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### 100 Subacute Central Nervous System Morbidity after Proton Therapy and Carbon Ion Therapy Against Head and Neck Cancers and Skull Base Tumors: Impact of Sequential Evaluation by MR Imagings

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**Purpose/Objective(s):** Particle therapy including proton therapy and carbon ion therapy can provide excellent dose distribution because of its physical characteristics. The particle therapy could provide a great advantage to increase tumor doses without increasing normal tissue toxicities of surrounding organs like parotid gland or pharynx. However, especially in the treatment of skull base tumors, certain parts of central nervous system (CNS) such as temporal lobe, brain stem, and cerebrum may not be excluded entirely from irradiated volumes. However, as for subacute or late morbidity of CNS after the particle therapy, there are no reports investigating evaluating sequential evaluation by magnetic resonance imagings (MRI). In this study, we retrospectively reviewed our experience of both the proton therapy and the carbon ion therapy in the Hyogo Ion Beam Medical Center.

**Materials/Methods:** Between May 2001 and December 2005, 16 patients with skull base tumor and 43 patients with head-and-neck cancer with intra cranial invasion were treated with particle radiotherapy. Patient characteristics were as follows; median age: 59 (range, 23–81), male/female: 25/34. Single protocol for proton therapy (65 GyE in 26 fractions using 150 or 190 MeV), and single protocol for carbon ion therapy (57.6 GyE in 16 fractions using 250 or 320 MeV) were employed in the period. Pathologic subtypes of tumor included adenoid cystic carcinoma in 17 patients, chordoma in 9, malignant melanoma in 7, squamous cell carcinoma in 7, olfactory neuroblastoma in 5, adenocarcinoma in 4, meningioma in 3, others in 7, respectively. Among these 59 patients, 43 patients received proton therapy and 16 patients received carbon ion therapy, respectively. Patients underwent MRI every 3 month during the first 2 years and every 3 to 6 month intervals thereafter. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, v3.0) grading system. Incidence rate of adverse event and survivals were estimated with Kaplan-Meier methods.

**Results:** Three (7%) of 43 patients who treated with proton therapy and 5 (31%) of 16 patients who treated with carbon ion radiotherapy had certain degree of MRI findings on CNS necrosis. One (2%) of the patients had some clinical symptoms, such as vertigo and headache (CTCAE Grade 2). The other 7 (12%) patients had no symptoms. Brain injuries were developed 3 to 48 (median, 9) months after proton therapy and 20 to 37 (median, 25) months after carbon ion radiotherapy. Actuarial occurrence rate of grade 1 or greater CNS necrosis at 2 year and 3 year was 7% and 10%, respectively. There was no statistically significant difference between the patients underwent proton radiotherapy and carbon ion radiotherapy.

**Conclusions:** Particle therapies were administered to the patients with skull base tumors or head-and-neck cancers, resulting in minimum symptomatic CNS toxicities. However, our sequential evaluation with MRI detected higher incidence of abnormal intensities. This discrepancy between symptom and MRI as for CNS damage may bring important information for the era of particle therapies. Further accumulation of patients and longer follow-up should be warranted.

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### 101 RTOG 0324: A Phase II Study of Cetuximab (C225) in Combination With Chemoradiation (CRT) in Patients (PTS) With Stage IIIA/B Non-Small Cell Lung Cancer (NSCLC): Correlation Between EGFR Expression and the Patients' Outcome

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**Background:** NSCLC commonly expresses EGFR, which is associated with aggressive tumor behavior and poor clinical outcome. Preclinical models demonstrate radiosensitization following molecular inhibition of EGFR signaling. Cetuximab (C225) is a chimerized monoclonal antibody that targets the epidermal growth factor receptor (EGFR).

**Materials/Methods:** Patients with stage III NSCLC, performance status  $\leq 1$ , weight loss  $\leq 5\%$  over past 3 months were treated with C225 (400 mg/m<sup>2</sup>) on day 1 of week 1, then weekly doses of C225 (250 mg/m<sup>2</sup>) until completion of therapy (weeks 2–17). During week 2, patients started CRT (63 Gy/35 fractions) with weekly carboplatin (C) AUC 2 and paclitaxel (P) 45 mg/m<sup>2</sup>  $\times$  6 doses followed by C (AUC 6) and P (200 mg/m<sup>2</sup>)  $\times$  2 cycles (weeks 12–17). Immunohistochemical staining for total EGFR protein was performed from paraffin sections. The parameters measured were the mean optical density (MOD) measured over the labeled areas within the tumor, the staining index (SI; proportion of stained area relative to total area of the structures), and the Quick Score (QS) (QS = MOD  $\times$  SI/100). The QS was correlated with patients' outcome.

**Results:** Ninety-three patients were accrued between March, 2004, and June 3, 2005, 87 of whom were evaluable for analysis. Though not mandatory, tumor specimens were collected from 51 (59%) of the evaluable patients for correlative studies. Pretreatment characteristics were not significantly different between patients who had EGFR data (E group) and those without tissue or were not evaluable for EGFR (n = 36, 41%) (NE group). However, NE group had significantly lower overall survival (OS) than E group [HR = 2.25,  $p = 0.008$ ]. The 18 month OS for E group for EGFR data was 68.5% compared to 34.4% in NE group for EGFR (log-rank  $p$ -value = 0.008).

Among E group, no difference was seen in OS by EGFR QS dichotomized using the median, 0.652 [HR = 1.72 (0.69, 4.31),  $p = 0.238$ ]. The 18 month time to progression (TTP) failure rate for the patients with EGFR QS  $\leq 0.652$  was 46.2% compared to 52.5% in those patients where EGFR QS  $>0.652$ . Patterns of failure have shown that 33% of patients with EGFR QS  $\leq 0.652$  had a primary failure only compared to 46% in patients with EGFR QS  $>0.652$  ( $p = 0.69$ ). In contrast, 42% of patients with EGFR QS  $\leq 0.652$  had a metastases failure only compared to 31% in patients with EGFR QS  $>0.652$  ( $p = 0.69$ ).

**Conclusions:** The evaluable group for EGFR data appears to be a favorable subset, which might be related to the investigators motivation. However there was no significant difference in the OS and TTP depending on the QS in patients who received RT in combination with carboplatin, paclitaxel, and cetuximab. Patterns of failure have shown that patients with lower EGFR QS had less primary failure, but more metastasis compared to patients with higher EGFR QS. The data suggest that higher expression of EGFR patients need more locally oriented treatment and lower expression of EGFR patients require more systemic treatment to reduce distant metastasis.

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## 102 PET-based Assessment of Local Failure Patterns in Non-Small Cell Lung Cancer (NSCLC) Treated With Definitive Radiotherapy

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**Purpose/Objective(s):** To assess the pattern of local failure using post-RT FDG-PET scans in patients with NSCLC stage I-IIIb treated with definitive radiotherapy whose GTV's were defined with the aid of pre-RT PET data.

**Materials/Methods:** Between 2001–2005 230 NSCLC patients were treated with involved-field RT to a dose range of 50–90 Gy at our institution. 82 of these patients were found to have local failure. A total of 26 patients with a post-RT PET/CT scan that could be registered with the treatment planning CT scan were analyzed. After registration recurrences were contoured based on a fixed threshold of 42% max SUV. Patterns of failure were visually scored by 3 independent observers and defined as follows: (1) within the gross tumor; (2) at the margin of the tumor volume; (3) marginal miss; and (4) geographic miss. Local failure was also evaluated as originating from nodal areas versus the primary tumor. The fraction of recurrence volume overlapping the PTV was measured to objectively confirm the results.

**Results:** 26 patients with 34 lesions were analyzed. Patient characteristics were as follows: median age 69 years; 12 (46%) stage I/II and 14 (54%) stage IIIA/IIIB; median dose 72 Gy (50–90 Gy); median follow-up 20 months; median time to local failure 13 months. Failures were scored based on the 4 definitions stated above and are reported in Table I. All patients had a recurrence originating from their primary tumor (n = 26) with the remaining 8 lesions (24%) in nodal areas. Of the 8 nodal failures, 5 (63%) were marginal or geographic misses as opposed to only 1/26 (4%) of the primary recurrences ( $p = 0.001$ ). If the primary tumors received a dose of  $<60$  Gy, 6/8 (75%) failures were within the gross tumor and 2/8 (25%) were at the margin of the gross tumor. If the primary tumor received a dose of  $\geq 60$  Gy then the failure patterns changed, with 6/18(33%) within the gross tumor, 11/18 (61%) at the margin of the gross tumor, and 1/18 (6%) a marginal miss ( $p < 0.05$ ).

**Conclusions:** At low doses ( $<60$  Gy) the pattern of primary recurrences was mostly within the gross tumor indicating insufficient dose for tumor control. The pattern of primary recurrences at higher doses was mostly at the margin of the gross tumor suggesting an inadequacy in target delineation, GTV-PTV margin, and/or need for tumor motion control. Nodal recurrences were mainly marginal or geographic misses. This analysis suggests that visual incorporation of PET data at the time of treatment planning for initial GTV delineation may be inadequate and more sophisticated approaches of registration should be evaluated to better determine the role of PET in target definition for NSCLC.

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## 103 Quality of Life (QOL) Supercedes the Classic Predictors of Survival in Locally Advanced Non-Small Cell Lung Cancer (NSCLC): An Analysis of Radiation Therapy Oncology Group (RTOG) 9801

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**Purpose/Objective(s):** This analysis was conducted to determine the added value of QOL as a prognostic factor for overall survival (OS) for patients (pts) with locally advanced NSCLC treated on RTOG 9801.