

Can multispectral optoacoustic tomography replace sentinel lymph biopsy in melanoma?

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With the establishment of the concept of sentinel lymph in the draining regional nodes for melanoma by Morton (1) in 1992, the surgical world has undergone a revolution from therapeutically resecting regional nodes, an established approach since the days of Halsted (2) in 1894 to a much less morbid procedure of selectively removing the relevant sentinel lymph nodes in the regional basin (3). Staging of the regional nodal basin by SLN biopsy has become the standard of care for assessing the status of the regional lymph node for melanoma (3,4) and breast cancer (5). About 80% of melanoma patients will be spared from a more radical regional lymph node dissection. The only way to assess the sentinel lymph nodes still requires a surgical intervention. The challenge is to assess the clinically non-palpable sentinel lymph nodes using a non-invasive method.

Photoacoustic tomography combines pulsed laser optical excitation and ultrasound detection of a chromophore. The excitation of a chromophore generates characteristic ultrasound waves, which are then detected by ultrasonic transducers to form images of optical contrast with ultrasonic resolution from several centimeters deep inside the tissue (6). Using multispectral optoacoustic tomography (MSOT) and exploiting the strong endogenous chromophores with unique spectra such as oxy- and deoxyhemoglobin, Bohndiek *et al.* studied the tumor blood vasculature regression in response to the experimental antiangiogenic therapy trebananib (7). The MSOT has been

demonstrated in detecting melanin, which is a naturally occurring black pigment, produced by melanocytes in the body as a sun blocker. As melanocytes become malignant melanoma, melanin is also produced except in rare cases as in amelanotic melanoma (2–8%) (8).

In an attempt to replace SLN biopsy, which is much less morbid than a lymph node dissection, but still an invasive procedure requiring radioactive tracers, Stoffels *et al.* (9) initiated a study to detect melanin in metastatic melanoma to sentinel lymph node, with the assumption that the detection of melanin in a sentinel lymph node may indicate the presence of melanoma cells in the sentinel lymph node. As a first human study, Stoffels *et al.* used noninvasive MSOT to identify melanin in SLNs *ex vivo*. In a melanin-embedded agarose phantom study, the authors were able to detect four melanoma cells in a volume of 0.02 uL. Of the 506 SLNs removed from 214 melanoma patients, MSOT was positive for 77 and negative for 71 lymph nodes. No metastasis was detected in the negative group. In the positive group, 34 lymph nodes showed metastasis with a positive metastasis detection rate of 22.9%. Forty three lymph nodes being MSOT positive and histology negative showed melanin-like spectral signals including capsular nevi [7% are present in the all lymph nodes (10)], hemorrhage, melanocytic lesions, melanophages and pigmented cells such as tattoo. Therefore, the sensitivity of detecting metastasis in the SLNs was 100% with a false negative rate

of 0%. The specificity rate was 62.3% with a false positive rate of 37.7%. The authors further studied 20 patients using the MSOT technique to detect melanin in 41 SLNs as detected by indocyanine green while lymph nodes were still within patients (*in vivo*). There were 18 SLNs being MSOT and histology negative with a sensitivity rate of 100% and false negative rate of 0%. There were 23 SLNs being MSOT positive and 4 were histology positive (4.9%) and 19 negative with specificity of 48.6% and a false positive rate of 51.4%. When these same SLNs were studied *ex vivo*, 15 SLNs were negative and 26 were positive by MSOT, with histology showing negativity in all the 15 MSOT negative SLNs. Among the 26 MSOT positive SLNs, again 4 were positive by histology (4.9%) and 22 were negative with a sensitivity rate of 100% and false negative rate of 0%, specificity of 40.5% and a false positive rate of 59.5%.

Although the authors assert that MSOT can improve the identification of melanoma SLN metastasis as an alternative to current invasive surgical excision of SLNs, such a statement should be modified that potentially MSOT may be used as a non-invasive imaging modality to assess the melanoma SLN basin. Based on both the *ex vivo* and *in vivo* data on the detection of metastasis in the SLNs by MSOT in the study by Stoffels *et al.*, the false negative rate is 0%, which is very important that if MSOT would become clinically applicable, every negative detection should truly reflect the biological status of the SLN that it is negative and free of metastasis, so that the patient does not need additional lymph node dissection. The more important data set is from the *in vivo* study. Although the false negative rate remains at 0%, the number of patients and SLNs is quite limited, thus, raising some concern to the statistical validity of their conclusions. The false positive rates are not as important, since every positive detection will warrant a surgical excision of the SLN. However, the false positive rates in this study is relatively high between 37.7% to 59.5%, indicating that these patients with a false positive finding would have to undergo SLN excision to make sure that the MSOT positive SLN did not contain metastatic melanoma.

Therefore, the study to date by Stoffels *et al.* begs the answers to two important questions: (I) how reliable is the MSOT to be used clinically on a routine basis to detect melanoma metastasis in SLNs? This question needs to address the multiplicity of SLNs, the depth of each SLN (and its effect of false negative rate) and its topography in different anatomical nodal basins such as in the neck, axilla, groin and pelvis; (II) MSOT is operator-dependent, what is

the learning curve to master the detection method of SLNs?

The only definitive approach to establish the clinical utility of MSOT is to conduct a clinical trial on a large patient population to correlate the preoperative MSOT recording with the final histological evaluation of the SLNs. The final false negative and positive rates will determine the true utility of the MSOT method in the detection of metastasis in the SLNs. Also, clinically applicable photoacoustic molecular imaging strategies that can target melanoma cells in SLN with intravenously injected imaging agents, have the potential to further improve the sensitivity and specificity, especially in the detection of deep SLNs to reduced false negative rate.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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