Contribution ID: **25** Type: **oral (invited speaker)**

# Hypoxia gene expression classifier predicts benefit from radiosensitizers

*Thursday, 18 October 2012 17:15 (30 minutes)*

Hypoxic tumours are associated with increased resistance to radiotherapy. In head and neck squamous cell carcinomas (HNSCC), this resistance can be counteracted via addition of hypoxic modification to the radiotherapy. Tumours are heterogeneous with respect to the degree and extend of hypoxia, and several methods have been developed to detect relevant tumour hypoxia. These include direct measurements in the tumour by an oxygen electrode, infusion and detection of exogenous hypoxia tracers, or quantification of endogenous hypoxia markers expressed by the tumour cells under hypoxic conditions. While there are extensive studies in relation to prognostic impact, less is known about the relevance of hypoxia assessing methods in relation to the prediction of response to hypoxic modification of radiotherapy.

A recently developed 15-gene hypoxia classifier has been shown to have predictive impact for identification of patients responding to hypoxic modification of radiotherapy with Nimorazole. Tumours from 323 HNSCC patients included in the randomized, double blinded DAHANCA 5 trial were classified using the 15-gene hypoxia as being "more"or "less"hypoxic. 114 (35%) were classified as "more"hypoxic. The prognostic impact of the classifier was demonstrated in the placebo arm of the trial in terms of loco-regional tumour control, LRC (5-year actuarial values 44% vs 18%, p = 0.004), and disease specific survival, DSS (51% vs 30%, p = 0.04). Importantly, only patients with "more"hypoxic tumours had a significant benefit of hypoxic modification with Nimorazole compared with placebo (LRC: 49% vs 18%, p = 0.001; DSS: 48% vs 30%, p = 0.04). "Less"hypoxic tumours had no significant effect of hypoxic modification and the outcome was similar to "more"hypoxic tumours treated with Nimorazole. When stratified for HPV-status, the benefit of Nimorazole was restricted to HPV-negative and "more"hypoxic patients. Patients with HPV-positive tumours had a generally improved outcome, irrespective of their hypoxic status and whether or not the patients received Nimorazole.

Studies are currently ongoing to implement the hypoxia classifier in clinical practice in Denmark, and to include the hypoxia classifier in international clinical trials on Nimorazole. Other ongoing studies are addressing the relevance of hypoxia in HPV-positive tumours and the correlations with other hypoxia assessing methods. Finally, the hypoxia classifier is being evaluated for other tumour sites.

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**Session Classification:** Modulation of Radiosensitivity

**Track Classification:** Modulation of Radiosensitivity