SYMPOSIUM: HYPOXIA AND RADIOTHERAPY - THE STATE OF THE SCIENCE

SP-0626
Omics in molecular profiling of tumour hypoxia
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The term 'omics' generally refers to fields of studies in biology and medicine ending in -omics. The related ending -ome refers to the objects of these studies, and implies some sort of totality (e.g. the genome is the entirety of the hereditary information in an organism). Some of the more popular 'omics' include genomics (except for some RNA viruses, this involves studies on DNA), epigenomics (studies on chemical changes to DNA and histone proteins), transcriptomics (studies on RNA), proteomics (studies on proteins), metabolomics (studies on chemical processes involving metabolites), pharmacogenomics (studies on the influence of genetic variation on drug response), and radiogenomics (studies on the influence of genetic variation on radiation-induced normal tissue toxicity). Molecular profiling can be used to identify novel targets for intervention and for pretherapeutic hypoxic evaluation. There is a high degree of heterogeneity in certain tumour sites with respect to hypoxia, which can lead to primary resistances to radiotherapy and selection of more aggressive tumour phenotypes. The development of markers and methods for prediction and proper patient stratification is a major research area. Besides molecular profiling, this is often addressed using oxygen sensing electrodes or by functional imaging. One of the preferred 'omics' for molecular profiling of tumour hypoxia is transcriptomics (1). The effect of hypoxia on genome-wide transcription levels can be studied *in vitro* under controlled conditions of oxygen tensions, time of exposure, and other environmental conditions like extracellular pH. This has led to the development of several different gene expression signatures (also known as profiles or metagenes). Another approach is to use xenograft models. Finally, hypoxia gene expression signatures can be generated by identifying candidate genes from *in vitro* studies and use data from genome-wide expression studies on tumour biopsies to analyse and identify coexpression networks. In general, and independent on how they have been developed, gene expression signatures are associated with poor prognosis for the two main cancer types where they have been studied most intensely, i.e. head and neck and breast cancer. Recently, one of the signatures has also been shown to have predictive value, being able to identify patients that benefit from hypoxic modification in a randomized trial evaluating the effect of the hypoxic radiosensitizer nimorazole (2). Clinical trials on hypoxic radiosensitizers are currently being planned, and will hopefully clarify the predictive value of hypoxia gene expression signatures.
Other 'omics' for molecular profiling of tumour hypoxia include proteomics and metabolomics. Hypoxia not only affects transcription but also translation, and these studies are essential when studying signalling pathways and identifying novel targets for intervention, and may also provide additional prognostic and predictive value. The technologies for genome-wide studies on proteins and metabolites have not been as comprehensive and established as for studies on DNA and RNA, but with recent technological developments proteomics and metabolomics will be increasingly important for molecular profiling of tumour hypoxia.
1. Toustrup K, Sørensen BS, Alsner J, Overgaard J. Hypoxia gene expression signatures as prognostic and predictive markers in head and neck radiotherapy. Semin Radiat Oncol 22:119-127, 2012.
2. Toustrup K, Sørensen BS, Nordsmark M, Busk M, Wiuf C, Alsner J, Overgaard J. Development of a hypoxia gene expression classifier with predictive impact for hypoxic modification of radiotherapy in head and neck cancer. Cancer Res 71:5923–5931, 2011.

SP-0627
Tumour hypoxia imaging to individualise radiotherapy
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In a first part of the talk, state-of-the art methods for non-invasive tumour hypoxia imaging using positron emission tomography (PET) will be revised. Furthermore, a short overview on currently practised or proposed strategies to individualise radiotherapy (RT) based on hypoxia PET imaging will be given.
In a second part, first results of a clinical hypoxia dose painting (HDP) carried out in Tübingen trial will be presented. Between 2009 and 2012, n=21 head and neck cancer (HNC) patients were included into a randomized clinical HDP trial. All patients underwent pre-treatment [18F]-fluorodesoxyglucose (FDG) PET/CT in addition to dynamic [18F]-fluoromisonidazole (FMISO) PET/CT imaging. n=16 patients presented with a moderate or high level of pre-treatment tumour hypoxia. Those were randomized into two different treatment groups: standard IMRT (n=8) or HPD consisting of a 10% dose escalation (77 Gy) inside the planning target volume of highest order (PTV70) (n=8). Hypoxic volumes (HV) were discriminated based on hypoxia and perfusion parameters determined by a kinetic analysis of the dynamic FMISO PET data. All patients completed pre-treatment imaging examinations and RT treatment as planned. Patients randomized into the HDP arm did not show increased levels of acute toxicity. After a median follow-up time of 7 months (0 - 40 months), also no increased levels of late toxicities were observed. The mean volume of the PTV was 186.83 ml (68.47 - 455.65 ml), whereas the HV had a mean size of 9.37 ml (0 - 49.17 ml). So far, n=6 local recurrences were observed: 2 in the experimental arm and 4 receiving standard IMRT. Technically, the integration of dynamic FMISO PET parameters to escalate the dose inside the PTV70 was feasible. However, HDP of volumes below a critical volume of approximately 2 ml could not be realized due to the finite size of dose gradients necessary to increase the dose level by 10%.
In a last part of the presentation, the potential of newly available hybrid imaging systems combining PET with magnetic resonance imaging (PET/MRI) for non-invasive hypoxia imaging will be discussed. n=3 patients of the above mentioned study were additionally examined with simultaneous PET/MRI including a FMISO PET scan approximately 3 h post injection together with a series of diagnostic and functional MRI techniques (diffusion weighted, DW and dynamic contrast enhanced, DCE). These first clinical FMISO PET/MRI data sets hint at a potential correlation of the voxel-based FMISO uptake and the local tumour perfusion as measured with DCE-MRI.
State-of-the-art hypoxia imaging with non-invasive methods is still an evolving field of research. Hypoxia imaging using PET/CT and also PET/MRI shows a high potential for individualising RT.

SP-0628
Treatment strategies targeting tumor hypoxia
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Tumor hypoxia is a negative prognostic factor in patients treated with radiotherapy. This is at least in part because hypoxic cells are radiation resistant. Many strategies have consequently been employed to overcome the problem of radiation resistant hypoxic cells in the clinic. These include the chemical substitution for oxygen with hypoxic radiosensitizers or efforts to increase tumor oxygen supply with vasodilators and breathing of high-oxygen content gas during radiotherapy. Such strategies have proven successful, improving loco-regional control and survival inpatients with head and neck cancer in randomized phase III trials. In spite of this, oxygen modification has not entered routine clinical practice in most countries, and we are still in need of safe, affordable and practical alternatives to mitigate radiation resistance due to tumor hypoxia. A novel class of drugs inhibiting mitochondrial activity may represent such an alternative. Hypoxia arises distal to blood vessels due to the high oxygen consumption of more proximal cells which thereby limit the diffusion distance of oxygen in the tumor tissue. Inhibition of oxygen consumption by targeting mitochondria can therefore promote redistribution of oxygen in tumors and reduce hypoxia. Recent promising preclinical data suggest that clinically available inhibitors of mitochondrial function are potent tumor radiosensitizers due to their ability to reduce the hypoxic fraction.

JOINT SYMPOSIUM: ESTRO-EFOMP: DOSE MEASUREMENTS/INDICATORS IN PET/CBCT/CT

SP-0629
Dosimetry for wide CT beams
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Introduction to the problem: CT was introduced into clinical practice in the early 1970s and developing concepts for CT dosimetry attracted the interest of many scientists. These efforts finally led to the paper by Shope et al. in which the computed tomography dose index (CTDI) was introduced. At that time the measurement of CTDI was optimized for a narrow CT fan beam geometry, the beam width was usually smaller than 10 mm. CTDI measurements are performed with either a cylindrical head or body phantom and a 100 mm long pencil ionization