9043 POSTER

Comparison of Three Approaches to Delineate Internal Gross Tumour Volume Based on Four-dimensional CT Simulation Images of Non-small-cell Lung Cancer

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Background: To compare positional and volumetric differences of internal gross tumour volume (IGTV) delineated separately by three approaches based on four-dimensional CT (4DCT) for the primary tumour of non-small cell lung cancer (NLCLC).
Materials and Methods: Twenty-one patients with NLCLC underwent big bore 4DCT simulation scan of the thorax. IGTVs were delineated using three approaches as followed: gross tumour volumes (GTVs) delineated on ten bins of 4DCT were fused to produce $IGTV_{10}$; GTVs delineated separately based on end-inspiration (EI) and end-expiration (EE) phases were fused to produce $IGTV_{EI+EE}$; the visible tumour on the MIP images were delineated to produce $IGTV_{MIP}$. The position of the target center, the volume of target, the degree of inclusion (DI) and the matching index (MI) were compared reciprocally among $IGTV_{10}$, $IGTV_{EI+EE}$ and $IGTV_{MIP}$. The definition of DI of volume X included in volume Y [DI (X in Y)] is the percentage of the overlap between volume X and Y in volume X.
Results: The mean centroid shifts among IGTVs in the LR, AP and CC directions were less than 1 mm, with no statistically significant difference. The $IGTV_{10}$ size was larger than $IGTV_{EI+EE}$ size, the difference was statistically significant ($t = 2.37$, $p = 0.028$); the $IGTV_{10}$ size was larger than $IGTV_{MIP}$, but the difference was not statistically significant ($t = 1.95$, $p = 0.065$). The mean size ratio of $IGTV_{EI+EE}$ to $IGTV_{10}$, $IGTV_{MIP}$ to $IGTV_{10}$ were 0.85 ± 0.08 and 0.92 ± 0.11, respectively. The mean DI of $IGTV_{EI+EE}$ in $IGTV_{10}$, $IGTV_{MIP}$ in $IGTV_{10}$ were $84.78\%\pm8.95\%$ and $88.47\%\pm9.04\%$. The mean MI between $IGTV_{10}$ and $IGTV_{EI+EE}$, $IGTV_{10}$ and $IGTV_{MIP}$ were 0.85 ± 0.09, 0.86 ± 0.09, respectively.
Conclusions: The centroid shifts among IGTVs delineated by the three manners based on 4DCT images are not obvious; $IGTV_{EI+EE}$ and $IGTV_{MIP}$ can not replace $IGTV_{10}$, however, $IGTV_{MIP}$ is closer to $IGTV_{10}$ comparing to $IGTV_{EI+EE}$. The size ratio of $IGTV_{EI+EE}$ to $IGTV_{10}$ is correlated to the tumour motion vector. As the vector increases, the size ratio of GTV_{EI+EE} to $IGTV_{10}$ decreases.

9044 POSTER

Phase 2 Study of Nimotuzumab in Combination With Concurrent Chemoradiotherapy (CRT) in Patients With Locally Advanced Non-small Cell Lung Cancer (NSCLC)

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Background: Nimotuzumab (Nimo), a humanized IgG_1 monoclonal EGFR antibody, is approved and widely used in patients (pts) with head and neck cancer or malignant glioma in combination with radiotherapy in several countries. In previous clinical studies, Nimo has demonstated a very mild and low incidence of skin toxicity compared to other EGFR antibodies. On nonclinical models using NSCLC cell lines, Nimo showed a radiosensitizing effect.
Material and Methods: This open-label, multicenter phase 2 study evaluated the tolerability and efficacy of Nimo in combination with concurrent CRT in pts with unresectable locally advanced NSCLC. All eligible pts received concurrent thoracic radiotherapy (60 Gy, 2 Gy/day, 6 weeks from day 1) and 4 cycles of chemotherapy (cisplatin 80 mg/m^2 on day 1, vinorelbine 20 mg/m^2 on days 1 and 8) once every 4 weeks as scheduled. Nimo (200 mg) was administrated once a week from cycle 1 to 4. The primary endpoint was tolerability in combination with concurrent CRT, which was measured by the percentage of pts who completed 60 Gy of radiotherapy within 8 weeks, completed 2 cycles of chemotherapy and received more than 75% of Nimo.
Results: Between June 2009 and May 2010, 40 pts were enrolled from 7 sites in this study in Japan, and 39 eligible pts received the study treatment. The pts characteristics (n = 39) were as follows: 62 years (median); male/female, 34/5; stage IIIA/B, 21/18; PS0/1, 25/14. Thirty-four pts (87%) met the criteria for treatment tolerability, and 38 pts (97%) completed 60 Gy of radiotherapy within 8 weeks. Infusion reaction, $\geqslant$grade 3 skin rash, $\geqslant$grade 3 radiation pneumonitis, or $\geqslant$grade 4 nonhematological toxicity were not observed. For the preliminary efficacy analysis, 37 pts were evaluable with appropriate radiotherapy planning. The response rate (CR+PR) was 70%; the median PFS was 11.1 months; and 92% pts were alive at the cutoff date (Jan 2011). There was no corelation observed between PFS and the above-mentioned pts characteristics. However, the PFS was longer in pts with squamous cell carcinoma (n = 16) than that in pts with adenocaricinoma (n = 14) (mPFS: not reached vs 9.9 months $p = 0.014$; progression free at the cut-off date: 71% vs 13%). Analysis of molecular markers and further survival followup is ongoing and will be presented and discussed.
Conclusions: Nimo's addition is feasible to the concurrent CRT consisting of cisplatin and vinorelbine. The preliminary efficacy result observed in pts with squamous cell carcinoma is interesting and further investigation is needed.

9045 POSTER

Advanced Lung Cancers − Combined Use of Stereotactic Body Radiation Therapy for Primary Tumour and Three-dimensional Radiotherapy for Mediastinal Nodes Versus Standard 3DRT. an Intra Individual Dosimetric Comparison

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Title: Advanced lung cancers: combined use of stereotactic body radiation therapy for primary tumour and three-dimensional radiotherapy for mediastinal nodes versus standard 3DRT. An intra individual dosimetric comparison.
Background: Radiation tolerance of lungs, spinal cord, heart and oesophagus does not allow to deliver efficient doses of irradiation in advanced non-small-cell lung cancers (NSCLC). The aim of the present study is to show a possible dosimetric gain for these organs et risk (OAR) when including only the nodal planned target volume (PTV-N) in the field of standard radiotherapy and covering the tumour planned target volume (PTV-T) by stereotactic body radiation therapy (SBRT), using Cyberknife®.
Methods and materials: Nine patients with peripheral stage III NSCLC were selected. They were simulated, planned, and treated with involved field 3DRT using a dose of 66 Gy in 33×2 Gy. Retrospectively, plan of primitive tumour irradiation by SBRT at a dose of 48 Gy in 4×12 Gy and plan of mediastinal lymph nodes irradiation by 3DRT were realised, optimized separately and coregistrated (=combined plan). Dosimetric parameters of the two plans were considered for PTV-T, PTV-N, lung, heart, spinal cord and esophagus.
Results: Similar coverage of the PTV-T was observed between the two plans ($p = 0.23$). Coverage of the PTV-N was significantly improved in the combined plan ($p = 0.01$), with a mean increase of 3%. The combined plan minimized the lung V20 and V30 doses with a respective mean decrease of 14.8% ($p = 0.008$) and 32.4% ($p = 0.008$). MLD was similar between the two plans ($p = 0.37$). The V30 of the heart was significantly decreased in the experimental plan ($p = 0.04$). There were no significant differences in the maximal dose delivered to the spinal cord and the length of esophagus irradiated at 46 Gy between the two plans (respectively $p = 0.21$ and $p = 0.41$).
Conclusion: Compared to the conventional approach, the combined plan, in advanced lung cancers, reduces significantly the V20 and V30 of the lung and the V30 of the heart. It also increases biological equivalent dose of the PTV-T and coverage of the PTV-N. These findings encourage us to conduct a phase I-II.

9046 POSTER

Radiation Pneumonitis and Treatment Outcome in Radical Radiotherapy of Stage III Non Small Cell Lung Cancer

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Background: The aim of the study was to investigate the relationship between different clinical and dosimetric factors contributing to the development of radiation induced pneumonitis (RP) as well as its possible influence on patients' survival.
Materials and Methods: Data from 103 consecutive patients with non-small-cell lung cancer (NSCLC) receiving curative radiotherapy (RT) from 2007 to 2009 were analysed. RP was graded by CTC version 3.3. Median follow-up was 16 months. The clinical and dosimetric parameters related to RP were analysed using SPSS. Median age was 66 (43 to 81); 55% were male, 47% had adenocarcinoma, while 34% had squamous cell carcinoma;

69% had co-morbidity and 20% had chronic lung disease. FEV_1 range was 0.84−4.1 L. 36% had weight loss prior RT. 33% were current smokers.
Results: A total of 47 (46.6%) had radiological changes only (CTC grade 1) while 18 patients (17.5%) presented neither clinical nor radiological signs of PR. Mild RP was observed in 21 patients (20.4%) and moderate to severe RP was observed in 16 patients (15.5%) including one death due to RP. Radiological changes were observed in 76 patients, in 59 patients these CT changes were confined to radiation field, while17 patients had out-of-field RP. Median time from RT start to the onset of symptoms was 4.5 months (CI 95% 4.2−4.9). All the severe RP incidents occurred in the first 6 months and 50% of patients with severe RP symptoms were dead at 6 months. The median OS of this group was 12 months, which was significantly lower then OS for patients with no/mild/moderate RP symptoms (21 months) ($p = 0.004$). Median overall survival for the whole group was 18 months (CI 95% 13−23). Among dosimetric factors, mean lung dose was significantly associated with the incidence of severe RP ($p = 0.03$ Fisher's exact test). Clinical factors, such as weight loss, co-morbidity and lung dysfunction did not show the significant association, but the trend was towards severe RP.
Conclusion: Severe RP is a significant side effect of curative RT and in some cases it can be potentially lethal. The incidence of severe RP in our study is similar to other published data. The mortality rate of NSCLC patients with severe RP is extremely high. Further studies on methods to reduce the lung toxicity are need.

9047 POSTER

Stage IIIa and IIIb NSCLC Treated With Sequential Chemo-radiotherapy Using Helical Tomotherapy

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Background: Despite of concomitant chemo-radiotherapy is considered the standard of care of locally advanced NSCLC, a large part of patients with IIIa-IIIb NSCLC at the time of diagnosis is not suitable of combined modality treatment. Aim of this study is to investigate the impact of Helical Tomotherapy in the sequential radiation treatment of locally advanced NSCLC.
Materials and Methods: At the Department of Radiation Oncology of S.Camillo-Forlanini Hospital, 30 consecutive patients with diagnosis of stage IIIA or IIIB NSCLC were treated with Helical Tomotherapy. Induction chemotherapy with a platinum-containing doublet or triplet was administered before radiotherapy for at least three cycles in all patients. After the chemotherapy a FDG-PET-TC was performed, in order to stage the disease and to define CTV in planning radiation treatment. The treatment was performed using the TomoTherapy HiArt II system (Tomotherapy Inc., Madison, WI) a new modality of combined image-guided and Intensity-Modulated Radiation Therapy. Mean radiation prescription to the PTV dose ranged from 64.5 to 68.4 Gy in 30 fractions with 2.15–2.28 Gy per fraction.
Results: Median follow-up was 10 months (range 6−20). Toxicity was evaluated using EORTC/RTOG scoring system: 21 patients experienced G1 and 7 G2 acute oesophagitis; 2 patients experienced G2 pneumonitis treated with pharmacological therapy. At the first follow-up, only one patient presented distant relapse (brain metastases); 15 patients presented stable disease, 12 partial and 2 complete response. Six months after the end of radiotherapy, 8 patients had complete local response, 13 stable disease and 8 local progression or metastatic disease.
Conclusions: Highly conformal radiotherapy techniques, such as Helical Tomotherapy, will be necessary to achieve significant dose-per-fraction escalation without morbidity. Attempts have been made to increase local control increasing total radiation dose.
Helical Tomotherapy allows to obtain good local control of disease with low toxicity in the treatment of locally advanced NSCLC.

9048 POSTER

Intratumoral Rapid Arc Boost Using PET/CT Delineation in Non-small Cell Lung Cancer

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Purpose: Lung tumours with high fluoro-deoxy glucose (FDG) uptake on PET/CT scans tend to have a more aggressive clinical course than those with a low metabolic rate and therefore may benefit from dose-escalation. The goal of this study was to assess the feasibility of delivering an intratumoral boost to a PET/CT-defined high SUV region using Rapid Arc (RA).
Materials and Methods: RA plans were created for 10 computer tomography (CT) data sets from patients previously treated with 3D-conformal radiotherapy (3D-CRT) for stage III non-small cell lung cancer to a dose of 60 Gy/30 fractions. Using PET/CT fusion with the CT data sets, a gross tumour volume boost (GTV_{boost}) was outlined based on 50% of the maximum standardized uptake value (SUV 50%max), while gross tumour volume (GTV) was defined as tumour volume with SUV $\geqslant$2.5. Planning tumour volume (PTV) was generated with GTV + 1 to 1.5 cm margin. The PTV was planned to receive 60 Gy/30 fractions and a simultaneous boost of 66 Gy-70 Gy/30 fractions was given to the GTV_{boost} with organs at risks (lungs, esophagus, spinal cord, heart, and brachial plexus) limited by the QUANTEC guidelines. The parameters evaluated included the doses to organs at risk and tumour volume parameters.
Results: RA technique was able to meet the assigned dose constraints to normal critical structures, while boosting the GTV_{boost} to >66 Gy. Average of the maximal SUV was 14.7 (4.6–19.9). The ratio of the GTV_{boost}/GTV was 26.6% (12.7–51.1%). The average mean dose to the PTV (volume excluding the GTV_{boost}) was 61.4 Gy (60.0–62.9 Gy) and to the GTV_{boost} was 68.7 Gy (67.2–71.1 Gy). The average V_{20} for the lungs was 22.1% (17.7–28.9%) and mean lung dose was 14.1 Gy (11.2–16.8 Gy). Mean doses to the esophagus and heart were 25.9 Gy (14.9–32.7 Gy) and 7.7 Gy (1.3–22.3 Gy), respectively. Maximal doses to the brachial plexus and spinal cord were 39.8 Gy (2.2–66.0 Gy) and 41.4 Gy (20.6–48.6 Gy), respectively.
Conclusion: The use of RA with intratumoral boost based on high FDG uptake is a feasible technique. It achieves a higher tumour dose while respecting the QUANTEC dose guidelines. Future analysis will examine tumour control probability and equivalent uniform doses.

9049 POSTER

Patterns of First Failure After Concurrent Chemoradiotherapy With Accelerated Hyperfractionation for Limited-stage Small Cell Lung Cancer

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Background: To retrospectively evaluate the patterns of first failure after concurrent-chemoradiotherapy (C-CRT) with accelerated hyperfractionation (AHF) for limited-stage small cell lung cancer (LS-SCLC).
Materials and Methods: Patients with LS-SCLC diagnosed between January 2006 and May 2010 at our institution were retrospectively recruited from our database. C-CRT consisted of 4 cycles of cisplatin/etoposide repeated every 4 weeks, with 30 fractions of twice daily radiotherapy of 45 Gy. Up to 30 Gy, radiotherapy was delivered to the primary tumour, metastatic lymph nodes and regional lymph nodes as elective nodal irradiation (ENI) except supraclavicular region. A booster dose of 15 Gy was delivered to the primary tumour and metastatic lymph nodes. To patients who responded to C-CRT, prophylactic cranial irradiation (PCI) of 25 Gy in 10fractions was performed. We assessed the patterns of first failure after CRT. First failure sites were detected by radiological imaging and classified into 4 categories; A: primary tumour and/or metastatic lymph nodes, B: regional lymph nodes within ENI field, C: supraclavicular region, D: distant metastases.
Results: 49 patients were included in this analysis. Their characteristics were as follows: median age, 69 years; male/female, 39/10; T1/T2/T3/T4, 19/20/0/10; N0/N1/N2/N3, 0/11/33/5. The median follow-up period for the surviving patients was 18.6 months. Complete response or partial response was achieved in 48 patients and only 1 patient had progressive disease. PCI was delivered to 35 patients. At the last follow-up, 17 patients achieved progression-free survival. The median progression-free and overall survivals were 11 months and 26 months, respectively. First failure sites among the remaining 32patients are shown in Table 1.
Conclusion: In our analysis, a most frequent first failure site was category D:distant metastases and there was no incidence of first failure in category B: regional lymph nodes within ENI field. This analysis suggests that reduction of distant metastasis may be one of the ways to improve survival. Reduction of local recurrence and necessity of ENI to improve survival is controversial.

Table 1. Patterns of first failure

Category	Patients
Progression-free	**17/49**
First failure	**32/49**
A: primary tumour and/or metastatic lymph nodes	11/32 (34%)
with distant metastases	8/11
B: regional lymph nodes within ENI field	0/32 (0%)
C: supraclavicular lymph nodes	2/32 (6%)
with distant metastases	1/2
D: distant metastases	28/32 (87%)