# Radiotherapy

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## SUMMARY OF PRESENTATIONS

### Positron Emission Tomography/Computed Tomography as Early Response Marker for Chemoradiation for Stage III NSCLC

Dr. Wally Curran discussed whether positron emission tomography-computed tomography (PET-CT) is sufficiently robust to use as an earlier marker of benefit in patients with locally advanced non-small cell lung cancer (NSCLC) because survival outcomes require a greater than 2-year patient follow-up period. Currently, FDG-PET-CT is used as a diagnostic aid for the workup of pulmonary nodules, staging utility for the mediastinum, and staging for distant metastases. ACRIN 6668/RTOG 0235 addresses the role of FDG PET scan to predict outcomes in patients with locally advanced NSCLC treated with chemoradiation. In this study, 235 patients with locally advanced NSCLC underwent pretreatment FDG-PET, then concurrent chemoradiation, followed by repeat FDG-PET 12 to 16 weeks after the completion of radiation. Central review of the mean $SUV_{peak}$ was highly correlated. Median SUV values dropped from 9.4 (pretreatment) to 2.5 (posttreatment). More follow-up is needed before one could discern the utility of posttherapy FDG PET in predicting outcomes. Kong et al. evaluated midcourse FDG-PET (40–50 Gy) and post-RT PET, which showed a trend toward improved PFS if SUV during RT less than 3.0.[1] A follow-up study has been proposed: pretreatment FDG-PET, followed by concurrent chemoradiation to 44 Gy. A midcourse FDG-PET would be performed. If the patient had progressive disease, the patient would be taken off study and discontinue radiation. If the patient demonstrated stable disease or response, they would be randomized to continue radiation to 64 Gy or radiation to 64 Gy, then followed by a 10-Gy boost based on the results of the FDG-PET.

### Combined Modality Therapy with EGFR and Radiation

Dr. Hak Choy discussed the results of three trials (SWOG 0023, RTOG 0324, and CALGB 30407) combining EGFR therapy with radiation. The first study SWOG 0023 combined two cycles of cisplatin and etoposide with concurrent thoracic radiation followed by three cycles of consolidation therapy with docetaxel followed by maintenance therapy with gefitinib versus placebo. Unfortunately, the gefitinib arm demonstrated a worse median overall survival compared with placebo (23 versus 35 months, $p = 0.01$). The second study RTOG 0324 combined weekly treatment of paclitaxel, carboplatin, and cetuximab with once daily thoracic radiotherapy followed by consolidation therapy with paclitaxel, carboplatin, and cetuximab. The trial demonstrated a median survival of 22.7 months and 2-year survival of 49.3%. These results were much higher than historical RTOG controls (median survival range, 14.6–17.3 months). The ongoing RTOG 0617 trial uses a four-arm, $2 \times 2$ factorial design with radiotherapy of 60 versus 74 Gy, cetuximab plus chemotherapy (paclitaxel and carboplatin) versus chemotherapy alone to study this concept further. Currently, 209 of an anticipated 500 patients are enrolled. A third study CALGB 30407 combining pemetrexed, carboplatin, and thoracic radiotherapy 6600 Gy ± cetuximab was demonstrated to be feasible and well tolerated. Median survival was 22 months, with a trend of increased survival in patients with nonsquamous histology. Unfortunately, there was no significant benefit to the addition of cetuximab to chemotherapy with maintenance beyond four cycles not being feasible in nearly half the patients enrolled in this study.

### Radiation Therapy and Angiogenesis Inhibitors

Dr. Michael O'Reilly discussed several trials evaluating the combination of radiation therapy and angiogenesis inhibitors. The National Cancer Institute of Canada Clinical trials Group Study BR.20 demonstrated a trend toward improved survival in patients with limited-stage small cell lung cancer treated with chemoradiation followed by vandetanib (ZD6474), a vascular endothelial growth factor (VEGF) and epidermal growth factor receptor agonist.[2] Vandetanib is also currently undergoing a phase I/II study in NSCLC. In the phase I portion, patients will be treated with ZD6474 followed by radiation. In the phase II setting, patients will receive palliative radiation (45 Gy) and ZD 6474, definitive radiotherapy (63 Gy) and ZD 6474 after induction chemotherapy, or definitive radiotherapy (66–70 Gy) and ZD 6474 for stage I inoperable patients.

Enthusiasm for angiogenesis inhibitors combined with radiation has been tempered recently with concern for side effects. Spigel et al. reported tracheoesophageal (TE) fistula in 6 of 35 patients with small cell or non-small cell lung cancer treated with bevacizumab and chemoradiation.[3] In a study of patients with small cell lung cancer treated with irinotecan, carboplatin, bevacizumab, and thoracic radiotherapy, the overall response rate was 88% with four complete responses and 11 partial responses. Nevertheless, two patients developed two TE fistulae (one which was fatal) prompting early closure. In addi-

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tion, there was one death due to aerodigestive hemorrhage and one death due to treatment-related bowel perforation. In a study of patients with non-small cell lung cancer treated with pemetrexed, carboplatin, bevacizumab, and thoracic radiotherapy, two patients developed TE fistulae, again prompting early study closure. Given these adverse effects, antiangiogenic therapies offer great potential, but it is unclear how to optimize their use with radiation therapy.

## Role of Radiation in Small Cell Lung Cancer

Dr. Ritsuko Komaki discussed the role of radiotherapy in small cell lung cancer. In the RTOG 0239, patients with limited stage small cell lung cancer (LS-SCLC) were treated with two cycles of cisplatin and etoposide with concurrent thoracic radiation 61.2 Gy in 1.8 Gy/fraction with 1.8 Gy twice daily boost off cord over 5 weeks. Median survival was 19 months with a 2-year survival rate of 37%. Two grade 5 toxicities (neutropenic sepsis and pneumonia) were reported. Patterns of failure were 20% local recurrence and 44% distant metastases. The current intergroup study CALGB 30610/RTOG 0538 treat patients with LS-SCLC with four cycles of cisplatin and etoposide with concurrent thoracic radiotherapy (45 Gy in 3 weeks with 1.5 Gy twice daily, 61.2 Gy in 5 weeks with Con boost, and 70 Gy in 7 weeks with 2.0 Gy once daily) followed by prophylactic cranial irradiation 25 Gy in 10 fractions. The target accrual is 700 patients, evaluating overall survival and several correlative studies. In addition, prophylactic cranial irradiation should be offered to patients with SCLC who achieve complete response. Future directions include clinical investigation of VEGF receptor or VEGF/epidermal growth factor receptor inhibitors with chemoradiation in patients with SCLC.

## REFERENCES

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