行政院國家科學委員會專題研究計畫  期中進度報告

B型肝炎帶原病人發生放射線引起肝臟病變的體內體外致病模式研究

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□ 赴國外出差或研習心得報告一份
□ 赴大陸地區出差或研習心得報告一份
□ 出席國際學術會議心得報告及發表之論文各一份
□ 國際合作研究計畫國外研究報告書一份

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Abstract

To integrate the biological factor into the parallel-architecture normal tissue complication probability (NTCP) model for describing radiation-induced liver disease (RILD) in patients with three-dimensional conformal radiotherapy (3DCRT) for gastrointestinal cancers. From 1993 to 2001 a total of 151 patients (89 with hepatocellular carcinoma and 62 with gastric cancer) underwent 3DCRT to part of liver were included in this study. The isocenter dose ranged from 33.0 to 66.0 Gy (mean: 48.0 Gy). Dose distribution and the corresponding volumetric data were obtained from the computerized planning system. A complication (RILD) was defined as grade 3 or higher RTOG liver toxicity within 4 months after completing 3DCRT. Patient-related and dosimetric factors were tested for their correlation with RILD in univariate and multivariate analyses. A maximal likelihood analysis was used to yield the best estimates for the NTCP model parameters of the whole group and the subgroups. Patients were divided by statistically significant non-dosimetric factors, which were integrated into the modeling process for better describing the occurrence of RILD. Goodness of fit analysis was used to estimate the deviance of NTCP model parameters between the subgroups. Twenty-five of 151 patients developed RILD. HBV carrier (p<0.001) was the only independent factor with statistically significant susceptibility to RILD in multivariate test. The 4 parallel NTCP model parameters, mean functional reserve (v50), width of functional reserve distribution (σ), dose at which half of liver subunits are...
damaged \((d_{1/2})\), slope parameter for subunit dose response \((k)\), were 0.54, 0.14, 50Gy, 0.18 (whole group); 0.53, 0.07, 50Gy, \(4 \times 10^{-7}\) (HBV carriers); 0.59, 0.12, 25Gy, 59.8 (non-HBV carriers), respectively. In comparing HBV carrier group with non-HBV carrier group, the goodness of fit deviance with the parameter set from one group would have been worse in the other group. For patients with complication in both subgroups, all of them had their fraction of liver damaged \((f) > 0.4\), as compared to a wider distribution in the whole group. The observed RILD can be better described with a parallel-architecture NTCP model in the subgroups of non-HBV carriers and HBV carriers, with a threshold effect of \(f > 0.4\). The main difference between HBV carriers and non-carriers is in the slope parameter for subunit dose response. The non-dosimetric biological impact on RILD may limit the risk prediction power of parallel model, and needs to be stratified before the modeling parameterization.

**Keywords**: Radiation-induced liver disease, Normal tissue complication probability, Hepatitis B virus, Parameterization.

二、計畫緣由與目的

Radiation-induced liver disease (RILD) has been one of the most serious complications in patients with hepatic malignancies undergoing three-dimensional conformal radiotherapy (3DCRT). Both clinical and dosimetric indicators are used to predict the occurrence of RILD. Normal tissue complication probability (NTCP) models, including Lyman NTCP model and parallel-architecture NTCP model, were tested to calculate the risk of radiation related complications. Parallel-architecture NTCP model plays the certain roles in describing the radiation induced parallel-type organ damage. Non-dosimetric biological factors were found to have the impact on NTCP parameterization. Our previous data showed the feasible application of Lyman NTCP method in patients with RILD, with the biological integration into the modeling process. This study is to investigate the usefulness of and biological impact on parallel-architecture NTCP model in our patients with hepatocellular carcinoma (HCC) or gastric carcinoma (GC) undergoing 3DCRT and developing RILD.

三、結果與討論

Twenty-five of 151 patients developed RILD after 3DCRT, including 17 patients with HCC and 8 patients with GC. In univariate test, hepatitis B viral (HBV) carrier status (22/76 vs. 3/75, \(p<0.001\)), mean liver dose (21.4 Gy vs. 17.5 Gy, \(p=0.006\)), and the volume fraction receiving more than 30Gy (34.6\% vs. 26.6\%, \(p=0.01\)) were the statistically significant factors associated with the occurrence of RILD. In multivariate analysis, HBV carrier status was the only independent factor (hazard ratio=4.02, \(p<0.001\)). Among the 22 HBV carriers who had RILD, serum HBV DNA quantification tests were available in 6 patients during their RILD. All 6 patients showed the serological evidence of viral hepatitis B reactivation (serum HBV DNA >5 pg/ml) at the time of RILD.

The best estimates of the 4 parameters in parallel-architecture NTCP model, \(v_{50}\), \(\sigma\), \(d_{1/2}\), \(k\), were 0.54, 0.14, 50 Gy, 0.18, respectively, for the whole group (151 patients). We divided patients into two groups by HBV carrier status, the statistically significant factor in multivariate test. The parameters were 0.53, 0.07, 50 Gy, \(4 \times 10^{-7}\), respectively, for patients who were HBV carriers. In contrast, the parameters were 0.59, 0.12, 25Gy, 59.8, respectively, for patients who were not HBV carriers.

The partial volume response with the best fit model parameters of the whole group, HBV carriers, and non-HBV carriers were shown. There seemed to be a threshold effect with the partial volume irradiated of 0.4-0.6. The dose response with the parameters of the whole group and the subgroups were shown. The threshold effect was again shown in non-HBV carrier group, but not in HBV carrier group. This difference was derived from the slope parameter difference of
dose-response curves between the two groups. In comparison of the observed complication rate with the fitted cumulative functional reserve, the correlation of complication probability with fraction of liver damaged expected from the model was shown. There appeared the more applicable threshold effects in both subgroups than in the whole group. No patient in both subgroups with fraction damaged less than 0.4 developed RILD.

In the HBV carrier group, the goodness of fit deviance for the estimated HBV parameter set was 90.21 (p>0.95). The deviance (58.73, p<0.2) was much worse when using the non-HBV parameter set in HBV carrier group. Similarly in the non-HBV carrier group, the deviance for the non-HBV parameter set was 102.11 (p>0.99). The deviance (63.0, p<0.3) would have been worse when using the HBV parameter set in the non-HBV carrier group.

In this study we included patients with either HCC or GC. All these patients underwent standard procedure of simulation and dose-volume calculation of the liver, regardless of treatment intent (definitive radiotherapy or post-gastrectomy adjuvant radiotherapy). In spite of the heterogeneity of the combined treatment with radiation (chemotherapy) and the preceding treatment to 3DCRT (chemoembolization) in these two diseases, the clinical observation and the univariate test precluded their adjunct interference in developing RILD. When dividing patients by the non-dosimetric biological factor of HBV carrier status, there existed a big difference in the slope parameter of dose-response curve. It was shown on the steep curve for non-HBV carriers and the shallow curve for HBV carriers. Among the two groups, the fits were proved acceptable for each group itself but were much worse with the estimates from each other. The results revealed that the estimates from parallel-architecture NTCP model were more effective after dividing patients by the non-dosimetric factors. From the rank-plan plots in order of risk of RILD, there showed a threshold of fraction damaged (around 0.4) in the two subgroups. Hence, the threshold was not as clear in the plots of the whole group. This subgroup threshold was consistent with the modeling work by Jackson et al.. This means that the stratification of patients by HBV carrier status improved the parameterization of parallel-architecture NTCP model. However, all but one HBV carrier patient had the fraction damaged of more than 0.4. In contrast, most of the non-HBV carrier patients had the fraction damaged of less than 0.4. The similar thresholds in both subgroups but the distribution difference in fraction damaged partly explained the effectiveness in grouping patients by this non-dosimetric factor, and emphasized the importance in the biological impact on the pathogenesis of RILD.

四、計畫成果自評

In the first year of this 2-year grant we have completed the modeling work of NTCP method. We again found the importance of HBV carrier status in the pathogenesis of RILD. Even with the mathematical model, the unique role of HBV carrier still deserves much attention and implies the biological impact on RILD in these carriers. We started the laboratory work in the pathogenesis of HBV-related RILD near the end of the first year. We believe the findings be really essential for HBV carriers in Asian countries. The research work of this 2-year grant has been based on the planned schedule. We plan to finish the molecular biology study of HBV-related RILD by the end of the second year. The results of this project should be published in at least 2 SCI papers.

五、參考文獻


