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Quantitative Mass Spectrometry Imaging Reveals Lack of Imatinib penetration in Liver Metastases of Gastrointestinal Stromal Tumors*

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IN A NUTSHELL

We here present the first extensive clinical MALDI-qMSI study of drug uptake and distribution in clinical specimen, analyzing 56 specimens of tumor and corresponding non-tumor tissues from 27 imatinib-treated patients with the biopsy-proven rare disease gastrointestinal stromal tumors (GIST). For validation, we compared MALDI-TOF-qMSI with conventional UPLC-ESI-QTOF-MS-based quantification from tissue extracts and with ultra-high resolution MALDI-FTICR-qMSI. We introduced a novel generalized nonlinear calibration model of drug quantities based on computational evaluation of drug-containing areas that enabled better data fitting and assessment of the inherent method nonlinearities. Imatinib tissue spatial maps revealed striking inefficiency in drug penetration into GIST liver metastases even though the corresponding healthy liver tissues in the vicinity showed abundant imatinib levels beyond the limit of quantification (LOQ), thus providing evidence for secondary drug resistance independent of mutation status.

GENERALIZED CALIBRATION MODEL

[Fig1.] We introduced a generalized nonlinear calibration model which could accommodate the situation where the signal intensity does not vary linearly with analyte concentration [**Fig1. a,b**] and, additionally, could accurately model a linear relationship [**Fig1. c**]. We observed a substantial decrease in the residual standard error of the fitted calibration models to the data [**Fig1. d**].

The nonlinear model is of the form

$$y = a\,x^{b} + c$$

a,b: constants; c is the superimposed noise error (background signal when the drug signal is absent). The limit of detection and quantification (LOD and LOQ) are defined by

$$x_{Limit} = \left(\frac{k\,\sigma_{Blank}}{a}\right)^{1/b}$$

Where $x_{Limit} = LOD$ for $k = 3$ and $x_{Limit} = LOQ$ for $k = 10$. σ_{Blank} is the standard deviation of the signal intensity in the blank (no drug) measurement area.

QUANTITATIVE ANALYSIS WITH MALDI-TOF, MALDI-FTICR and UPLC-ESI-QTOF-MS

[**Fig2.**] we systematically compared the average imatinib content in GIST (and corresponding normal tissue) specimens on MALDI-TOF, MALDI-FTICR and UPLC-ESI-QTOF.

78% of all samples, in which imatinib could be quantified, were inside a window of a 2-fold difference [**Fig2. a**]. MALDI-FTICR-qMSI matched the UPLC-ESI-QTOF-MS results even more closely [**Fig2. b**] where 87% of all samples that reached the MALDI-FTICR-qMSI measurement round were within a 2-fold difference relative to UPLC-ESI-QTOF-MS.

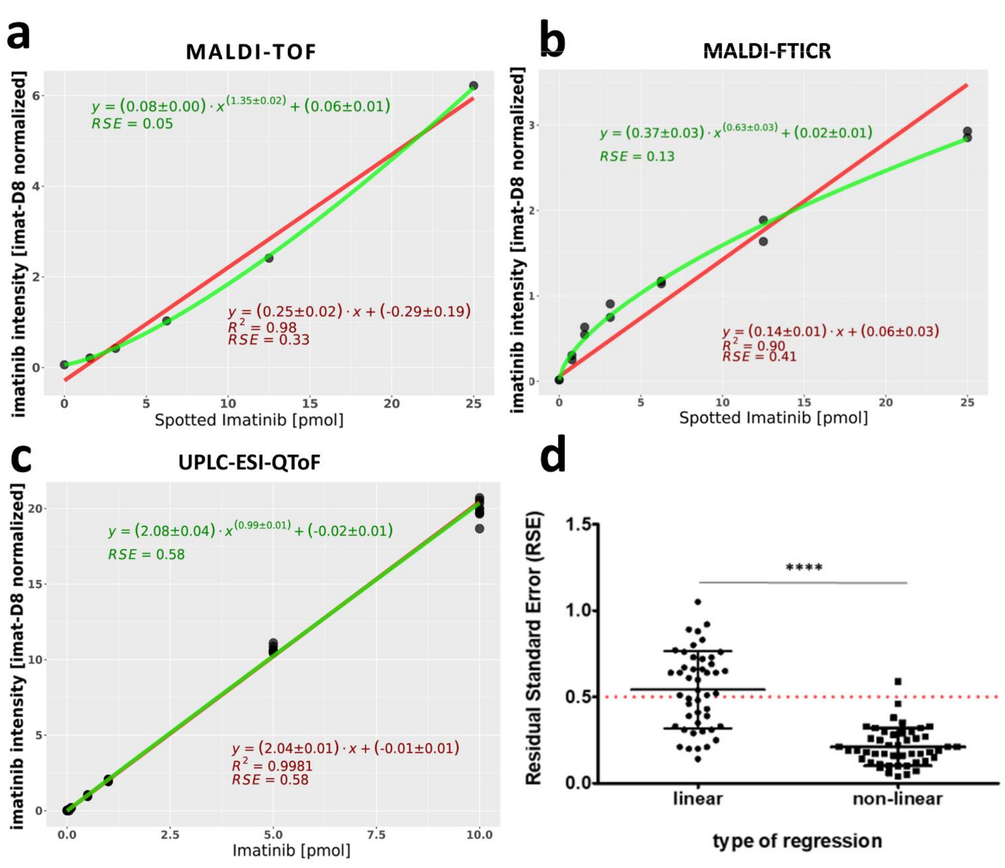

Fig1. *Generalized nonlinear calibration model for qMSI.*

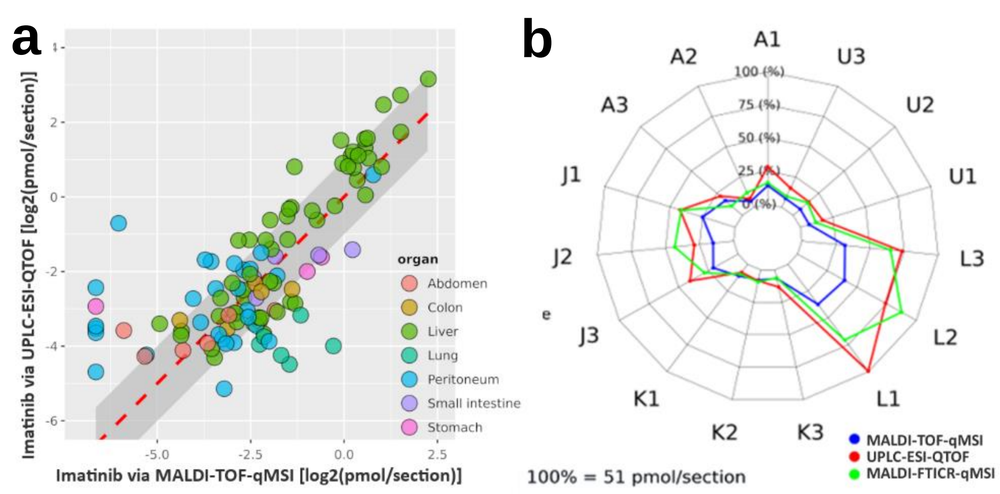

Fig2. *Comparison of qMSI in MALDI-TOF against UPLC-ESI-QTOF and MALDI-FTICR.*

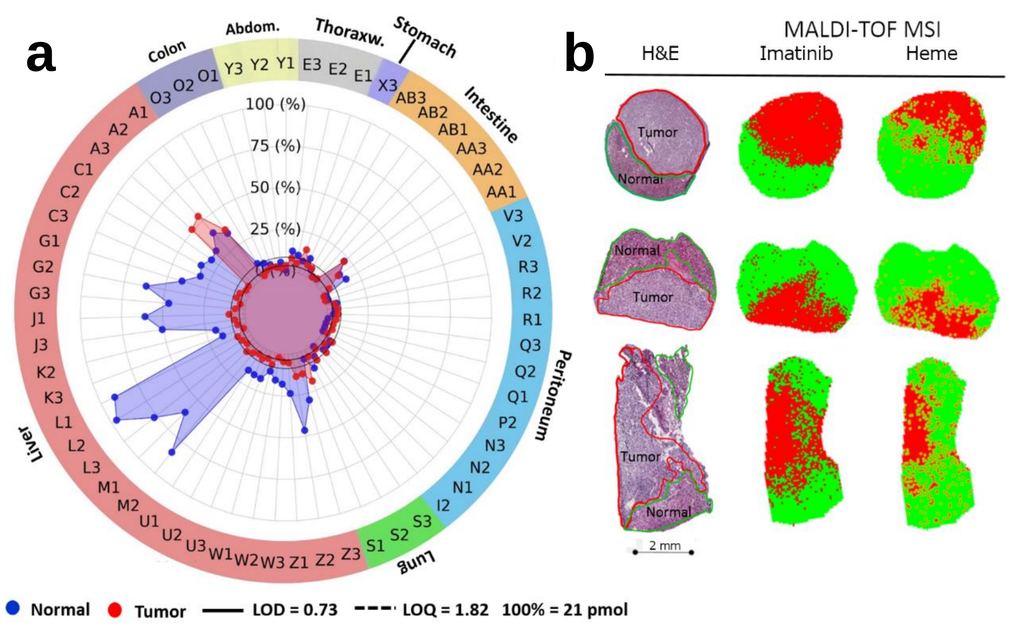

Fig3. *Liver metastases of GIST display limited imatinib content independent of mutation status.*

DRUG LIMITED UPTAKE IN METASTATIC GIST IN LIVER

[**Fig3.**]To be effective, cancer-targeting drugs must adequately penetrate into tissue. We found that the orally administered imatinib had limited uptake or retention in metastatic GIST in liver tissue, leading to amounts below LOQ despite the high abundance of the drug (well above LOQ) within surrounding normal liver tissue [**Fig3. a**].

An exemplary sample A (3 replicates) clearly highlighted this tendency where, the drug was unable to penetrate the seemingly hard borders of the metastatic tumor despite high concentrations within the surrounding tissue as revealed by the spatially-resolved-qMSI [**Fig3. b**].

CLINICAL RELEVANCE

Spatial mapping of imatinib distribution within GIST patient tissues revealed striking inefficiency in its penetration into liver metastases irrespective of their mutation status. Our study therefore strongly suggests that also mechanisms other than driver mutations in receptor tyrosine kinases such as alterations in drug uptake due to decreased intra-tumor vasculature may play an important role in imatinib resistance in GIST.

CONCLUSION

This study shows that MALDI-qMSI can enter clinical application as an orthogonal post-surgical approach to evaluate pharmacokinetics of administered drugs and their metabolites in resected specimens to cast light into the resistance to treatment as a function of anticancer drug uptake and tissue penetration efficiency.