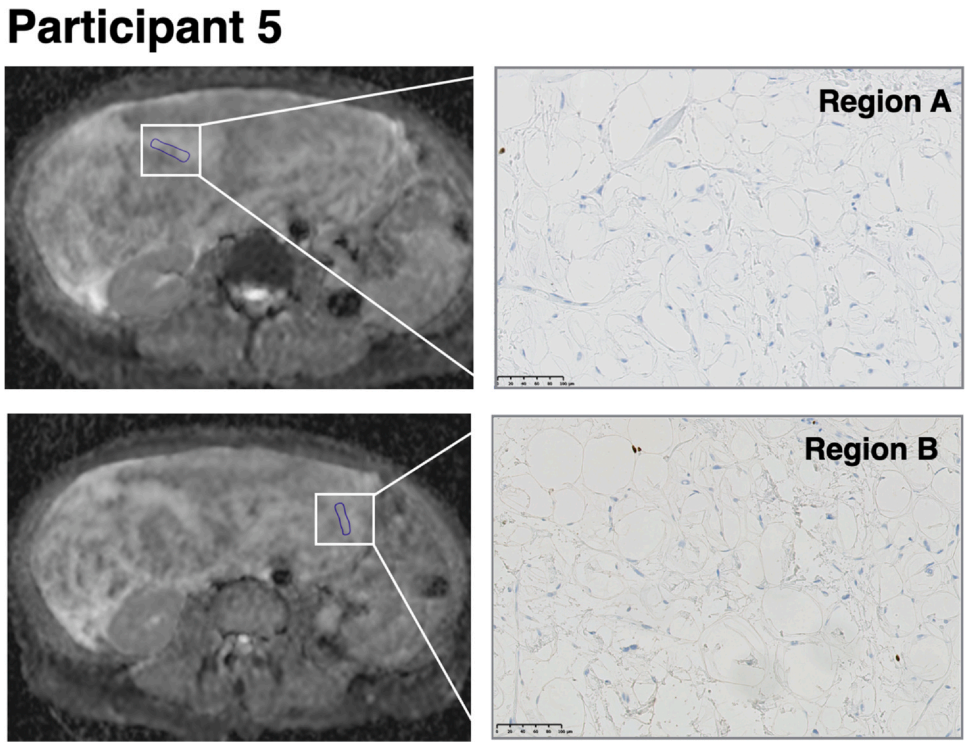

Figure 5. Participant 5 was a 66-year-old woman with well-differentiated liposarcoma. Imaging appearances are generally homogeneous, where the apparent diffusion coefficient (ADC) values of regions **A** and **B** measured 2261 and 2201 x 10–6 mm2/s, respectively, with a range of 60 x 10–6 mm2/s between these two regions. Ki-67 labeling shows histological homogeneity, where %Ki-67 in region A was scored as 3% and 5% in region B, with a range of 2% between these two regions.

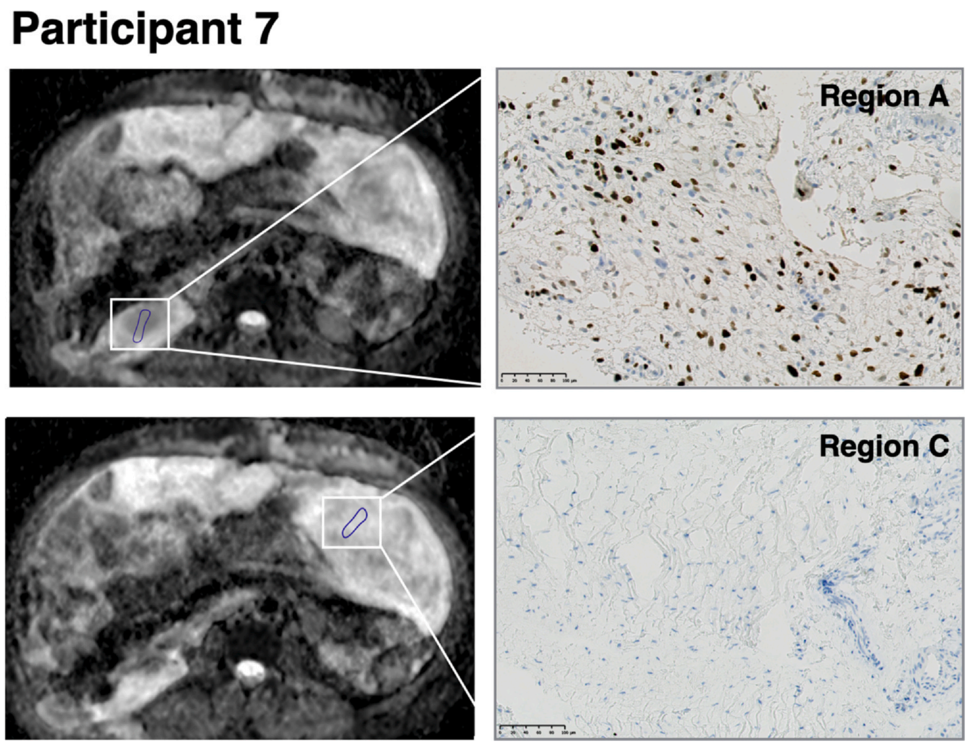

Figure 6. Participant 7, a 49-year-old woman with dedifferentiated liposarcoma. Imaging appearances are generally heterogeneous, where the apparent diffusion coefficient (ADC) values of regions **A** and **C** measured 2206 and 2833 x 10–6 mm2/s, respectively, with a range of 667 x 10–6 mm2/s between these two regions. Ki-67 labeling shows histological heterogeneity, where %Ki-67 in region **A** was scored as 50% and 1% in region **C**, with a range of 49% between these two regions.

study and the lack of prospective randomization limits the strength of conclusions. However, introducing randomization at this early stage might have hindered technique development and optimization. Although the three-site sampling did not impact patients' clinical care in this study and remains theoretical at this point, it lays the groundwork for future translational research pipelines.

Future work will be needed to make ‘smart biopsy’ more acceptable and widespread, which may include simplifying the procedural workflow, studying in an IDEAL phase IIb study, comparing with standard-of-care biopsy, translating to other tumor types—including smaller, more mobile tumors (e.g., lymphomas and myeloma) —and replicating at other centers. Challenges faced include a greater need for high targeting accuracy, increased complications due to greater proximity to critical structures, and the impact of tumor motion. Potential strategies involve advanced immobilization techniques, real-time image guidance, and robotic enhancements with motion-tracking capabilities. Ultimately, large-scale, prospective randomized studies with extended follow-up periods will be required to address whether robotic and ‘smart biopsy’ can help improve outcomes.

CONCLUSION

Multiregional MRI-informed, CT-guided ‘smart’ biopsy is feasible and can be safely carried out using either freehand or robotic guidance, although the latter confers several advantages. Sampling three distinct regions within tumors provides a more comprehensive and accurate representation of tumor biology compared to conventional single-site biopsy. The observed close relationship between imaging and histological intratumoral heterogeneity has broader implications for pancancer biopsy techniques, imaging characterization, and personalized treatment selection.

DECLARATION OF COMPETING INTEREST

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Edward W Johnston reports financial support was provided by Royal College of Radiologists. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest, either financial or nonfinancial.

APPENDIX A. SUPPORTING INFORMATION

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.acra.2024.10.055.

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