minimized phototoxicity and photobleaching at out-of-focus regions, yet preserves submicron spatial resolution and subcellular detail of cell and tissue structures.
Using invasive HT-1080 fibrosarcoma xenografts in the dorsal skin-fold chamber in nude mice, we here show the dynamics of tumor growth, neoangiogenesis, and tumor invasion into the adjacent tissue microenvironment. Using fluorescent labels, not only single cells but also extensively invading collective cell strands were reconstructed to move along and around preexisting blood and lymphatic vessels, not however neovessels. Using dual-color cells expressing Histone-H2B/eGFP in the nucleus and cytoplasmic RFP, the combined dynamics of collective invasion and mitotic activity defines the hallmarks of 'invasive growth'. In future studies, time-resolved two-photon microscopy will allow to gain novel insight into the mechanisms cancer progression, regression, and persistence during experimental therapy.

141 INVITED

The use of iron particles in MRI

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Pelvic lymph node metastases have a significant impact on the prognosis of patients with malignancies. In prostate cancer, for example, even micro metastases in a single node rule out surgical cure by the available treatment protocols. For bladder cancer lymph node metastasis are also significant. More than 5 lymph node metastasis or extra capsular growth precludes curative surgical treatment. Thus, the status of the lymph nodes largely dictates the management of the primary tumour. Surgical open pelvic lymph node dissection (PLND) considered being the only reliable method for assessing lymph node status is an invasive procedure associated with potential complications and side effects. A noninvasive, reliable method for detecting and staging nodal metastasis would reduce unnecessary surgery. Routine cross-sectional imaging modalities like CT and MRI lack the desired sensitivity in identifying metastases as they largely rely on size criteria only, and small metastases in normal size nodes can be missed. Moreover, differences in signal intensity on MR images between normal and cancerous nodes as well as gadolinium enhancement have also proven to be unreliable. Ultra small super paramagnetic iron oxide particles (ferumoxtran-10) with a long plasma circulation time have been shown to be suitable as a MR contrast agent for intravenous MR lymphangiography. After IV injection the ferumoxtran-10 particles are taken up by macrophages are transported to the interstitial space and from there through the lymph vessels to the lymph nodes. Once within normally functioning nodes the intracellular ferumoxtran-10 within the macrophages reduces the signal intensity of normal node tissue, because of the T1- and T2*-susceptibility effect of iron oxide, thus producing a signal drop or negative enhancement. In areas of lymph nodes that are involved with malignant cells, macrophages are replaced by cancer cells. Therefore, there is in these areas no uptake of the ferumoxtran-10 particles. Using a macrophage-(= cell-) specific MR-contrast agent and high resolution MR imaging allows the detection of small and otherwise undetectable lymph node metastases in patients with cancers cancer. This has an important clinical impact, as the diagnosis will be more precise and less invasive to obtain. Subsequently this will reduce morbidity and health care costs. However, thorough knowledge of sequence parameters and planes, lymph node anatomy, appearance of normal and abnormal nodes, and pitfalls is essential when using this technique. This implies a very important role for education by expert radiologists, MR-manufacturers, and contrast agent companies.

Special session (Wed, 26 Sep, 13:30−14:30)
Recent progress in characterising sarcoma subtypes

142 INVITED

Progress in characterising sarcoma subtypes

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In the last ten years, significant improvements have been made in the classification of sarcomas. New antibodies allow to identify specific categories of sarcomas and numerous genomic abnormalities have been described: specific reciprocal translocations, gene amplifications, deletions and mutations. These DNA lesions are now daily used for subtyping sarcomas.
Immunohistochemistry plays an important role to characterise sarcomas. Numerous antibodies are now available and allow to define some sarcoma subtypes: myogenin for rhabdomyosarcomas, CKIT or CD117 for GIST, TFE3 for alveolar soft part sarcoma, INI1 for rhabdoid tumors.

Major improvements have been made in the molecular approach of sarcomas and a molecular classification of these tumors can be proposed:

- Sarcomas with a specific translocation: about 25% of soft tissue sarcomas bear a specific translocation which can be used as a diagnostic marker (see table). From a practical point of view, it is currently almost necessary to demonstrate these translocations for the diagnosis of PNET, synovial sarcoma, alveolar rhabdomyosarcoma, low grade fibromyxoid sarcoma, infantile fibrosarcoma and desmoplastic small round cell tumor given the therapeutic consequences. Translocation can be desmonstrated by RT-PCR or by FISH with commercially available break apart probes.
- Sarcomas with activating mutations: about 85% of GIST show activating mutation of either KIT or PDGFRA receptor tyrosine kinase genes. The most frequent mutation involves exon 11 of KIT followed by exon 9 of KIT and exon 18 of PDGFRA. Demonstration of these mutations are useful for the diagnosis of CD117 negative GIST, for predicting response to imatinib and to explain secondary resistance to imatinib.
- Sarcomas with inactivating mutations: malignant rhabdoid tumors show biallelic inactivation of INI1 gene with a lost of INI1 expression which can be demonstrated by immunohistochemistry. Other sarcomas, such as epithelioid sarcomas and some epithelioid malignant schwannomas show the same molecular and immunohistochemical abnormalities.
- Sarcomas with simple genomic profile showing gene amplification of a few genes. Well differentiated liposarcomas, dedifferentiated liposarcomas and intimal sarcomas show a simple genomic profile characterised by MDM2 and CDK4 amplifications associated with amplification of other genes in dedifferentiated liposarcomas. The presence of this DNA lesion can be used for differentiating a well differentiated liposarcoma-lipoma-type from a lipoma with secondary changes and for identifying dedifferentiated liposarcomas among pooly differentiated sarcomas. These amplifications can be demonstrated by immunohistochemistry, FISH or CGH-array.
- Other sarcomas usually show a complex genomic profile characterised by numerous gains and losses of genes with a frequent loss of Rb1 and alterations of P53. Leiomyosarcomas, pleomorphic rhabdomyosarcomas, pleomorphic liposarcomas, myxofibrosarcomas, poorly differentiated sarcomas (so-called MFH and fibrosarcomas) belong to this category and show no specific molecular abnormality.

In conclusion, major improvements have been made in the characterisation of sarcoma subtyping thanks to immunohistochemistry and molecular biology.

Translocations in sarcomas

Tumor	Translocation	Genes involved
PNET	t(11;22)(q24;q12)	EWS-FLI1
	t(21;22)(q22;q12)	EWS-ERG
	t(7;22)(q22;q12)	EWS-ETV1
	t(17;22)(q12;q12)	EWS-E1AF
	t(2;22)(q33;q12)	**EWS-FEV**
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3-FKHR
	t(1;13)(p36;q14)	**PAX7-FKHR**
Synovial sarcoma	t(X;18)(p11;q11)	SYT-SSX1
		SYT-SSX2
		SYT-SSX4 (rare)
Infantile fibrosarcoma	**t(12;15)(p13;q25)**	**ETV6-NTRK3**
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11)	FUS-CREB3L2
	t(11;16)(p11;p11)	**FUS-CREB3L1 (rare)**
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23)	TPM3-ALK
	t(2;19)(p23;p13)	TPM4-ALK
	t(2;17)(p23;q23)	CLTC-ALK
	t(2;2)(p23;q13)	**RANBP2-ALK**
Angiomatoid fibrohistiocytoma	**t(12;16)(q13;p11)**	**FUS-ATF1**
Dermatofibrosarcoma protuberans	**t(17;22)(q22;q13)**	**COL1A1-PDGFB**
Desmoplastic small round cell tumor	**t(11;22)(p13;q12)**	**EWS-WT1**
Clear cell sarcoma	**t(12;22)(q13;q12)**	**EWS-ATF1**
Alveolar soft part sarcoma	**t(X;17)(p11;q25)**	**TFE3-ASPL**
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	FUS-DDIT3
	t(12;22)(q13;q12)	**EWS-DDIT3**
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	EWS-NR4A3
	t(9;17)(q22;q11)	RBP56-NR4A3
	t(9;15)(q22;q21)	**TCF12-NR4A3**