**Purpose/Objective:** High-dose thoracic radiation therapy can cause significant adverse effects. Therefore, radical radiotherapy has historically been reserved for patients with stage I-III disease non-small cell lung cancer (NSCLC), and the most common indication for radiation therapy to the primary site for patients with metastatic (stage IV) NSCLC has been palliation for pain or other symptoms directly resulting from tumor. However, stage IV NSCLC contains a broad spectrum of patients, and prior studies have suggested that select patients with stage IV disease with a limited number of distant metastases ('oligometastasis') may benefit from radical therapy. We investigated prognostic factors associated with survival in patients with NSCLC and oligometastatic disease at diagnosis, particularly the influence of local treatment to the primary site on prognosis.
**Materials and Methods:** From January 2000 through June 2011, 78 consecutive patients with oligometastatic NSCLC (<5 metastases) at diagnosis without prior thoracic surgery or radiation therapy, no prior or concurrent other malignancy and who underwent aggressive radio(chemo)therapy (≥45 Gy) to the primary site were assessed. Forty-four of these patients also received definitive local treatment for the oligometastases. Pulmonary and esophageal acute toxicity was scored according to the Common Terminology Criteria for Adverse Events version 3.0. Survival outcomes were estimated using the Kaplan-Meier method, and risk factors were identified by univariate and multivariate analyses.
**Results:** The median follow-up time for patients alive at the time of analysis was 35 months (range, 2–109). Rates of grade 2 radiation pneumonitis and esophagitis were 16.7% and 39.7%. Rates of severe (grade ≥3) pulmonary and esophageal toxicity were 6.4% and 19.4%. The locoregional relapse rate was 22% (17 patients, with 10 experiencing recurrence inside the radiation field), and 50 of the original 78 patients had new sites of distant metastases. For all patients, the 1-, 2-, and 3-year overall survival (OS) rates were 62%, 32%, and 25%, respectively. Univariate Cox proportional hazard analysis revealed better OS for those patients who received at least 63 Gy of radiation to the primary site (*P*=0.002), received definitive local treatment for oligometastasis (*P*=0.041), had a Karnofsky performance status (KPS) score >80 (*P*=0.007), had a gross tumor volume ≤124 cm3 (*P*=0.002), had adenocarcinoma histology (*P*=0.002), or had no history of respiratory disease (*P*=0.016). On multivariate analysis, radiation dose, performance status, and tumor volume retained significance (*P*=0.004, *P*=0.006, and *P*<0.001, respectively).
**Conclusions:** Tumor volume, KPS, and receipt of at least 63 Gy to the primary tumor are associated with improved OS in patients with oligometastatic NSCLC at diagnosis. Our results suggest that a subset of such patients may benefit from aggressive local therapy.

OC-0500
CLINICAL AND DOSIMETRIC PREDICTORS OF LATE ESOPHAGUS TOXICITY AFTER IMRT AND CONCURRENT CHEMOTHERAPY FOR NSCLC
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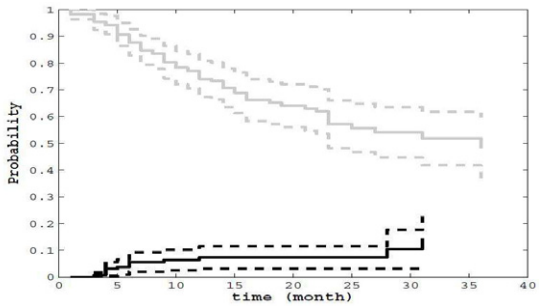
**Purpose/Objective:** Concurrent chemoradiation has improved the local control and survival for NSCLC patients at the cost of a higher incidence of side-effect, such as acute esophagus toxicity (AET). However the incidence and cause of late esophagus toxicity (LET) has not been thoroughly studied. Severe LET includes esophagus stenosis, perforation or fistulae, which may seriously affect the patients' quality of life or even lead to death. With higher incidence and longer survival in patients treated with accelerated IMRT and concurrent chemotherapy, it has become relevant and feasible to analyze LET. Therefore, we analyzed the relations between severe LET and the clinical and dosimetric variables.
**Materials and Methods:** Between 2008–2010, 231 consecutive NSCLC patients were treated with IMRT and concurrent chemotherapy. The treatment consisted of high dose accelerated radiotherapy (66Gy/24 fractions of 2.75Gy) preceded by a daily dose of cisplatin (6mg/m²) administered 1-2 hours before each fraction. Patients with a different or multiple treatment regimens, or with missing follow-up, were excluded. Clinical variables included age, pre-treatment weight loss, performance status, Charlson co-morbidity index, the number of cisplatin doses, and maximum AET score. The maxAET was scored according to CTCAE3.0 within 3 months after the treatment. After the third month, the severe LET was scored if patients had severe swallowing problem, or developed esophagus fibrosis, necrosis, perforation, fistula or relevant death. Dosimetric variables for LET included esophagus V5Gy up to V80Gy (normalized with α/ß=3), Dmean, Dmax, location of the maximum dose, volume of the primary tumor and the lymph nodes. Univariate and multivariate Cox regression analysis were applied and significant predictors were considered at p<0.05 level.
**Results:** A total of 171 patients were eligible for this analysis, with a median follow-up of 22 months. Thirteen (7%) patients developed severe LET. Figure 1 plots the survival and severe LET. The median onset time was 6 months (range, 3~31 months). Eight out of the 13 severe LET patients died: 1 had tumor progression close to esophagus; 3 were without proof of tumor recurrence adjacent to esophagus; 4 had either distant tumor progression, or non-treatment related causes. Univariate analysis showed that Dmean, Dmax and V20Gy up to V80Gy were all predictive of severe LET (p<0.05). The most significant variable was V75Gy (p<0.001). While for clinical variables, maxAET≥3 (p=0.005) was predictive of severe LET. Seven out of 38 maxAET≥3 patients developed severe LET. In Multivariate analysis, V75Gy and maxAET remained significant predictors.

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | p-value | HR (95%CI) | p-value | HR (95%CI) |
| V75Gy | <0.001 | 1.09 (1.05–1.13) | <0.001 | 1.09 (1.04–1.13) |
| maxAET (0–2 vs ≥3) | 0.005 | 4.90 (1.63–14.73) | 0.046 | 3.04 (1.01–9.09) |




**Conclusions:** Severe LET is an important complication after high dose concurrent chemoradiation, with a crude incidence of 7% at a median follow-up of 22 months. The higher V75Gy and the maxAET Grade≥3 were significant predictors.

OC-0501
IRRADIATION OF THE LEFT VENTRICLE OF THE HEART IS CORRELATED WITH POST-TREATMENT DYSPNEA IN NSCLC PATIENTS
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**Purpose/Objective:** Dyspnea is a very important and dose-limiting side-effect of radiotherapy (RT) of non-small cell lung cancer (NSCLC). Dyspnea is measured qualitatively on a zero-to-five scale according to the Common Toxicity Criteria system. Apart from lung damage, it is known that a decrease of cardiac output is a major cause of dyspnea. We therefore hypothesized that the amount of radiation dose delivered to the left ventricle of the heart is related to post-treatment development of dyspnea.
**Materials and Methods:** A cohort of 78 NSCLC patients has been retrospectively obtained in Center 1. All patients have been treated between 2008 and 2009 with IMRT with individualised iso-toxic accelerated radiotherapy. CT, PETSUV and dosimetric 3D images are available per each patient. For all patients dyspnea scores before (baseline) and after RT are available. The aim of the present study was to predict the difference between maximal dyspnea score within 9 months after RT and baseline score. The left ventricle was defined according to PET-CT. An external dataset of 30 patients from Center 2 in another country was obtained.
**Results:**
1: Overlap between the left ventricle and high radiation dose levels, adjusted for the mean heart dose (Figure 1, upper panel). Patients from both centers were pooled and we divided in two groups – those with improved dyspnea scores after RT (16%) and those who worsened

or stayed the same (84%). Visual inspection reveals a very high separation between the two groups, with only a few outliers. A formal statistical logistic-regression model produced an area under the curve (AUC) estimate of 0.82.
2: Relationship between heart volume and the overlap of high radiation dose and the left ventricle (Figure 1, lower panel). This revealed that smaller heart volumes (as well as smaller PETSUV-dose overlap) are less susceptible to post-radiation dyspnea. We note that heart volume and mean heart dose are slightly positively related (correlation of 0.11). Our findings were confirmed on the external validation dataset.

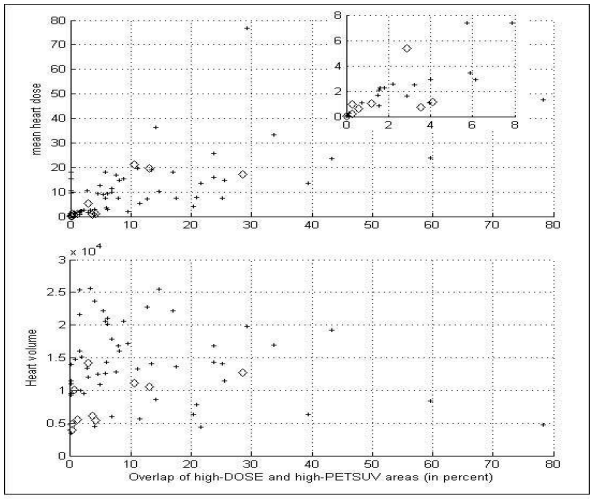


Figure 1. Relationship between heart volume and mean heart dose on the one hand, and overlap of high-dose and high-PETSUV areas on the other, on pooled dataset from two Centers. Crosses: dyspnea increases or stays the same after RT; diamonds: dyspnea decreases after RT. The upper panel contains in the upper-right corner a zoomed area of the 0-8 range from both axes.

**Conclusions:** Post-radiation dyspnea is associated with the radiation dose to the left ventricle of the heart. This should be taken into account in predictive models.

## PROFFERED PAPERS: CLINICAL 8: HEAD AND NECK

OC-0502
DOSE-RESPONSE OF HYPOTHYROIDISM AFTER PRIMARY RADIOTHERAPY IN CARCINOMA OF THE HEAD AND NECK (HNSCC)
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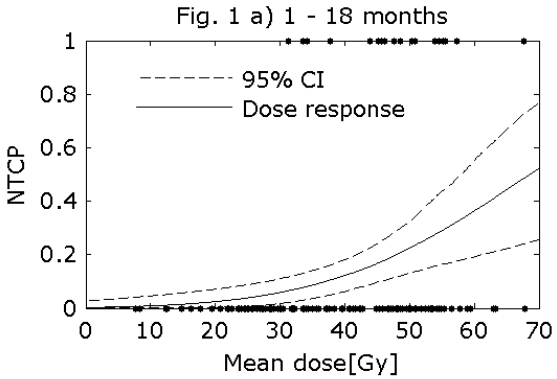
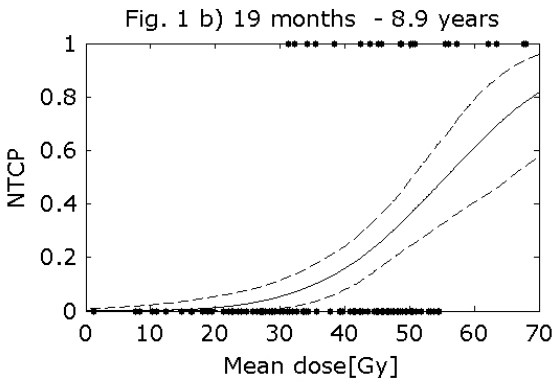
**Purpose/Objective:** To estimate the normal tissue tolerance level of the thyroid gland to external beam radiation in HNSCC with biochemical hypothyroidism (HT) as endpoint.
**Materials and Methods:** Patient and treatment characteristics of HNSCC patients treated with primary 3D conformal photon treatment or IMRT between 2002 and 2010 in a single university hospital were retrieved from our national database. This included 190 patients (oral cavity 6, oropharynx 97, hypopharynx 13, and larynx 74) who received primary radiotherapy, 66-68 Gy in 33-34 fx, 5-6 fx/w. No primary surgery was allowed for this study, however, 34 patients received weekly concomitant platinum (40 mg/m2). All patients were euthyroid at the time of treatment and without a previous history of thyroid disorder.
The patients were followed with post treatment repeated thyrotropin (TSH) assessment. Patients were censored from the study in case of recurrent disease treated with chemotherapy or surgery involving the thyroid.
HT was defined as TSH >4.0 mU/l. Median follow-up was 20.6 months (1.4 months - 8.9 years). The thyroid gland was delineated by a single person in the treatment dose planning system, and dose-volume parameters were derived for each patient for correlation analysis to HT. Multivariate regression analysis was applied to determine risk factors of HT. The Lyman-Kutcher-Burman (LKB) model based on mean thyroid dose (MTD) with two free parameters, median toxic dose (TD50) and a steepness parameter m, was used to describe the dose-response relationship (NTCP). Fitting was done by adjusting the parameters to maximum log-likelihood, and bootstrapping was used to derive 95% CI.
**Results:** The median MTD was 40.7 Gy (1.6-68.0 Gy). HT occurred in 29/190 patients (15.3%) with the first incident after 2.4 months. The only independent factors associated with HT were thyroid volume (ml) (OR=0.84 (0.77-0.92); p<0.001) and MTD (OR=1.09 (1.04-1.13; p<0.001). No interaction was observed between thyroid volume and mean dose. NTCPs after 30, 40 and 50 Gy during early follow-up (1-18 months, n=129) were 5.9% (95% CI: 1.8-11.0), 12.2% (95% CI: 6.2-18.2) and 22.5% (95% CI: 13.1-32.3%), respectively (Fig.1 a). The equivalent NTCPs after > 18 months follow-up (n=117) were 5.4% (95% CI: 1.0-11.5%), 15.9% (95% CI: 8.0-24.2%) and 36.0% (95% CI: 24.2-48.7%) (Fig.1b).




**Conclusions:** This study helped to define the tolerance level of the thyroid gland by exploring a consecutive cohort of HNSCC patients treated primarily with IMRT and no surgery. Mean thyroid dose and low thyroid volume were significantly associated with biochemical HT. HT was observed after only a few months in this cohort. Dose-response analysis showed a 12-15% risk of HT after 40 Gy, depending on observation time.

OC-0503
QUANTEC DOSE VOLUME CONSTRAINTS FOR PAROTID GLANDS ARE FEASIBLE ONLY IN A MINORITY OF H&N PATIENTS TREATED WITH IMRT
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