MRI of Ovarian Cancer: When & How?
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Introduction
Ovarian cancer spreads by direct invasion, intraperitoneal seeding and through the lymphatic and vascular circulation. Peritoneal seeding is the most common route of extraovarian disease dissemination and signifies a grim prognosis with a 5-year survival rate of 32%-47%. The extent and anatomical location of peritoneal involvement determines the feasibility of cytoreductive surgery and predicts the surgical result. In the setting of rising tumor markers in previously treated patients, imaging of the peritoneum is crucial in order to detect sites of relapse and to designate surgical versus chemotherapeutic management options. Staging of ovarian cancer has been routinely practiced by means of Contrast Enhanced Computed Tomography (CECT), the sensitivity of which is determined by the size and location of peritoneal implants because of their similar density and hence poor contrast to adjacent normal structures. However, purely anatomical imaging uses only size criteria when assessing the impact of cytotoxic therapy and does not recognize the functional alterations within tissue that precede frank volume changes. Thus, there has been a growing awareness of the potential of functional imaging in improving staging accuracy and quantifying early treatment response. This session will describe the principles and techniques of functional imaging modalities currently employed in ovarian cancer, discusses their advantages and limitations compared to conventional imaging and presents their prospective role in patient management.

Morphological Imaging of Peritoneal Disease in Ovarian Cancer
The cornerstone of treatment in advanced ovarian cancer is cytoreductive surgery in combination with platinum-taxane chemotherapy. According to the guidelines of the International Federation of Gynecology and Obstetrics, definitive staging of ovarian cancer is performed surgically at laparotomy with contemporary establishment of tissue diagnosis and attempt at primary cytoreduction. Preoperative imaging identifies the cohort of patients with advanced disease, in whom primary surgical debulking is not feasible either due to anatomical site or disease volume and who will benefit from neoadjuvant chemotherapy. Moreover, preoperative imaging can delineate suspicious sites that warrant targeted biopsy at surgery, in addition to the routine blind sampling of the omentum, diaphragm, mesentery and pelvic and para-aortic lymphnodes. Postoperative imaging can confirm surgical outcome; an optimal cytoreductive result is achieved when individual residual tumour foci do not exceed 1 cm in maximum diameter and has been proven to significantly improve survival. Finally, repeat imaging after completion of chemotherapy most often obviates the need for second-look laparotomy.

Computed Tomography (CT) is the standard modality for non-invasive staging and follow-up in ovarian cancer due to its wide availability and reproducibility. Magnetic Resonance Imaging (MRI) has an established role as a problem-solving tool in the characterisation of sonographically equivocal ovarian lesions due to its superior contrast resolution. Presurgical staging benefits from multiplanar MRI, which can provide accurate delineation of local disease extent. The overall sensitivity of gadolinium-enhanced MRI in depicting peritoneal disease has been reported equal to CT (95% and 92% respectively), but MRI may be advantageous in the detection of small implants. The administration of oral contrast material in order to opacify the gastrointestinal tract improves sensitivity in subcentimeter lesions (72%-80%) and in subphrenic, serosal and mesenteric sites (96%). However, high cost and long scan duration have prevented the wide acceptance of MRI as a staging modality for ovarian cancer.
Functional Imaging of Peritoneal disease in Ovarian Cancer

**Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI)** exploits the thermally driven motion of water molecules, which in biological tissue is modified by extracellular microarchitecture as well as active transport mechanisms and microcirculation. The restrictive net effect of the forces that modulate water diffusion in vivo reflects the tortuosity of extracellular space and the integrity of cellular membranes. Although as a morphological imaging modality DW-MRI has a spatial resolution in the order of millimeters, as a functional modality it detects molecular displacements at a cellular scale (in the order of 10-30 μm) and can therefore interrogate tissue microenvironment.

DW-MRI in ovarian cancer can be interpreted qualitatively because the high contrast-to-noise ratio of optimized sequences allows the detection of small-volume disease even in complex anatomical locations, such as serosal bowel surface, omentum and mesentery. Malignant deposits retain high signal intensity with increasing $b$ values, whereas their environment, whether mesenteric fat, bowel lumen or ascites, is strongly suppressed. The addition of DW imaging to conventional MRI has been shown to increase the number of depicted peritoneal lesions in patients with ovarian cancer by 21% - 29%\(^5\): on a per-site basis the combination of techniques is superior with an accuracy of 84-88% compared to 52-72% for MRI alone and 71-81% for DW-MRI alone.\(^9\) Another study indicates a 90% sensitivity and 95% specificity in detecting sites of ovarian-related peritoneal dissemination with a substantial interobserver agreement ($κ=0.77$).\(^7\) DW-MRI can reveal foci of omental and serosal disease of the order of 5mm irrespective of their anatomic location. Subdiaphragmatic and subcapsular hepatic implants are also satisfactorily visualized, although respiratory and cardiac motion artifact may degrade image quality. Problematic sites are the spleen and lymphnodes, which demonstrate relatively restricted diffusion even in the absence of malignancy. Care must be taken in the interpretation of a diffuse pattern of moderately restricted diffusion, which is frequently observed in the wall of the bowel and arises from normal hypercellular mucosa. Cystic and calcified peritoneal deposits and mucinous histology may produce false-negative findings so correlation with anatomical images is essential to avoid pitfalls in interpretation. Initial findings also suggest that site-specific diffusion patterns (peritoneum vs. omentum) reflect disease heterogeneity and may predict differential response to treatment.\(^8\) Histogram analysis of lesions following chemotherapy indicate that an early increase of ADCs and later decrease of skew and kurtosis characterize response.\(^9\)

**Dynamic contrast enhanced MRI** quantifies the pharmacokinetic profile of an injected contrast agent with the consecutive, rapid image acquisition before, during and after its administration. The passage of the paramagnetic agent increases signal intensity; the degree of enhancement is determined by blood flow, vascular density, capillary permeability and capillary surface area in the early vascular phase and by extravascular space volume in the interstitial phase.

DCE-MRI has been used to provide proof of action of antiangiogenic and vascular disrupting drugs. Although antivascular agents have shown clinical efficacy in ovarian cancer\(^10\), technical challenges have restricted the implementation of DCE-MRI as a provider of surrogate biomarkers of treatment response. The demand for fast dynamic acquisition imposes limitations on the extent of anatomic coverage, which in advanced ovarian cancer needs to be considerable. The shape, location and heterogeneity of peritoneal deposits complicate the selective, operator-dependent definition of regions of interest (ROI) and may warrant alternative methods of visualizing the dynamic data, such as pixel mapping, which require dedicated software. Standardization of image acquisition, processing and analysis protocols is needed before DCE-MRI can be expanded in multi-center phase II/III trials. Adoption into wider clinical practice will also depend on its feasibility in multifocal or disseminated disease, where coverage of the entire peritoneal cavity is crucial.

**Proton Magnetic Resonance Spectroscopy (MRS)** derives its signal from the different resonant frequencies of protons within a molecule due to magnetic diatomic interactions within the molecular structure. MRS has been validated sparsely in ovarian malignancy. *Ex vivo* studies of fluid from ovarian cysts showed a significantly increased presence of lactate
and alanine in combination with low glucose in malignant lesions, indicating the predominance of anaerobic metabolic pathways in the setting of malignancy.\textsuperscript{11,12} The absence of lactate peaks was a powerful predictor of benignity.

\textit{In vivo} MRS of ovarian disease has to address inherent technical problems, such as peristaltic motion artifact, accurate voxel localization and external volume suppression, and presence of local susceptibility effects from surrounding fluid or air, which result in spectral contamination. In a small cohort examined at 3T, a choline/creatine ratio greater than 3 in ovarian masses could be predictive of malignancy.\textsuperscript{13} Okada et al. found that lactate peaks were significantly higher in malignant lesions, in accordance with \textit{ex vivo} results, but choline concentrations were not discriminatory.\textsuperscript{14} McLean et al. detected choline in almost all primary adnexal sites but in less than 50\% of metastatic omental lesions.\textsuperscript{15} The discrepancy was attributed to technical imperfections arising from magnetic field inhomogeneities, respiratory and peristaltic bowel motion and reduced SNR due to smaller applicable voxels. A persistent difficulty was also encountered in excluding adjacent adipose tissue, which resulted in predominance of large lipid peaks in the omental spectra.

\textbf{Conclusion}: Integrated anatomical and functional imaging of peritoneal carcinomatosis can overcome the deficiencies of conventional imaging in fully delineating the extent of ovarian cancer and in assessing treatment effects at a cellular level.

\section*{References: