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CORR Insights®: Quantitative Primary Tumor Indocyanine Green Measurements Predict Osteosarcoma Metastatic Lung Burden in a Mouse Model

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Where Are We Now?

In their study, Fourman and colleagues demonstrated that uptake of indocyanine green (ICG) dye can quantify primary osteosarcoma in vivo and metastatic disease ex vivo. Perhaps most interestingly, the authors found that quantitative fluorescence of the primary tumor also correlates linearly with metastatic burden.

Tumor targeting with fluorescence imaging has been suggested as a potential tool in personalized oncology [5]. With more-accurate imaging modalities, physicians would be able to diagnose cancers more accurately, assess treatment effect of drugs, and surgically resect tumor without removing healthy tissue. At the same time, scientists would be able to study the effect of novel therapeutics accurately, efficiently, and noninvasively, increasing the identification successful drugs. Effective imaging, however, is reliant on the development of stable, sensitive, and specific molecular probes.

ICG was first introduced after World War II as a photographic dye but was “rediscovered” decades later as a nonspecific fluorophore that absorbed and emitted light in the near-infrared spectrum [11]. Since 2005, ICG has been widely implemented in cancer imaging as it is retained in or around tumor tissue due to impaired secretion or increased vascular permeability and decreased lymphatic drainage [2]. In fact, a recent review [11] suggested that more than 99 peer-reviewed PubMed-indexed articles describing ICG use in staging, treatment or surveillance of cancer have been published since 2000, with the vast majority since 2011.

Despite widespread investigation [2, 11], the clinical use of ICG imaging continues to be limited by a lack of specificity and issues with tissue penetrance. A recent study [7] found clinical false-positive rates as high as 62%. Tissue penetrance in ICG and other near-infrared imaging modalities is only several millimeters, rendering it of limited value in noninvasive imaging on human subjects. Fourman and colleagues highlight the challenges of extrapolating successful preclinical imaging from potential human use by imaging metastatic pulmonary disease ex vivo (rather than in vivo) presumably because a signal would not penetrate the overlying ribs, muscle, and skin even in an animal as small as a mouse. Most clinical successes are found in intraoperative margin assessment, where overlying tissues have been surgically removed, rather than in noninvasive imaging [1, 3].

Perhaps the most-substantial finding in the current study is that ICG quantification correlated linearly with metastatic burden in this mouse model. When studying osteosarcoma, most animal models use primary tumor size or histologic assays of lungs to assess success of an intervention [4]. The former ignores the lungs—arguably the only site that matters for survival—and the latter provides a static time point and cannot assess efficacy over time. One can argue that these limitations are partially responsible for why so many drugs have been successful preclinically and yet provided no survival benefit to our patients [4]. If ICG quantification of the primary tumor could serve as a noninvasive surrogate for the development or progression of metastatic disease in a mouse, longitudinal study of response to therapeutics may be possible in vivo. Does increased vascular permeability drive both phenomena? If we can answer this question, we may better understand why some osteosarcoma seem more apt to metastasize than others.

Where Do We Need To Go?

This manuscript highlights two fundamental gaps in osteosarcoma science: (1) Our limited ability to study metastatic disease in preclinical models, and (2) the challenges in bridging the chasm between laboratory and clinical medicine.

A highly sensitive, specific, stable, nontoxic imaging probe with high tissue penetrance should be our goal. Such an imaging modality would let us study osteosarcoma in the mouse, but also use it to diagnose, prognosticate, assess, and treat patients with osteosarcoma. This probe, if sensitive enough to detect single-cell micrometastases, would help us determine which patients would benefit from chemotherapy, and who can be safely treated with surgery alone. It would allow us to assess responsiveness to chemotherapy, targeted therapies, or immunotherapies in real-time for patients, rather than relying on tumor necrosis at surgery. If the sensitivity was high enough, it would let us develop thernostics, attaching cytotoxic drugs to the probe knowing they would seek out tumor cells alone, limiting the side effects of therapy.

How Do We Get There?

Several approaches can be employed to improve the specificity and tissue penetration in osteosarcoma probes. One such strategy conjugates the fluorophore with tumor specific ligands (small molecules, peptides, proteins, antibodies) [5]. While conjugating ICG to monoclonal antibodies often reduces the fluorescence of ICG, recent work outside of sarcoma has circumvented this challenge by adding “activatable” probes that release the fluorescence-dimming antibody once the probe has successfully targeted and been internalized [6].

The tissue penetration challenge in probe development has been even more challenging. Recent work in the arena of photoacoustics has capitalized on the sound released by fluorophores, suggesting that better audio sensors could “visualize” the tumor [8, 9]. Interestingly, recent conjugation of ICG to single-wall carbon nanotubes has shown an ability to capitalize on the higher tissue penetration of photoacoustics with an increase in specificity of tumor identification [10].

As biochemists and physicists continue to improve tumor-specific fluorophores and tissue penetration of near-infrared dyes, we as sarcoma physicians must continue to advocate for osteosarcoma to remain in the forefront as a disease of importance despite its relative rarity.

Footnotes

This CORR Insights® *is a commentary on the article* “Quantitative Primary Tumor Indocyanine Green Measurements Predict Osteosarcoma Metastatic Lung Burden in a Mouse Model” *by Fourman and colleagues available at:* DOI: 10.1007/s11999.0000000000000003.

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