randomized and treated with either vehicle or ABT-737 (50 mg/kg, i.p., daily) for 3 days. Then mice underwent microCT and were irradiated in the left lung at a dose of 20 Gy using X-rad 320. In 2 weeks, 2nd round microCT was performed and lungs were harvested for histological analysis.

Results: When the changes in the expression of pro-apoptotic and anti-apoptotic molecules after 20 Gy of irradiation were evaluated by immunoblotting, the decrease of BCL2-like 11 (BCL2L11) was most prominent in the irradiated lung. The tumor area was decreased in the irradiated lung of both vehicle and ABT-737 pretreated mice and inhibitory effect was remarkable when the mice were pretreated with ABT-737. Disputed tumor structure with apoptotic bodies were most frequently observed in the irradiated lung of ABT-737 pretreated mice. To quantify the apoptotic effect of this combination, immunohistochemical analysis against activated caspase-3 was performed. Counts of activated caspase-3 were significantly higher in the irradiated lung with ABT-737 pretreatment, suggesting ABT-737 possesses radiosensitizing property.

Conclusion: Decrease of BCL2L11 expression in the irradiated lung is one of prominent findings, which might compromise therapeutic effect of radiation. Pretreatment of ABT-737 enhanced anti-tumor effect of ionizing radiation in Kras:p53$^{fl/fl}$ lung cancer model, suggesting BH3 mimetics would be a good candidate of radiosensitizer in lung cancer. Further studies are warranted for identification of optimal dosing and schedule of this combination treatment.

Keywords: apoptosis, radiosensitizer, BH3 mimetics, ABT-737

P2.05-005
Mechanism of Radiotherapy in Reduction/Delay of T790M-Mediated EGFR TKI Resistance

Topic: Biology

Yasi Xu,[1] Shirong Zhang,[1] Bing Xia,[2] Lucheng Zhu,[3] Shenglin Ma[4] *[1]Center for Translational Medicine, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou/China, [2]Department of Radiation Oncology, Hangzhou Cancer Hospital, Hangzhou/China, [3]Department of Radiation Oncology, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou/China, [4]Department of Oncology, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou/China*

Background: EGFR T790M mutation accounts for more than 50% of acquired resistance to TKI. In pre-clinical, EGFR-TKI resistant cells with T790M exhibited enhanced sensitivity to radiation, suggesting the potential of radiotherapy in reduction and delay of T790M-mediated EGFR TKI resistance.

Methods: Under different radiotherapy dose and times, we use droplet digital PCR to observe the emerging time of T790M and its proportion during chronic exposure to gefitinib in TKI-sensitivity cell lines, and to evaluate the anti-tumor effect of early radiation combined with gefitinib in xenograft model with different proportion of T790M. Furthermore, we performed miRNA microarray to screen miRNAs differentially expressed in the paired NSCLC gefitinib-sensitivity cell lines and gefitinib resistant cell lines and find potential molecular markers of T790M mutation.

Results: Our data showed radiation combined with gefitinib delayed the occurrence of EGFR T790M mutation compared to gefitinib alone in T790M wild type (TKI-sensitive) cell line and it also reduced the T790M mutation abundance in de novo T790M mutation (TKI-resistant) cell line. The phenomena was also confirm in mice xenograft model. In addition, our results showed TKI-resistant (induced T790M mutation) cells had higher radiosensitivity than TKI-sensitive cells. miRNA array showed miR-1275 was the one of the most significantly elevated miRNAs in TKI-resistant cells. Knockdown of miRNA-1275 significantly decreased the radiosensitivity of TKI-resistant cells. Western blot showed knockdown of miR-1275 affected proteins relating to cell proliferation and apoptosis. Bioinformatics showed SPOCK1 might be one of the targets of miRNA-1275.

Conclusion: Our results contribute to understand molecular mechanisms of T790M-mediated EGFR-TKI resistance, but also provide a new therapeutic strategy for patients in advanced NSCLC to aid expansion of the effectiveness of TKI treatment through radiotherapy.

Keywords: EGFR-TKI, Acquried resistance, radiation, T790M

P2.05-006
Radiotherapy as Definitive Treatment in Patients Aged 70 Years and Older with Non-Small Cell Lung Cancer

Topic: Clinical Outcome

Sureyya Sarihan,[1] Türkkan Evrensel,[2] Deniz Sigirli[3] *[1]Radiation Oncology, Uludag University, Faculty of*

Medicine, Bursa/Turkey, [2]Medical Oncology, Uludag University, Faculty of Medicine, Bursa/Turkey, [3]Biostatistics, Uludag University, Faculty of Medicine, Bursa/Turkey

Background: The factors affecting survival were evaluated in patients aged ≥ 70 years with non-small cell lung cancer (NSCLC) treated with definitive radiotherapy (RT).

Methods: Between January 1996 and April 2012, 52 patients were treated. The median age was 73 (range: 70-80), 73% and 75% of patients with stage III according to AJCC 2002 and 2010, respectively. Radiotherapy was performed median 6160 cGy (range: 3600-6660) and chemotherapy (CHE) were given 75% of the patients as neoadjuvant, concurrent or adjuvant. Statistical analyses were calculated with Kaplan-Meier and Cox regression methods.

Results: Median follow-up was 12.5 months (range: 2.5-103). Median overall (OS), disease-free (DFS) and locoregional-progression-free (LRPFS) survival were 22 (95% CI 12-31), 18.5 (95% CI 7-29) and 25 months (95% CI 15-34), respectively. Two-year OS, DFS and LRPFS rates were 50%, 47% and 52%, respectively. Acute ≥ Grade 3 esophagitis and neutropenia were seen 6% and 10% of patients. Whereas the mortality associated with CHE were seen of 5 (10%) patients, RT-related death was not observed. In univariate analysis; AJCC 2002 stage I-II (72.5 vs 20 months, $p = 0.05$), RT dose ≥ 60 Gy (27.5 vs 12.5 months, $p = 0.01$), RT duration >49 days (31 vs 11 months, $p < 0.001$) for OS and RT dose ≥ 60 Gy (25 vs 11 months, $p= 0.02$), RT duration >49 days (26.5 vs 10.5 months, $p <0.001$) neoadjuvant CHE ≤ 3 cycles (mean 58 vs 19 months, $p = 0.03$), complete response (72.5 vs 18.5 months, $p = 0.03$), ≥ 4 cycles of CHE (25 vs 11 months, $p = 0.05$) for DFS were significant. In multivariate analysis, RT duration > 49 days were found a positive impact on OS (HR: 3.235, 95% CI: 1:25 to 8:32 $p = 0.01$).

Conclusion: Definitive and palliative RT plays an important role in elderly lung cancer patients have multiple co-morbidities with limited treatment options. In our study, elderly patients with NCSLC can be given ≥ 60 Gy without complications and was seen positively impact on survival.

Keywords: survival, non-small cell lung cancer, Elderly patients, Radiotherapy

P2.05-007
Outcomes after Stereotactic Body Radiothrapy/Proton Beam Therapy or Wedge Resection for Stage I Non-Small-Cell Lung Cancer

Topic: Clinical Outcome

Yasuhisa Ohde,[1] Hideyuki Harada,[2] Shoko Hayashi,[1] Kiyomichi Mizuno,[3] Yoshiyuki Yasuura,[1] Reiko Shimizu,[1] Hiroyuki Kayata,[1] Hideaki Kojima,[1] Shoji Takahashi,[1] Mitsuhiro Isaka,[1] Toshiaki Takahashi,[4] Shigeyuki Murayama,[2] Tetsuo Nishimura,[2] Keita Mori[5] *[1]Thoracic Surgery, Shizuoka Cancer Center, Shizuoka/Japan, [2]Radiation and Proton Beam Therapy Center, Shizuoka Cancer Center, Shizuoka/Japan, [3]Shizuoka Cancer Center, Shizuoka/Japan, [4]Thoracic Oncology, Shizuoka Cancer Center, Shizuoka/Japan, [5]Clinical Research Center, Shizuoka Cancer Center, Shizuoka/Japan*

Background: Recently, excellent results of stereotactic body radiotherapy (SBRT), proton beam therapy (PBT) for stage I non-small-cell lung cancer (NSCLC) have been reported, however any phase III trial comparing SBRT and surgery have not been completed yet. The aim of this study is to compare outcomes between SBRT, PBT and wedge resection (WR) for patients with peripheral stage I NSCLC who intolerable for anatomical resection, and analyze prognostic factors in this population.

Methods: We retrospectively compared overall survival (OS), local recurrence rate (LRR), relapse-free survival (RFS) and cause-specific survival (CSS) between WR (n=172) and SBRT / PBT (n=188) for pathologically proven clinical stage I NSCLC in our institute from 2002 to 2015. Patients underwent WR were all high risk patients who intolerable for anatomical resection and achieved complete resection without any adjuvant therapy. Of radiation group (RT: SBRT+PBT), 56% was medically inoperable, with 44% refusing surgery. SBRT; 60 Gy in 8 fractions, PBT; 60-80 GyE in 10-20 fractions was prescribed. Propensity score matching was used to adjust the confounding effects in estimating treatment hazard ratios. 59 WR patients and 59 radiotherapy (RT) patients (SBRT 27, PBT 32) were matched blinded to outcome (1:1 ratio). There are 70 men and 48 women, median age was 81, and median follow-up period was 39 months.

Results: 3, 5 - year overall survival (OS) of WR and RT was 84.5%, 70.8% vs 89.7%, 59.6% (p=0.802), respectively. 3-year LRR, RFS, CSS were 94.7% vs 95.9%