

MET-receptor targeted fluorescent imaging and spectroscopy to detect multifocal papillary thyroid cancer

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Background

- Low-risk papillary thyroid cancer (PTC) is defined by absence of multifocality.
- Multifocality remains undetected by preoperative ultrasound in 52% of patients.
- Intraoperative targeted fluorescence guided imaging (MFGI) and spectroscopy may improve detection of multifocality.
- The near infrared fluorescent tracer EMI-137 binds to MET, which is overexpressed in PTC.
- This study aims to assess the feasibility of MFGI and spectroscopy guided detection of PTC multifocality after intravenous injection of EMI-137.

Methods

- Multicenter phase 1 dose escalation study (NCT03470259)
- 0.09 mg/kg, 0.13 mg/kg, or 0.18 mg/kg EMI-137 administered 2 hours pre-operatively
- Fluorescence imaging: IVIS Spectrum (backup Illumina 2)
- Spectroscopy measurements performed in triplicate
- Fluorescence intensity between PTC foci, benign nodules and normal thyroid tissue compared
- Selective binding of EMI-137 to MET assessed using immunohistochemistry and fluorescence microscopy
- Diagnostic accuracy of MFGI for multifocal PTC was compared to pre-operative ultrasound.

Results

- 14 PTC patients underwent hemi- or total thyroidectomy after administration of 0.09 mg/kg (n=1), 0.13 mg/kg (n=8), or 0.18 mg/kg (n=5) EMI-137.
- MFGI and spectroscopy could differentiate PTC from normal thyroid tissue (figure 1).
- 0.13 mg was the lowest dosage EMI-137 allowing for differentiation between PTC and normal thyroid tissue (figure 1 and figure 2).
- The smallest detected PTC focus was 1.4 mm.
- MFGI restaged 80% of patients from unifocal to multifocal PTC compared to ultrasound.

Conclusion and future perspectives

- EMI-137 guided MFGI and spectroscopy can be used for intraoperative detection of multifocal PTC.**
- EMI-137 guided MFGI may upstage patients from unifocal to multifocal PTC compared to pre-operative ultrasound.**
- The use of MFGI and spectroscopy may improve PTC staging and treatment selection between hemi- and total thyroidectomy by better differentiation between unifocal and multifocal PTC.**

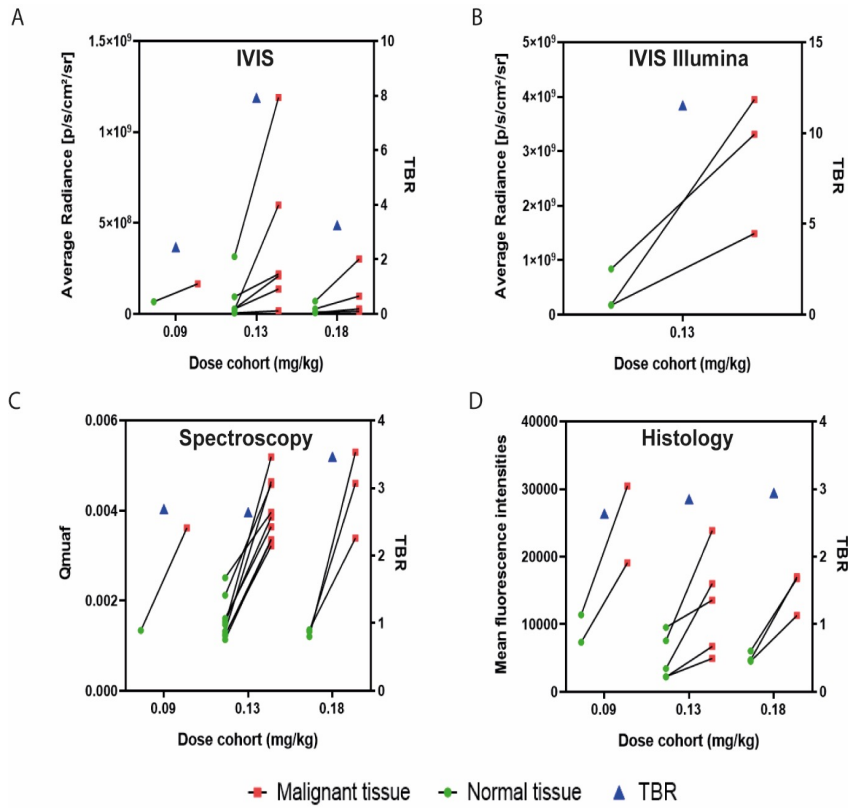


Figure 1. Figure 1 (A) An overview of fluorescent intensities per dosage cohort of formalin-fixed papillary thyroid cancer (PTC) and normal thyroid tissue imaged with the IVIS Spectrum, the IVIS Illumina (B) and spectroscopy (C). The mean fluorescence intensity per dosage cohort acquired from histological slides is provided in figure D. Green dots resemble normal thyroid tissue, red squares resemble malignant tissue, and blue triangles resemble the TBR per dosage cohort (depicted on the right y-axis).

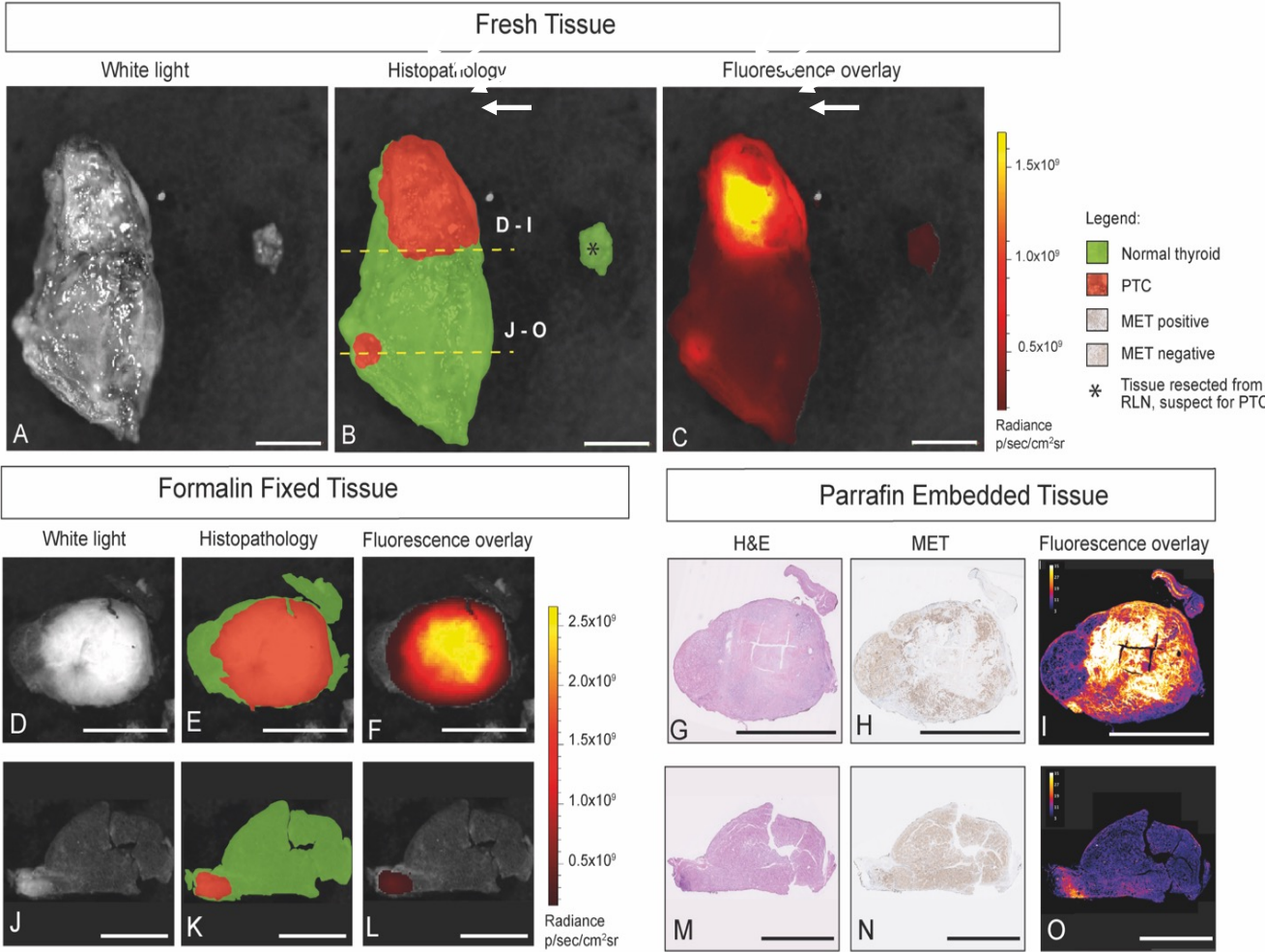


Figure 2. Representative images of a patient in the 0.13 mg/kg dosage cohort without detection of multifocal PTC on pre-operative ultrasound. Fresh specimen of right thyroid lobe, dorsal perspective (A). Histopathology confirmed PTC Foci (B) with primary tumor in the cranial part of the right thyroid lobe. A fluorescent focus close to the ligament of Berry can be seen, confirmed as multifocal PTC on final histopathological assessment (M-O). The non-fluorescent tissue next to the right thyroid lobe (B, C) is histopathology negative for PTC, but was resected from the recurrent laryngeal nerve because of clinical suspicion. Arrows indicate a positive margin described during final histopathology and detected by fluorescence imaging (B, C). Bread Loaf Slices (BLS) are marked with dotted lines in image B. BLS from primary tumor (D-F) and secondary PTC focus (J-L), visualize higher fluorescence in PTC compared to normal tissue. H&E, anti-MET staining and fluorescence microscopy images acquired from BLS of primary tumor (G-I) and multifocal PTC (M-O), confirming higher MET staining (H, N) and fluorescence (I, O) in PTC compared to normal tissue.

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