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Purpose or Objective
The European Organization for Research and Treatment of Cancer (EORTC) phase II prospective multicentre Lungtech trial 22113-08113 assesses safety and efficacy of stereotactic body radiotherapy (SBRT) in inoperable patients with centrally located non-small cell lung cancer (NSCLC). The trial was closed early due to poor accrual. Here we report on two lethal complications.
Material and Methods
Patients with centrally located ("tumor within 2 cm or touching the zone of the proximal bronchial tree (PBT) or tumor that is immediately adjacent to the mediastinal or pericardial pleura, with a planning target volume expected to touch or include the pleura") non-metastatic NSCLC (T1-T3, ≤7cm) were included. After prospective imaging review and radiation quality assurance (RTQA) patients were treated with SBRT (8x7.5Gy, ICRU 83). Follow-up is performed 6 weeks after treatment, then 3-monthly for 3 years, 6-monthly in year 4 and 5, including history, clinical examination, toxicity assessment and CT, FDG-PET and biopsy in case of suspected progression. The protocol included recruitment stop in case of potentially SBRT-related death triggering safety review.
Results
Between 08/15 and 12/17, 39 patients from 13 sites and 6 European countries were included in the trial, 33 passed imaging and RTQA review (58% male, age 57-89 years, tumor size 1.4 - 5.5cm) and were treated per protocol. So far, 2 potentially treatment related deaths were observed.
An 88 year old patient died 3 months after SBRT and death was attributed to radiation pneumonitis. Safety review could not decide on the definite cause of death, also potentially related to pre-existing cardiac disease (CD) or amiodarone lung disease. As a consequence, patients with severe pre-existing CD, interstitial lung disease or concomitant amiodarone intake were excluded from recruitment and a formal policy to treat pneumonitis was added in the protocol. As this patient had a relatively high contralateral mean lung dose (CMLD), the amended recommendation restricted CMLD to < 3.6Gy.
An 83 year old patient with a tumor broadly abutting the right lower lobe bronchus died 15 months after SBRT, scored as SBRT-related hemoptysis. The PBT received 46.5Gy to 0.54cc, considered as acceptable protocol variation. Safety review revealed that in this patient taking anticoagulants, bronchoscopy, including a biopsy of a necrotic patch at the right lower lobe was performed 4 days before death. The event was categorized as expected toxicity and recommendations for a more careful management of procedures after SBRT were made available to investigators. Although it was not recommended to stop the study for safety reasons, the repeated safety-related halt in recruitment contributed to the early closure of the trial.
Conclusion
Safety of SBRT in centrally located lung tumors remains unclear. For the prospective investigation of radiotherapy related toxicities, alternative trial designs to those typically used to investigate medicinal products might be needed.

OC-0062 Development & validation of prognostic and predictive models in limited-stage small-cell lung cancer

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Purpose or Objective
Assessment of prognosis & selection of limited-stage small-cell lung cancer (LS-SCLC) patients who benefit from chemoradiotherapy (CTRT) could aid clinical decisions. We used the CONVERT trial & validation cohorts to investigate LS-SCLC prognostic & predictive covariates.
Material and Methods
CONVERT is a phase III trial that randomised patients between twice-daily (45Gy in 30 fractions) & once-daily (66Gy in 33 fractions) CTRT, followed by prophylactic cranial irradiation if indicated. The following covariates were investigated for prognostic & predictive significance (benefit from twice-daily radiotherapy & CTRT completion) in CONVERT: clinical (age, performance score (PS), TNM stage, tumour laterality, smoking status, weight loss >10% & lung function), laboratory (alkaline phosphatase, sodium & lactate dehydrogenase) & dosimetric (gross tumour volume (GTV), % heart dose & lung V20). Chemotherapy & radiotherapy completion were defined as delivery of all pre-planned cycles (4 or 6) & all radiotherapy fractions, respectively. Multivariate overall survival (OS) & chemotherapy completion regression analyses were conducted after correcting for multiple comparisons with a final model derived via a backward elimination approach using the likelihood ratio-test. The CONVERT OS model was validated in 2 independent LS-SCLC retrospective patient cohorts, treated in the routine setting at The Christie.
Results
459 CONVERT participants & 2 Christie cohorts treated with CTRT (cohort 1; n=108) and radiotherapy ± chemotherapy (cohort 2; n=228) were included (table 1). In CONVERT, GTV was the strongest OS prognostic covariate (HR 1.3 (95% CI 1.14-1.48); p<0.001). The addition of PS (ECOG 1/2 vs 0) & tumour laterality (bilateral/midline/unknown vs unilateral) modestly improved the models' concordance index (0.59 to 0.61). The HR for OS between high & low risk groups using this model, derived by splitting on the median risk score, was 1.96 (95% CI 1.54-2.49); median OS: 21 m (95% CI 18-25) vs 45 m (95% CI 34-NR), respectively (figure 1A). The models' prognostic significance was validated in the 2 independent Christie cohorts (cohort 1 concordance index=0.62, SE=0.04 & cohort 2 concordance index=0.59, SE=0.02); figure 1B-C. None of the covariates predicted benefit from twice-daily radiotherapy in CONVERT. In CONVERT, increasing patient age (continuous) alone or with hyponatremia & decrease in forced expiratory volume in 1sec (continuous) predicted non-completion of

6 or 4 pre-planned chemotherapy cycles ($p<0.05$), respectively. Due to high radiotherapy completion in CONVERT (≥80% in both trial arms), a multivariate analysis to predict radiotherapy completion was not performed. Data on treatment completion were currently unavailable in the routinely treated cohorts.

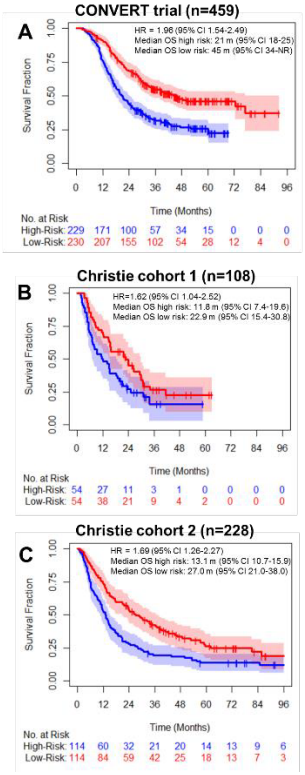
Table 1: Baseline characteristics of patients across all groups

	CONVERT (events=278; n=459)	Christie Cohort 1 (events=80; n=108)	Christie Cohort 2 (events=181; n=228)
Age	62 (29-81)	64 (41-84)	71 (36-93)
Gender			
Male	255 (56%)	36 (33%)	102 (45%)
Female	204 (44%)	72 (67%)	126 (55%)
Therapy			
Concurrent CTRT	454 (99%)	48 (44%)	0 (0%)
Sequential CTRT	2 (<1%)	60 (56%)	0 (0%)
No RT	3 (1%)	0 (0%)	0 (0%)
RT alone[1]	0 (0%)	0 (0%)	228 (100%)
Smoking Status			
Current	163 (36%)	46 (43%)	52 (23%)
Ex	291 (63%)	54 (50%)	39 (17%)
Never	5 (1%)	4 (4%)	1 (<1%)
Unknown	0 (0%)	4 (4%)	136 (60%)
ECOG PS			
0	215 (47%)	18 (17%)	23 (10%)
1	232 (51%)	59 (55%)	115 (50%)
2	12 (3%)	23 (21%)	67 (29%)
3	0 (0%)	8 (7%)	23 (10%)
GTV (cubic cm)			
median (range)	83.8 (0.5-593.0)	36.9 (0.5-535.0)	23.6 (0.1-375.3)
Laterality			
1	126 (27%)	23 (21%)	80 (35%)
2	323 (70%)	85 (79%)	148 (65%)
3	10 (2%)	0 (0%)	0 (0%)
IMRT			
Yes	79 (17%)	83 (77%)	69 (30%)
Linear Predictor -Cox Model			
Median (Range)	1.56 (0.14-2.28)	1.27 (-0.20 – 2.08)	1.05 (-0.74 – 1.97)

[1]: A small number of patients received chemotherapy, in addition to radiotherapy

ECOG PS – Eastern Cooperative Oncology Group Performance Score; GTV – Gross Tumour Volume; RT- Radiotherapy

Figure 1: Kaplan-Meier survival curves for CONVERT (**A**) and Christie cohorts 1 (**B**) and 2 (**C**) split into high & low risk groups using the median value derived from final Cox model (GTV, ECOG PS and tumour laterality)



Conclusion

We report an independently validated LS-SCLC prognostic model form the CONVERT trial, providing information clinicians can relay to patients to aid clinical decisions. The addition of biological covariates could refine this model.

OC-0063 CREO Project: exploratory radiomics for predicting adaptive radiotherapy in NSCLC

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Purpose or Objective

The primary goal of precision medicine is to minimize side effects and optimize efficacy of treatments. Recent advances in medical imaging technology allow the use of more advanced image analysis methods beyond simple measurements of tumor size or radiotracer uptake metrics. The extraction of quantitative features from medical images to characterize tumor pathology or heterogeneity is an interesting process to investigate, in order to provide information that may be useful to guide the therapies and predict survival. The aim of this study was to investigate whether the radiomic features of initial imaging were able to predict tumor reduction during radio- chemotherapy (RCT) in patients with stage III non-small cell lung cancer (NSCLC).

Material and Methods

We studied 91 patients with stage III NSCLC treated with concurrent RCT: 50 patients were treated at radical dose with adaptive approach (adaptive group), 41 patients underwent radical concurrent RCT in the same period, but who did not achieve target reduction (non-adaptive group). Clinical characteristics of these patients are listed in Table 1.

The characteristics investigated were extracted from the initial simulation CT on which the Clinical Target Volume was manually delineated by expert radiation oncologists, providing a 3D ROI. Given each 3D ROI in the images, we computed the radiomic features using our in-house software tool coded in MATLAB (Mathworks Inc, MA, U.S.A.), taking into consideration 12 statistics features and 230 textural features extracted from the CT images. In our study, we used an ensemble learning method to classify patients' data into either the adaptive or non-adaptive group during RCT on the basis of the starting CT simulation. All the experiments were conducted according to a 10-fold cross validation, i.e., a model validation technique which provides a nearly unbiased estimate using only the original data.