981 POSTER DISCUSSION 1

Lung cancer after breast cancer: The role of radiation therapy and smoking

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The joint effects of cigarette smoking and ionizing radiation in primary lung cancer following breast cancer remain unresolved. We conducted a case-control study to further examine lung cancer risk associated with radiation therapy (XRT) and smoking among breast cancer patients at The University of Texas M.D. Anderson Cancer Center (MDACC). Cases (n = 280) were women diagnosed with primary lung cancer between 1960 and 1997, were between 30–89 years of age, had a prior history of breast cancer, and were United States residents. Controls (n = 300) were frequency matched to cases on age at diagnosis (in 5 year strata), ethnicity, year of breast cancer diagnosis (in 5 year strata), and had survived at least as long as the latency of lung cancer diagnosis in the cases. We randomly selected controls from 37,000 breast cancer patients evaluated at MDACC during the same time period as the cases. Medical record review yielded smoking information on 93% of cases and 84% of controls. We used stratified analyses to evaluate the main effects of smoking and XRT on risk of lung cancer as well as comparing ipsilateral versus contralateral lung cancer risk. Among cases, 45% received XRT versus 44% of controls. Smoking increased the risk of lung cancer in women who did not receive radiation therapy (OR = 6.0, 95% CI, 3.6–10.1) whereas XRT was not associated with increased risk (OR = 0.1, 95% CI, 0.04–0.2) in women who did not smoke. Overall the odds ratio for both XRT and smoking compared with neither exposure was 16.8 (95% CI, 8.1–34.6) showing a greater than multiplicative effect. Also, for the ipsilateral lung (OR = 24.4, 95% CI, 9.0–66.4) and contralateral lung (OR = 10.4, 95% CI, 4.2–25.8), there was an increased risk for the joint effect. In conclusion, smoking was a significant independent risk factor for lung cancer after breast cancer. Moreover, a greater than multiplicative effect was observed with smoking and XRT combined with the joint effect being especially evident for the ipsilateral lung.

(Supported by National Cancer Institute Grant R25 CA 57730)

982 POSTER DISCUSSION 1

Prognostic value of p53 abnormalities in non-small cell lung cancer (NSCLC)

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We investigated the association of p53 abnormalities (gene mutations, protein overexpression and serum antibodies against p53 protein) with clinical data and prognosis in 74 patients with resected NSCLC. DNA sequencing of the p53 gene showed 34 mutations (45.9%). The IHC study of the p53 protein revealed that 41 (55.4%) samples had positive staining. 17 (23%) of 74 analyzed patients had positive result of the serum p53 antibodies (p53-Abs) by ELISA test.

We found strong agreement between results of the p53 protein expression test (p53-PE) and the p53 gene mutation test (p53-M) [Cohen's Kappa: kappa = 0.65, 95% c.i.: (0.48, 0.82)]. Joint distribution of the results was mainly influenced by histological type of tumor. In the multivariate analysis (Cox's model) positive result of the p53-M test significantly increased relative risk for both overall (RR = 9.56; 95% c.i.: (2.62, 34.87); $p < 0.001$) and disease-free survival (RR = 11.64; 95% c.i.: (3.10, 43.37); $p < 0.001$). When result of the p53-M test was accounted for, positive result of the p53-PE and p53-Abs tests did not offer any additional prognostic information. However, when result of the p53-M test was removed from the model, positive result of the p53-PE and p53-Abs tests became a significant unfavorable prognostic factor for both overall ($p = 0.009$) and disease-free survival ($p = 0.005$).

983 POSTER DISCUSSION 1

Assessment of variations in contouring volumes in lung cancer – Evaluation of a treatment planning protocol

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Purpose: A planning protocol for conformal radiotherapy of lung cancer was adopted at the UHR, with mediastinal clinical target volumes (CTV) based upon surgical nodal regions (Naruke 1978). This study was performed to evaluate compliance with the protocol, and to study variations between clinicians.

Methods: 6 radiation oncologists (RO) contoured the GTV and/or CTV, and PTV in 3 patients with non-small cell lung cancer (NSCLC) on 2 separate occasions. The patients had a well circumscribed peripheral (T1N0) tumour (pt.A), a poorly circumscribed T2N0 tumour (pt.B), and a stage III (T2N2M0) lesion (pt.C), respectively. Detailed diagnostic radiology reports were provided. Contours were directly entered into a 3D planning system (Cadplan ver 2.7.9). PTV's were also generated using a 3D margin programme.

Results: Significant inter-RO variations were observed in contouring target volumes, including pt.A, and these were greater than intra-RO differences. In all patients, the PTV derived using a 3D margin programme was larger than the manually contoured PTV. The BEV plots revealed significant inter-RO variations in the choice of the cranial and caudal extent of the mediastinal CTV. The observed variations did not correlate with experience and workload of RO's.

Conclusion: Despite the use of a standard protocol, significant variations exist in contouring target volumes in NSCLC. Measures to decrease such variations must be incorporated into routine clinical practice and in multicentre trials. 3D software tools appear superior in generating adequate PTV's.

984 POSTER DISCUSSION 1

A meta-analysis of the role of etoposide (VP16) and cisplatin (CDDP) in small cell lung cancer (SCLC) with a methodology assessment

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Purpose: We performed a meta-analysis in order to evaluate the influence of chemotherapy including CDDP and/or VP16 on survival in patients with SCLC.

Methods: Randomised trials published between 1980 and 1998 were selected. Trials methodology was assessed by the Chalmers and ELCWP scores. For each trial, we estimated the hazard ratio (HR) of the survival distributions on the basis of reported statistics or by extracting, from the survival graphical representations, the data required to construct the difference between expected and observed numbers of events as calculated in the logrank statistic. A combined hazard ratio was obtained by the Peto method (<1 meaning a benefit for CDDP and/or VP16).

Results: 36 eligible trials were classified into 4 groups; I: CDDP versus no CDDP (n = 1); II: VP16 (without CDDP) versus no VP16 (n = 17); III: CDDP/VP16 versus no CDDP/VP16 (n = 9); IV: CDDP/VP16 versus VP16 (n = 9). Overall median Chalmers and ELCWP scores were respectively 50.3% and 63.7% ($r_s = 0.76$, $p < 0.001$). There was no significant difference in quality between the 4 groups. The number of eligible patients did not have a significant impact on the scores as well as the trials "positivity" and the year of publication. Combined hazard ratios with 95% confidence intervals were respectively for groups I, II, III and IV: 0.70 (0.41–1.21), 0.73 (0.67–0.78), 0.57 (0.51–0.64) and 0.74 (0.66–0.83).

Conclusions: After performing a qualitative evaluation, this meta-analysis shows that the use of CDDP and/or VP16 has a significant impact on survival in patients with SCLC. These results have to be confirmed by prospective randomised trials.