hemorrhage, bronchial- or mainstem stenosis are relatively unusual and may develop beyond 4 years after treatment. Estimation of the probability to develop RP is important for patients with inoperable lung cancer. Studies of the risk of RP have used various dosimetric parameters like the Mean Lung Dose (MLD) or V20. To increase the sensitivity to predict RP, dosimetric and non-dosimetric factors can be combined. Palma et al (ref 1) performed a meta-analysis of both dosimetric and non-dosimetric factors based on individual patients treated with concurrent chemoradiation. The factors predicting RP were type of chemotherapy (carboplatin/paclitaxel vs cisplatin/etoposide or other chemotherapy), age, MLD and V20. Pre-existing radiological interstitial lung disease (ILD) findings were analyzed in a recent Japanese study of 157 patients and correlated with the incidence of RP after stereotactic body radiation therapy (SBRT) for stage I NSCLC (ref 2). Multivariate analysis identified ILD as risk factor for ≥ Gr2 RP, as well as the irradiated lung volume.

Recall radiation pneumonitis describes a rare reaction in previously irradiated lung tissue after application of triggering agents. Recall RP has been associated with multiple drugs such as taxanes, gemcitabine, vinca alkaloids, adriamycin and epirubicin. Tyrosine kinase inhibitors (erlotinib, cetuximab, sunitinib) have also been associated with recall RP and increased risk of severe RP following palliative or definitive radiation therapy. Some researchers (erlotinib, cetuximab, sunitinib) have also been associated with recall RP and increased risk of severe RP following palliative or definitive radiation therapy. Some researchers have found a significant correlation between pulmonary toxicity and pre- and post radiation therapy pulmonary function tests. However, reduction in e.g. diffusion capacity varies widely between the grades of RP, making it less useful in routine clinical practice.

To improve the quality of lung toxicity reporting investigations of Patient Reported Outcome (PRO) tools are being developed. In literature discrepancies between patients and clinicians reported toxicity as well as low correlation with CTCAE scoring are reported. Generally clinicians tend to underreport the incidence and severity of symptoms. In a recently published analysis of lung cancer patients treated with radiotherapy/chemoradiation agreement ranged from slight to substantial (ref 3). These differences underline the significance of the introduction of PROs in clinical trials.

Summary: Dosimetric and clinical factors help us to estimate the incidence and severity of radiation induced pulmonary toxicity in clinical practice. In addition to these factors PROs tools on toxicity should be integrated in daily routine and in clinical trials to facilitate the doctors and patients decisions in the near future.

References:

SP-0203
Dose / fractionation / IMRT / Imaging
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Radiotherapy (RT) plays a major role in the management of lung cancer as most patients are not surgical candidates due to stage, fitness and comorbidities. In the last decade we have witnessed tremendous changes in the role of radiation for the radical treatment of lung cancer as a result of the optimisation of chemo-radiotherapy combinations and technological advances.

The technology available for RT planning, delivery and verification of lung cancer treatment is evolving at a fast pace. Unfortunately the evidence to demonstrate the benefit of such technology in terms of toxicity, local control, survival or quality of life is limited. Despite advances in the field of advanced RT techniques, local control with current RT doses delivered with standard 3D conformal RT is poor with local progression-free survival rates of about 30%, even with concurrent CRT. It is now well accepted that that improved local control in lung cancer can lead to improvement in survival [Aupérin A. J Clin Oncol 2010]. The following strategies can be combined to improve outcome in lung cancer include:

- Use of Intensity-modulated radiotherapy (IMRT) is a technique that adds fluence modulation to beam shaping, which improves radiotherapy dose conformity around the tumour and spares surrounding normal structures. Treatment with IMRT is becoming more widely available for the treatment of lung cancer, despite the paucity of high level evidence supporting the routine use of this more resource intense and complex technique [Chan. JTO 2014]. It allows the treatment of patients with large volume disease, close to critical organs at risk with curative doses.
- Dose escalation
A clear radiation dose-response relationship exist in locally advanced NSCLC [Martel. Lung Cancer 1999]. The relationship between local control and BED is further suggested by data from SABR studies. The encouraging results of phase 1 and 2 dose studies conducted in the 1990s formed the basis for the RTOG 0617 study [Bradley. ASCO 2013]. In that 2 x 2 factorial design study, patients with stage III NSCLC were randomized to receive high dose (74 Gy in 37 fractions) or standard dose (60 Gy in 30 fractions) RT concurrently with weekly paclitaxel/carboplatin with or without cetuximab. Disappointingly, there was a significant increase in the risk of death in the high-dose arms (median survival, 19.5 months vs 28.7 months; p=0.0007), and a 37% increase in the risk of local failure in the high-dose arms (hazard ratio, 1.37; p=0.0319). There is therefore no role for dose escalation in stage III NSCLC using conventional dose fractionation.
- Acceleration
Hyperfractionated and/or accelerated fractionation schedules have demonstrated superior survival compared to conventional fractionation at the expense of greater oesophageal toxicity [Mauguen JCO 2012].
- Dose redistribution based on functional imaging
Targeted dose escalation to tumour volumes resistant to treatment or at increased risk for recurrence is under evaluation [NCT01024829 and NCT01507428]
- Individualisation of the dose (concept of isotoxic RT)
The recognition of cancer heterogeneity has driven us away from the ‘one size fits all’ approach and has allowed tailoring of treatment to individualised patient-tumour characteristics. Isotoxic radiotherapy is a novel concept of personalised radiotherapy treatment allowing the individualised administration of radiotherapy dose based on predefined normal tissue constraints.

OC-0204
The first toxicity results of the PET-boost trial (NCT01024829)
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