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Accurate and Reproducible Diagnosis of Canine Soft Tissue Sarcoma Using Mass Spectrometry: A Step in the Right Direction

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In this issue of *Cancer Cell*, Saudemont et al. describe the real-time *ex vivo* molecular diagnosis and histologic subtyping of canine soft tissue sarcomas using SpiderMass, a technology using water-assisted laser desorption/ionization mass spectrometry. In the future, SpiderMass has the potential to aid in diagnosis and intraoperative margin assessment.

Adult soft tissue sarcomas (STSs) encompass a heterogeneous group of over 50 mesenchymal malignancies that differ not only in their underlying molecular pathogenesis but also in their clinical behavior, local recurrence, and metastatic risk, as well as response to radiation and systemic therapies. Even when controlling for tumor grade, outcomes for patients with STSs are largely driven by histology (Gronchi et al., 2015), highlighting the need for accurate histological classification. Based on these observations, the multimodality treatment of STSs over the last ~10 years has evolved from an approach based on tumor location (extremity, retroperitoneum, etc.) to one driven by sarcoma histology. Further, as differences in biologic behavior and response to therapy across STSs histologies are increasingly recognized and understood, there has been an evolution in clinical trial design in which patients are increasingly being included (or possibly excluded) from clinical trials based on the basis of histologic criteria.

Core needle biopsy (CNB) to obtain tissue for pathologic diagnosis is a necessary and critical step for both prognostication and in guiding treatment choice, sequencing in the multimodality care of the STSs patient, and in the selection of patients for participation in clinical trials (von Mehren et al., 2018). Given the rarity and heterogeneity of these tumors, and the diagnostic limitations of CNB (Ikoma et al., 2015), accurate and precise histologic diagnosis of STSs subtypes on the basis of CNB remains, at times, elusive.

In this issue of *Cancer Cell*, Saudemont et al. report the real-time *ex vivo* molecular diagnosis of STSs specimens from canine patients using SpiderMass, a water-assisted laser desorption/ionization mass spectrometry (MS)-based technology (Saudemont et al., 2018). 1-mm-thick sections obtained from canine STSs biopsies were subjected to SpiderMass with MS performed several meters away and with very low degree of tissue ablation or destruction. Initially, the system was evaluated for its ability to differentiate normal tissue from cancer. Although the system was able to differentiate cancer from normal tissue, heterogeneity observed by principal-component analysis in the cancer group suggested there were areas of necrosis, which are often associated with high-grade sarcoma. Therefore, grossly normal, necrotic, and viable tumor regions of CNB specimens were separately analyzed using SpiderMass and suggested that necrosis possesses a specific molecular signature when compared to viable tissues. Importantly, SpiderMass technology was able to separate grade III STSs from normal tissue and grade I and II STSs as well as to discriminate among osteosarcoma, fibrosarcoma, and undifferentiated sarcoma subtypes with a high accuracy. Lastly, real-time tissue analysis and classification was performed in the operating room using a SpiderMass prototype to demonstrate the feasibility and low invasiveness of implementing this technology at the time of surgery.

Accurate histologic diagnosis is the cornerstone of histology-based treatment for STSs, not only for treatment planning per standard of care but also for clinical trial participation. Unfortunately, there is significant variability, even among highly specialized STSs pathologists, as classification of STS based on histology alone can be challenging, and there is often a lack of molecular signatures to distinguish the majority of STSs subtypes. The landscape of systemic treatment for STSs is rapidly evolving, with the identification of novel chemotherapeutic agents and immunotherapy. In the last 5 years, clinical trials in liposarcoma and leiomyosarcoma have resulted in FDA approval of agents in these particular subtypes, but not all STSs, highlighting the importance of accurate and consistent histologic subtyping and diagnosis (Demetri et al., 2017; Demetri et al., 2016). Further, early clinical trials of anti-PD-1 and anti-CTLA 4 immunotherapy in patients with metastatic STSs demonstrate treatment response in dedifferentiated liposarcoma and undifferentiated pleomorphic sarcoma, but not leiomyosarcoma or synovial sarcoma (D'Angelo et al., 2018; Tawbi et al., 2017), with further trials open in these specific subtypes. Time is of the essence in the need for a standard process for accurate and reliable histologic subtyping.

This SpiderMass technology is similar to that of the Intelligent Knife (iKnife) system first described by Balog et al. in 2013 in which near-real-time characterization of human tissue was performed *in vivo* by analysis of the aerosol ("smoke") released during electrosurgical dissection by evaporative ionization MS (Balog et al., 2013; Phelps et al., 2018). An advantage of SpiderMass over the iKnife system is that the former allows acquisition of real-time information without tissue destruction or damage and could thus be applied to

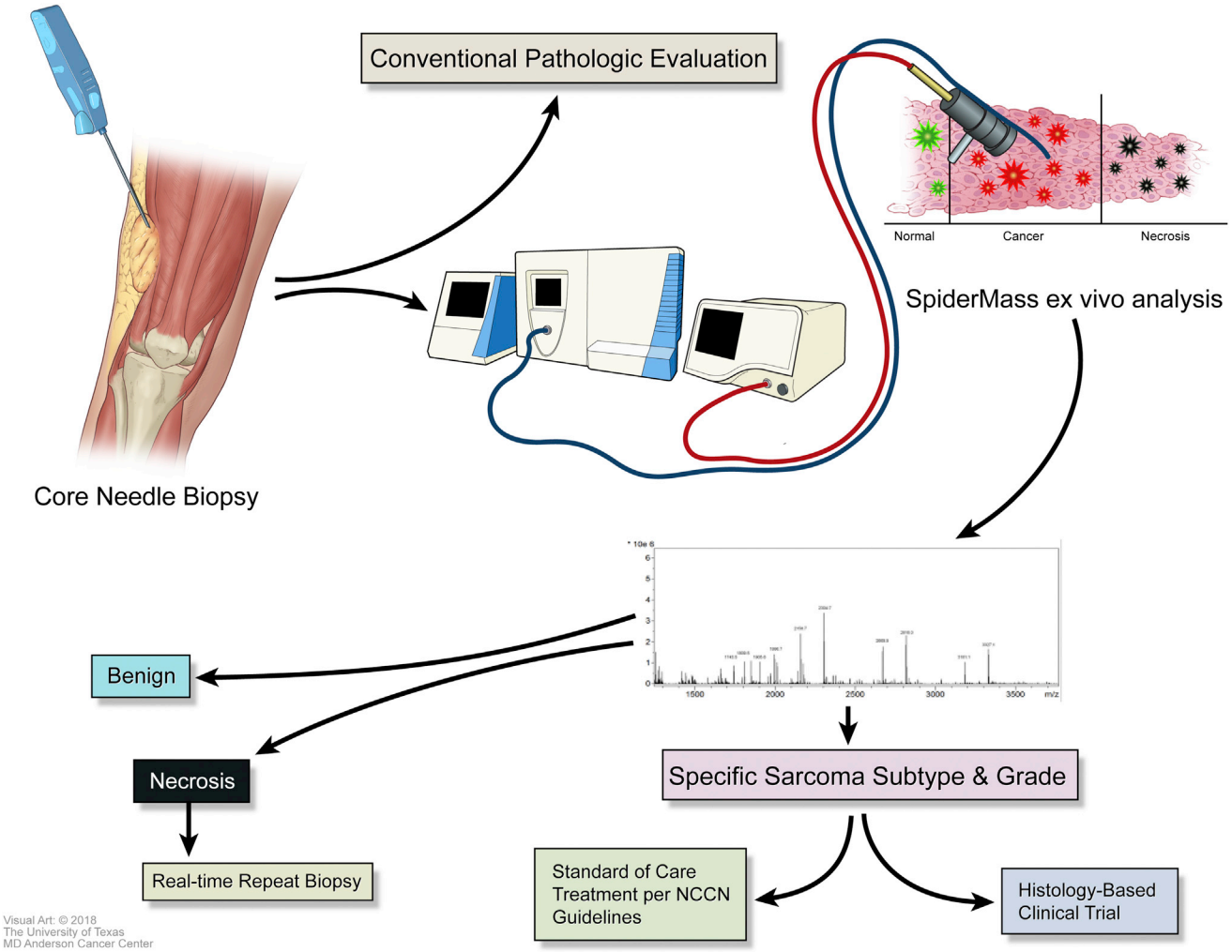

Figure 1. Schematic of Possible Implementation of SpiderMass in Diagnosis and Treatment Planning of Soft Tissue Sarcoma

diagnostic CNB specimens prior to formalin fixation for subsequent histologic examination.

The appeal and power of the SpiderMass technology lays, in part, on (1) its ability to perform MS on CNB with excellent diagnostic capability for differentiating malignancy from normal and necrotic tissue, (2) its ability to further classify sarcoma by grade and histologic subtype, and (3) its potential to help standardize STSs diagnosis across different institutions. Another advantage is that SpiderMass can be performed without sample destruction, allowing current standard of care processing and pathologic examination of CNB and surgical resection specimens. In order to move this technology forward, the next steps should be to (1) evaluate its generalizability to human STSs as well as other cancer types *ex vivo* and (2) further evaluate this technology *in vivo*. We could envision applying this technology to CNB samples to aid and complement in cancer diagnosis, prognostication, and treatment planning (Figure 1). Additionally, this technology could aid at time of surgery (tumor resection) in guiding extent of resection and assessing adequacy of margins in real time.

REFERENCES

Balog, J., Sasi-Szabó, L., Kinross, J., Lewis, M.R., Muirhead, L.J., Veselkov, K., Mirnezami, R., Dezső, B., Damjanovich, L., Darzi, A., et al. (2013). Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. Sci. Transl. Med. *5*, 194ra93.

D'Angelo, S.P., Mahoney, M.R., Van Tine, B.A., Atkins, J., Milhem, M.M., Jahagirdar, B.N., Antonescu, C.R., Horvath, E., Tap, W.D., Schwartz, G.K., and Streicher, H. (2018). Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. *19*, 416–426.

Demetri, G.D., von Mehren, M., Jones, R.L., Hensley, M.L., Schuetze, S.M., Staddon, A., Milhem, M., Elias, A., Ganjoo, K., Tawbi, H., et al. (2016). Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase iii randomized multicenter clinical trial. J. Clin. Oncol. *34*, 786–793.

Demetri, G.D., Schöffski, P., Grignani, G., Blay, J.Y., Maki, R.G., Van Tine, B.A., Alcindor, T., Jones, R.L., D'Adamo, D.R., Guo, M., and Chawla, S. (2017). Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase iii study of eribulin versus dacarbazine. J. Clin. Oncol. *35*, 3433–3439.

Gronchi, A., Miceli, R., Allard, M.A., Callegaro, D., Le Péchoux, C., Fiore, M., Honoré, C., Sanfilippo, R., Coppola, S., Stacchiotti, S., et al. (2015). Personalizing the approach to retroperitoneal soft tissue sarcoma: histology-specific patterns of failure and postrelapse outcome after primary

extended resection. Ann. Surg. Oncol. *22*, 1447–1454.

Ikoma, N., Torres, K.E., Somaiah, N., Hunt, K.K., Cormier, J.N., Tseng, W., Lev, D., Pollock, R., Wang, W.L., and Feig, B. (2015). Accuracy of preoperative percutaneous biopsy for the diagnosis of retroperitoneal liposarcoma subtypes. Ann. Surg. Oncol. *22*, 1068–1072.

Phelps, D.L., Balog, J., Gildea, L.F., Bodai, Z., Savage, A., El-Bahrawy, M.A., Speller, A.V., Rosini, F., Kudo, H., McKenzie, J.S., et al. (2018). The surgical intelligent knife distinguishes normal, borderline and malignant gynaecological tissues using rapid evaporative ionisation mass spectrometry (REIMS). Br. J. Cancer *118*, 1349–1358.

Saudemont, P., Quanico, J., Robin, Y.M., Baud, A., Balog, J., Fatou, B., Tierny, D., Pascal, Q., Minier, K., Pottier, M., et al. (2018). Real-time molecular diagnosis of tumors using water-assisted laser desorption/ionization mass spectrometry technology. Cancer Cell *34*, this issue, 840–851.

Tawbi, H.A., Burgess, M., Bolejack, V., Van Tine, B.A., Schuetze, S.M., Hu, J., D'Angelo, S., Attia, S., Riedel, R.F., Priebat, D.A., et al. (2017). Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. *18*, 1493–1501.

von Mehren, M., Randall, R.L., Benjamin, R.S., Boles, S., Bui, M.M., Ganjoo, K.N., George, S., Gonzalez, R.J., Heslin, M.J., Kane, J.M., 3rd, et al. (2018). Soft tissue sarcoma, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Canc. Netw. *16*, 536–563.