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Studies on selective use of proton therapy in primary liver cancers
using Normal Tissue Complication Probability (NTCP) model
(正常組織有害反応発生確率モデルを用いた肝臓がん患者に
対する陽子線治療の選択的適用に関する研究)

Background and Objectives:

Radiotherapy (RT) has been one of the backbone treatments in primary liver cancers (PLC) including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). But radiation-induced liver disease (RILD) remains a dose-limiting complication of traditional liver-directed RT and can lead to deterioration of liver function followed by liver failure and death. With many attempts to improve tumor control and minimize toxicity, modern RT techniques have been emerging but with come at high cost. Proton beam therapy (PBT) has both physical and biological advantages and is effective for PLC. Although randomized controlled trial (RCT) between PBT *versus* standard x-ray treatment (XRT) is expected, there were several obstacles in conducting RCT. Normal tissue complication probability (NTCP) model-based approach is currently captivating as alternative method.

For PLC, NTCP model translates dosimetry of normal liver into estimated risk of RILD. However, clinical factors also influence the radiosensitivity of liver tissue. Therefore, NTCP model considering both clinical and dosimetric parameters in PLC needs to be established. Then, for each patient, risk of RILD is estimated from PBT plan ($NTCP_{PBT}$) and XRT plan ($NTCP_{XRT}$) and compared, $NTCP_{XRT} - NTCP_{PBT}$, referred as $\Delta NTCP$. The patient is eligible for PBT if his/her $\Delta NTCP$ is larger than predefined $\Delta NTCP$ threshold. Nevertheless, there are considerable sources of model uncertainties. Underestimation of $\Delta NTCP$ can lead to the loss of opportunity to benefit from PBT while overly cautious practice might cause unnecessary use. Estimation of uncertainties of NTCP and $\Delta NTCP$ helps improve the reliability of the model-based patient selection strategy for PBT in the general practice.

The aims of our studies are to establish the NTCP model by integrating clinical and dosimetric factors for better prediction of RILD risk and to demonstrate the NTCP model-based approach considering uncertainties of NTCP and $\Delta NTCP$ to improve the clinical implementation of patient selection for PBT.

Materials and Methods:

We studied the methodology to assess uncertainties of NTCP and $\Delta NTCP$ considering variance (var) and covariance (cov) of the model parameters from Lyman-Kutcher-Burman (LKB) NTCP model. Virtual simulated data of 203 patients were generated mimicking a landmark (Michigan) study and classified into 3 types of dataset (individual patient, organized dose-bin and bootstrap dataset) to estimate for LKB NTCP parameters, their var and cov . Different algorithms were used to obtain uncertainties, which was confidence interval (CI), of NTCP and $\Delta NTCP$, namely, Delta method and bootstrapping method.

Subsequently, we collected data of 239 eligible PLC patients and modeled dose-response relationship between mean liver dose (MLD) and grade ≥ 2 liver toxicity according to Common Terminology Criteria for Adverse Events (CTCAE grade ≥ 2 RILT) based on LKB NTCP model. We developed subgroup-specific LKB NTCP models and determined LKB NTCP parameters, their var and cov . Then, the Delta method was used to estimate $\Delta NTCP$ with uncertainty.

Lastly, we introduced the multivariable NTCP model for predicting RILD using 326 patients. The clinical and dosimetric parameters were analyzed using multivariate regression analysis. Final model was reported along with model performance and validation.

Results:

The virtual simulated patient data was a good representative of the Michigan data despite a small difference in MLD. The re-identified model parameters were remarkably comparable to the original ones. The uncertainty of Δ NTCP was determined by Delta method. Our results demonstrated that LKB NTCP model parameters, *var* and *cov*, and Δ NTCP contours derived from dose-bin dataset were very similar to those from individual patient dataset. However, the contours from bootstrapping techniques yielded a little difference which might be due to larger *cov* in bootstrap dataset. Additionally, we proposed that the use of CI-lower boundary (LB) of Δ NTCP provided more conservative threshold compared to central estimate.

From 239 patient data, CP classification was the strongest clinical predictive factor for CTCAE grade $\geq$ 2 RILT, followed by viral hepatitis infection. We stratified patients into 3 subgroups according to CP classification and hepatitis status, i.e., CP-A, nonhepatitis subgroup; CP-A, hepatitis subgroup; and CP-B/C subgroup. Estimated LKB NTCP parameters and NTCP curves were determined for each subgroup. Likewise, Δ NTCP varied between subgroups. CI-LB of Δ NTCP was more conservative in all subgroups.

Finally, we firstly reported the multivariable NTCP model for predicting RILD using relatively large patient cohort. The model consisted of 4 parameters including diagnosis (HCC *versus* ICC), pretreatment CP classification (CP-A *versus* CP-B/C), HBV/HCV infection status (positive *versus* negative) and MLD. The model had good performance and validity. Uncertainty of model parameters (regression coefficients) were reported for further studies.

Discussion:

To assess uncertainties of LKB NTCP and Δ NTCP, we found that Delta method considering *var* and *cov* of model parameters was effective for both individual dataset and dose-bin dataset whereas bootstrapping method was limited by statistical instability and longer computational time. This also suggested the feasibility of using dose-bin dataset for data sharing among institutions.

According to our 239 patients, assuming a different CP classification and hepatitis status, NTCP and Δ NTCP markedly varied indicating different radiosensitivity among patients. This finding suggested the use of subgroup-specific LKB NTCP model and further underlined the differential benefit from PBT between subgroups which may have a potential impact on the decision regarding selective PBT use. In addition, these studies suggested that the CI-LB of Δ NTCP provided more conservative threshold and increased confidence for patient selection for PBT.

More clinical and dosimetric parameters were studied using the multivariable analysis. The 4-variable model consisted of 3 clinical risk features and 1 dosimetric parameter. Patients with 2 clinical risk factors had increased baseline risk of RILD. As a result, treatment plan should be optimized with high respect to MLD based on NTCP model in these patients. For those with all 3 risk factors, RT might not be an appropriate treatment due to very high baseline NTCP value regardless of MLD. The uncertainty of regression coefficients reported in this study would be further analyzed for obtaining NTCP and Δ NTCP uncertainties in our future studies.

Nevertheless, appropriate Δ NTCP threshold as well as proper confidence level for the selective use of PBT is still unknown. Therefore, challenges are to determine the appropriate threshold for identifying patients who would most likely benefit from PBT based on clinical outcomes and cost-effectiveness study.

Conclusion:

NTCP model for predicting RILD was established based on subgroup-specific LKB model and multivariable model. We proposed a clinical decision support using NTCP model-based approach to select patients for PBT and suggested the use of Δ NTCP with uncertainty to improve confidence in decision making.