Real-time pathology to guide breast surgery: seeing alone is not believing

Irving J Bigio
Departments of Biomedical Engineering, Electrical & Computer Engineering, Medicine, Boston University, Boston, MA

Corresponding author: Irving J Bigio, Boston University, Biomedical Engineering, 44 Cummington Mall, Boston, MA 02215. Phone: 617-358-1987; E-mail: bigio@bu.edu

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Abstract/Summary
Tissue diagnostic techniques based on optical spectroscopy, in various incarnations, are approaching clinical reality for intraoperative guidance of surgical procedures. Examination of tissue properties by elastic light-scattering spectroscopy may constitute a preferable alternative to frozen-section pathology or touch imprint cytology, for intraoperative assessment of resection margins during breast conserving surgery.

In this issue of Clinical Cancer Research, Laughney et al. [1] report on a significant step in the quest for real-time assessment of resection margins during breast-conserving surgery. As amply cited in that report, the high incidence of repeat surgeries resulting from positive margins is costly, both in terms of patient well-being, and as a financial burden on the health care system. The only currently available clinical options have limitations when addressing this problem: frozen-section pathology (FSP) suffers from confounding artifacts and sample changes that limit follow-up histology; touch-imprint cytology (TIC) exhibits significant sampling error and limited predictive value. Moreover, both methods require the immediate availability of a pathologist/cytologist, a costly manpower resource not available in most healthcare settings (especially those outside the US).

A similar, related problem arises for the assessment of sentinel lymph nodes during surgery. A metastatic node would indicate a more radical procedure [2], including axillary dissection. Consequently, real-time node assessment during the initial surgery for presumed local disease, could provide immediate therapeutic guidance, steering towards a more radical procedure when indicated, thus also helping to reduce the number of repeat surgeries [3].

Sabel and coworkers reported a decrease in second-surgery rate from 26% to 9% with intraoperative assessment [4], despite the limitations of FSP and TIC, in a study comparing intraoperative vs. postoperative margin assessment. The result implies that, for the rare settings where expert pathology/cytology is available on-call and the cost is not a consideration, the availability of intraoperative diagnostic information about the two predictors (resection margin and sentinel node) is clearly beneficial. This bodes well for translating novel technologies that have the potential for good diagnostic accuracy without the burden of an on-call cytopathologist.

The drive exemplified by the current report is for a real-time imaging or sensing system that would not require additional manpower or expertise. Established imaging modalities are either not applicable or not adequately sensitive. Recent translational research on diagnostic techniques based on optical spectroscopy, however, has opened new avenues for attack, and a number of groups have been striving to demonstrate clinical potential for these methods [5,6]. For the examination of breast resection margins, the common goal is instrumentation that can enable low-cost and real-time tissue assessment with accuracy as good or better than FSP or TIC when compared against histopathology on surgical samples.

The exigencies of clinical translation for a novel diagnostic method vary with the application. For assessing resection margins during breast surgery, in addition to obvious expectations of user friendliness and reasonable cost, important criteria for successful translation include:
1. Rapid assessment of a large tissue surface area (up to 20 cm²), without resorting to sparse measurements that can lead to sampling error.
2. Measurement on unfixed specimens.
3. Ability to sense the presence of malignant tissue up to 1-2 mm from the surface, deemed to be necessary to minimize local recurrence [7].
4. Ideally, accuracy comparable to the agreement rate among individual pathologists performing post-surgery histology. Performance as good as or better than intra-operative FSP and TIC, although less accurate, would still offer benefits.
5. Quantitative, objective assessment that is not based on subjective interpretation of an image and does not require additional staff with specialized training or expertise to interpret results.

Different approaches to real-time assessment succeed variably in meeting some or most of the numbered criteria. Optical coherence tomography (OCT) is the only clinically-tested optical scheme that approximates histological examination of excised tissue by imaging with microscopic resolution and also exhibits the potential to satisfy criterion 1. As reported by Boppart and colleagues [8], OCT can, in principle, satisfy criteria 1-4, but not yet criterion 5, as the reported study invoked the subjective interpretation of the OCT images by a trained researcher [8]. The other reported optical approaches do not generate microscopic-resolution images, but display a spatial distribution of one or more measured tissue properties. The spatial distribution, or pseudo-image, is typically generated by scanning a spot measurement of the properties or by combining the information from wide-field images at different wavelengths. Ramanujam and coworkers demonstrated a promising clinical system based on diffuse reflectance spectroscopy, which yields information about the tissue’s absorption and scattering properties, albeit with 5-mm spacing of probing sites on the surface of the breast tissue specimen [9]. Although the measurement sites were sparse, denser coverage of the tissue surface by that method would be feasible.

The present study invokes elastic light-scattering spectroscopy [1], a point measurement at the tissue surface that is exquisitely sensitive to micromorphology changes at the cellular and subcellular levels and has previously shown promise for breast tissue assessment [10]. Figure 1 provides a conceptual depiction of how this spectroscopic method works. This method is challenged in satisfying criterion 1 and avoiding sampling errors, due to a measurement spot size as small as 100 microns diameter. In the current report, however, Laughney and colleagues [1] describe a sophisticated optical design that facilitates rapid scanning of the measurement point over a large tissue surface (>1 cm²), with high sampling density and with minimal optical distortion. Perelman and coworkers [11] have also demonstrated a clinical system for rapid, high-pixel-density scanning of elastic scattering spectroscopy over large tissue surface, but their system was designed for a cylindrical geometry, better suited to examining the GI mucosa, and was demonstrated for assessing Barrett’s esophagus. A limitation for any application of elastic-scattering spectroscopy to breast margins is that the small effective illumination-source-to-detector separation, which enhances the sensitivity to micromorphology, also limits the ability to satisfy criterion 3. In the current report the geometry would limit sensing depth to ~200 microns in cellular (parenchymal) tissue and 1 mm in adipose tissue. Nonetheless, the sensing is deeper than TIC, and the reported statistics suggest that this method is likely to be more accurate than either FSP or TIC, when compared against postsurgical histopathology.

An additional exciting feature of the current report is that Laughney and coworkers have introduced new methods for analyzing the spectral data [1], which take advantage of the high pixel density of scattering spectral information to assess the “texture” of tissue properties. Such
information may provide new insights to important factors, such as the degree of invasiveness. Importantly, the authors demonstrate improved diagnostic accuracy with a simple but elegant analysis that averages the classification parameter for a given pixel with the values for its nearest neighbors, reducing the confounding effects of measurement heterogeneity often associated with point measurements.

While the outlook is promising, caveats are always in order. Regarding criterion 4, most studies reported to date, including the present study, have effectively been retrospective studies. That is, the data set is used to identify an optimum classification parameter, or the threshold of a classification parameter, that most effectively separates the classes, for the current data set. The performance of the trained algorithm is then reported for the same set. A prospective study requires a totally naïve data set to test the performance of an already-trained algorithm. Moreover, even when training and testing sets are kept separate, a potential limitation of studies performed in one research center is that the diagnostic algorithm may have been trained to mimic one pathologist. The most promising methods must be studied in multiple centers and with a variety of practitioners. Nonetheless, the current trend, and the present report, are highly encouraging.


Figure caption:
Diagnostic scattering spectroscopy: In this cartoon illustration of the underlying principles of the method described in Laughney et al.[1], an excised tissue sample sits on a glass plate, with normal cells depicted schematically on the left, and tumor cells on the right. In contrast to the normal cells, the tumor cells are represented as having enlarged nuclei, with increased granularity of the chromatin, and, perhaps, a disrupted cytoskeleton resulting in cellular disorder. Light, from a broadband source, and after manipulation through an optical system, is collimated (parallel rays) and impinges on the tissue at normal incidence. While most light is scattered in the near-forward direction, some of the light is scattered directly backwards after one (in most cases) or a few scattering events, and is collected to be analyzed by a spectrometer (not depicted). The spectrometer provides a backscattering spectrum that is representative of the tissue properties. The wavelength dependence of the probability for backscattering varies with changes in the sizes and densities of the dominant scattering centers, such that the backscattered light spectrum changes with pathology, as manifested in the mean cellular micromorphology. In this way, the recorded spectrum relates directly to some of the micromorphology features that a pathologist recognizes as indicative of pathology when looking at histology slides, but in a quantitative manner, without the need to generate an actual microscopic image and without requiring subjective interpretation. (Of course, this physicist’s oversimplification ignores many tissue components that also affect scattering, such as extracellular matrix and vasculature.)
Figure 1:

Tissue

Normal cells

Cancer cells

Broadband illumination light

Optical element

Backscattered light

Spectra of backscattered light

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