of radiation sensitivity. A subset of these candidate molecules could be validated having an impact in clinical outcome of radiation therapy treated HNSCC patients.

**Conclusion:** Our study demonstrates that multi-level radiation systems biology allows gaining deeper insights into chief mechanisms of radiation sensitivity, thereby paving the way for targeted individualised therapy approaches in radiation oncology.

**Debate: This house believes that progress in the treatment of locally advanced NSCLC will come from:**

### SP-0102 Radiation treatment intensification

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A large proportion of non-small cell lung cancer (NSCLC) patients are diagnosed with locally advanced (stage III) disease. For this patient group the treatment of choice is definitive concurrent chemoradiation (CCRT). CCRT results in an improved overall survival (OS) compared to sequential chemoradiotherapy or radiotherapy alone because of improved locoregional control. However 2-year OS rates of 30-35% are still poor because many patients develop locoregional failures (about 30%) and distant metastases (about 40%)[1]. Currently locally advanced NSCLC patients selected for CCRT have FDG-PET scanning and imaging of the brain (MRI or CT scan). Despite this brain imaging with the present chemotherapy regimens used we are faced with the problem of brain metastases in about 10% of the patients within 1 year after chemoradiation.

In several chemoradiation studies it was reported that the Gross Tumor Volume is correlated with OS. This is rational since the tumor volume represents the number of clonogenic tumor cells that needs to be eradicated. To improve locoregional control the dose prescription could be escalated taking into account the individual Gross Tumor Volumes and tolerances using image guided adaptive Intensity Modulated Radiotherapy (IMRT). However there are radiation oncologists who challenge the usefulness of RT dose escalation and intensification in patients with stage III NSCLC. The outcome of a randomized phase III trial, RTOG 06171, revealed that NSCLC patients within the 74 Gy arm given in 7.5 weeks had worse local control and significantly worse overall survival as compared to the patients treated to 60 Gy arm in 6 weeks[2]. Patients in all study arms received two additional cycles of consolidation chemotherapy ± cetuximab. So the obvious question is: How do we continue?

Dose escalation with prolonged overall treatment time in NSCLC has previously been proven disappointing because of accelerated repopulation[3].In an individual patient data meta-analysis in patients with non-metastatic lung cancer, which included trials comparing modified radiotherapy with conventional radiotherapy, a significant OS benefit from accelerated or hyperfractionated radiotherapy was reported[4]. Another issue is the use of consolidation chemotherapy after concurrent chemoradiation. In the RTOG 0617 trial the increase in mortality started < 3 months after randomization during the period of consolidation paclitaxel-carboplatin chemotherapy. Generally taxanes given after RT increases toxicity and the combination of high dose to the heart and consolidation taxane-based chemotherapy might have caused toxic deaths and biased the outcome. RT dose intensification while using modern image guided adaptive IMRT and accelerated schemes is an important area of ongoing clinical research and should not be discontinued.

In Stereotactic Ablative Body Radiotherapy (SABR) much higher biologically equivalent doses are delivered compared to conventionally fractionated RT (typically EQD2 of 70-85 Gy), and has generated outstanding tumor control in early stage NSCLC. For SABR a significant dose–response relationship was observed for prescription EQD2 of 105 Gy or more (2-year LC 96%) or of less than 105 Gy (2-year LC 85%)[5]. Tumor size and overall treatment time were also important factors influencing outcome.

The tumor control probability of SBRT (small tumor volume) and conventionally fractionated chemoradiation (large tumor volume) were successfully described in a single model[6] suggesting that a dose-response relation in NSCLC does exist.

Recently there is a growing interest in genetic profiles that predict a patient's response to radiotherapy, because severe toxicity in a minority of patients limits the doses that can be safely given to the majority. Recent progress in genotyping raises the possibility of genome-wide studies. If we know the normal tissue reactions to radiotherapy by genotype we will really be able to tailor the individual radiation dose.

In conclusion: Besides the unsolved problem of the occurrence of distant metastases there is room for improvement of locoregional control in locally advanced NSCLC patients treated with chemoradiation. In the era of personalized treatment, radiotherapy dose intensification using image guided adaptive IMRT could be directed towards individual tumor volumes and tolerances. RT dose intensification while using accelerated schemes is an important area of ongoing clinical research

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### SP-0103
### Better systemic therapy

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About one third of patients with non-small cell lung cancer (NSCLC) present with locoregional disease extension in either the mediastinum (T4) or the mediastinal lymph nodes (N2/3). Apart from a fraction in which resection after induction therapy is sometimes considered, selected patients with stage 3 are candidate for a so-called definitive radiochemotherapy, administered either sequentially or concomitantly. Despite staging with PET-CT scan and endosonographic mapping of mediastinal lymph nodes and notwithstanding a patient selection for this radical treatment, the outcome in stage 3 is nevertheless moderate with a median survival of 2 years [1]. Progression occurs after a median of 10 months and is due to local relapse or distant metastasis in 30 and 45% of cases, respectively. Any advance in the outcome in stage 3 NSCLC will hence depend on improvements in systemic therapy directed at distant metastasis. The past 10 years have seen important changes in the paradigm of treatment in selected patients with advanced NSCLC, in whom platinum-based doublet chemotherapy used to be the standard of care. The discovery of drugable genomic alterations has introduced precision medicine in oncology. Patients whose NSCLC harbour either an activating EGFR mutation, EML-ALK translocation or ROS1 amplification are now routinely treated with oral small molecule kinase inhibitors of the 1st, 2nd and 3rd generation instead of chemotherapy, with a significant improvement in outcome and a substantial impact on quality of life. Similar, although less pronounced effects have been observed when adding monoclonal antibodies directed at targets associated with angiogenesis or cell growth to the chemotherapy backbone. Unfortunately, the incorporation of these