

## RESEARCH ARTICLE

# Dosimetric predictors and Lyman normal tissue complication probability model of hematological toxicity in cervical cancer patients with treated with pelvic irradiation

Dandan Wang<sup>1</sup> | Yueju Yin<sup>2</sup> | Qichao Zhou<sup>3</sup> | Zirong Li<sup>3</sup> | Xingmin Ma<sup>1</sup> |  
Yong Yin<sup>1</sup> | Baosheng Li<sup>4</sup> | Tong Bai<sup>1</sup> | Dapeng Li<sup>2</sup> | Jian Zhu<sup>1,4</sup>

<sup>1</sup> Department of Radiation Oncology Physics and Technology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, P.R. China

<sup>2</sup> Department of Gynecological Oncology, Shandong Cancer Hospital and Institute Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, P.R. China

<sup>3</sup> Manteia Technologies Co., Ltd, Xiamen, P.R. China

<sup>4</sup> Shandong Medical Imaging and Radiotherapy Engineering Center, Jinan, P.R. China

## Correspondence

Jian Zhu, Department of Radiation Oncology Physics and Technology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, 440# Jiyuan Road, Jinan 250117, Shandong Province, P.R. China.  
Email: zhujian.cn@163.com

Dapeng Li, Department of Gynecological Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, 440# Jiyuan Road, Jinan 250117, Shandong Province, P.R. China.  
Email: drldp@126.com

Dandan Wang and Yueju Yin contributed equally.

## Funding information

The National Natural Science Foundation of China, Grant/Award Number: 82172072; Natural Science Foundation of Shandong Province, Grant/Award Number: ZR2020LZL001; Department of Science and Technology of Shandong Province, Grant/Award Number: 2018GDF118237; Taishan Scholar Foundation of Shandong Province, Grant/Award Number: tsqn201909140; National Key Research and Development Program of China (973 Program), Grant/Award Number: 2016YFC105106

## Abstract

**Purpose:** To identify dosimetric parameters associated with acute hematological toxicity (HT) and identify the corresponding normal tissue complication probability (NTCP) model in cervical cancer patients receiving helical tomotherapy (Tomo) or fixed-field intensity-modulated radiation therapy (ff-IMRT) in combination with chemotherapy, that is, concurrent chemoradiotherapy (CCRT) using the Lyman–Kutcher–Burman normal tissue complication probability (LKB-NTCP) model.

**Methods:** Data were collected from 232 cervical cancer patients who received Tomo or ff-IMRT from 2015 to 2018. The pelvic bone marrow (PBM) (including the ilium, pubes, ischia, acetabula, proximal femora, and lumbosacral spine) was contoured from the superior boundary (usually the lumbar 5 vertebra) of the planning target volume (PTV) to the proximal end of the femoral head (the lower edge of the ischial tubercle). The parameters of the LKB model predicting  $\geq$ grade 2 hematological toxicity (Radiation Therapy Oncology Group [RTOG] grading criteria) ( $TD_{50}(1)$ ,  $m$ , and  $n$ ) were determined using maximum likelihood analyses. Univariate and multivariate logistic regression analyses were used to identify correlations between dose–volume parameters and the clinical factors of HT.

**Results:** In total, 212 (91.37%) patients experienced  $\geq$ grade 2 hematological toxicity. The fitted normal tissue complication probability model parameters were  $TD_{50}(1) = 38.90$  Gy (95%CI, [36.94, 40.96]),  $m = 0.13$  (95%CI [0.12, 0.16]), and  $n = 0.04$  (95%CI [0.02, 0.05]). Per the univariate analysis, the NTCP (the use of LKB-NTCP with the set of model parameters found,  $p = 0.023$ ), maximal PBM dose ( $p = 0.01$ ), mean PBM dose ( $p = 0.021$ ), radiation dose ( $p = 0.001$ ), and  $V_{16-53}$  ( $p < 0.05$ ) were associated with  $\geq$ grade 2 HT. The NTCP (the use of LKB-NTCP with the set of model parameters found,  $p = 0.023$ ; AUC = 0.87),  $V_{16}$ ,  $V_{17}$ , and  $V_{18} \geq 79.65\%$ ,  $75.68\%$ , and  $72.65\%$ , respectively

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Medical Physics* published by Wiley Periodicals LLC on behalf of American Association of Physicists in Medicine

( $p < 0.01$ , AUC = 0.66~0.68),  $V_{35}$  and  $V_{36} \geq 30.35\%$  and  $28.56\%$ , respectively ( $p < 0.05$ ; AUC = 0.71), and  $V_{47} \geq 13.43\%$  ( $p = 0.045$ ; AUC = 0.80) were significant predictors of  $\geq$ grade 2 hematological toxicity from the multivariate logistic regression analysis.

**Conclusions:** The volume of the PBM of patients treated with concurrent chemoradiotherapy and subjected to both low-dose ( $V_{16-18}$ ) and high-dose ( $V_{35,36}$  and  $V_{47}$ ) irradiation was associated with hematological toxicity, depending on the fractional volumes receiving the variable degree of dosage. The NTCP were stronger predictors of toxicity than  $V_{16-18}$ ,  $V_{35,36}$ , and  $V_{47}$ . Hence, avoiding radiation hot spots on the PBM could reduce the incidence of severe HT.

#### KEYWORDS

acute hematologic toxicity, bone marrow, cervical cancer, dose–volume parameter, normal tissue complication probability model

## 1 | INTRODUCTION

Cervical cancer-related morbidity and mortality rates are second and fourth, respectively, among women with cancer worldwide.<sup>1</sup> The standard treatment for locally advanced cervical cancer is concurrent chemoradiotherapy (CCRT) and brachytherapy.<sup>2</sup> However, these treatment options have been reported to culminate in hematological toxicity (HT), which is one of the treatments' most common acute adverse effects, even more so in patients who receive these treatments concurrently than in those who receive radiation therapy (RT) alone.<sup>3,4</sup>

HT is one of the most significant clinical adverse events that could interfere with treatment, prolong the treatment duration, and diminish quality of life, which would impact the survival rate of cervical cancer patients, particularly high-risk patients.<sup>5</sup> Studies have suggested that survival and local control decrease by 1% for each extra day of treatment beyond 55–60 days.<sup>6,7</sup> Therefore, the prediction and prevention of severe HT are critical for survival. A series of other studies have demonstrated that intensity-modulated radiation therapy (IMRT) can be further optimized to decrease the dose of irradiation to the bone marrow (BM) compared to conventional radiotherapy techniques.<sup>8,9</sup> However, severe acute HT during CCRT remains common in clinical practice.

In adults, approximately 51% of the pelvic bone marrow (PBM) is located in the os coxae (22%), sacrum (14%), proximal femora (4%), and lower lumbar spine (11%).<sup>10</sup> These data are indicative of why pelvic radiotherapy causes severe HT. Furthermore, BM activity decreases after treatment with high doses of RT, and its recovery requires a significant amount of time.<sup>11</sup> A previous study suggested that the compensation of unirradiated active BM and the regeneration of irradiated BM are associated with the clinical cumulative dose.<sup>12</sup> It stands to reason, therefore, that HT is linked to the radiotherapy cumulative dose to the pelvic bone; however, tests are needed to verify this claim.

The Lyman–Kutcher–Burman (LKB) model estimates normal tissue complication probability (NTCP) based on a dose–volume histogram (DVH). The Lyman model assumes that there is a sigmoidal relationship between a homogeneous radiotherapy dose within the subunit of the organs at risk (OARs) and the risk of normal tissue complications.<sup>13</sup> The Kutcher–Burman simplified algorithm for DVHs converts a dose evolution DVH of a nonuniform radiation dose distribution in an organ to a partial volume of uniform radiation in that organ at a given reference dose.<sup>14</sup> The LKB model applies the Kutcher–Burman simplified algorithm in the Lyman probit model and is the most widely used model for estimating the NTCP.

The purpose of this study was to identify dosimetry prediction factors for acute HT and identify the corresponding NTCP model in cervical cancer patients receiving helical tomotherapy (Tomo) or fixed-field intensity-modulated radiation therapy (ff-IMRT) with CCRT. To the best of our knowledge, this is the first study to propose NTCP model parameters and for the volume effect of the PBM on cervical cancer patients receiving radiotherapy to predict acute HT.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient characteristics

We enrolled 232 pathologically diagnosed stage IIA–IVA cervical cancer patients per the staging criteria of the International Federation of Gynecology and Obstetrics (FIGO 2009) in this study. All 232 patients—220 with squamous cell carcinoma, 9 with adenocarcinoma, and 3 with adenosquamous carcinoma—were randomly received the Tomo or ff-IMRT radiotherapy; 114 received Tomo; and 118 received ff-IMRT between January 2015 and July 2018. Data were collected and analyzed retrospectively.

The patient, tumor, and treatment characteristics are described in Table 1. Of all 232 patients, the median age

was 53 years, and the Karnofsky performance status (KPS) for all patients was  $\geq 70$ . The majority of patients were diagnosed with stage IIIB disease (159), and 212 (91%) experienced  $\geq$  grade 2 HT. The median radiation prescription dose was 50.4 Gy (45–60 Gy). The average follow-up duration for a blood cell count was 38 days (35–42 days) from the start of radiotherapy, and the number of chemotherapy cycles (cisplatin) was four for all patients.

## 2.2 | BM delineation

For each patient, all pelvic bones on each transverse slice from superior boundary (usually the lumbar 5 vertebra) of the planning target volume (PTV) to the proximal end of the femoral head (the lower edge of the ischial tubercle) were contoured to represent the PBM. The outlines of all pelvic bones (and not the low-density regions within the bones [cancellous substance]) were contoured to reduce dependence on MRI or PET-CT images during the contouring process.<sup>10</sup>

## 2.3 | Radiation therapy

All patients were placed in the supine position with their arms overhead, and a vacuum cushion was used to improve reproducibility during daily treatment. CT scan slices (5 mm thick) were obtained from the T12–L1 interspace to the mid-femur. The images were then directly transferred to a 3D planning system (Pinnacle3 treatment planning system [TPS], Philips Healthcare; or Eclipse TPS, Varian Medical Systems) for contouring and planning. The clinical target volume (CTV) consisted of the cervix, uterus, parametrial/paravaginal tissues, upper one-third the vagina, and pelvic lymph nodes (LNs) (which commonly include the iliac LNs, external and internal iliac LNs, obturator LNs, and anterior sacral LNs).<sup>15–17</sup> To reduce immobilization errors from organ motion and repeated setup, a 0.5 cm margin was uniformly expanded from the CTV in three dimensions and was defined as the planning target volume (PTV). The bladder, small bowel (the entire peritoneal cavity was contoured as a surrogate structure), and rectum were contoured as OARs. Prescription doses were planned for at least 95% of the PTV and 100% of the CTV, with 6-MV x-rays to be administered via the ff-IMRT or Tomo technique. The ff-IMRT plans consisted of 7 ( $0^\circ$ ,  $51^\circ$ ,  $102^\circ$ ,  $153^\circ$ ,  $204^\circ$ ,  $255^\circ$ , and  $306^\circ$ ) or 9 ( $0^\circ$ ,  $40^\circ$ ,  $80^\circ$ ,  $120^\circ$ ,  $160^\circ$ ,  $200^\circ$ ,  $240^\circ$ ,  $280^\circ$ , and  $320^\circ$ ) coplanar beams. Tomo planning parameters were set as follows: jaw width = 2.5 cm or 5 cm, pitch = 0.287, and modulation factor = 1.8–2.4.

Each patient received one or two (sequential boost) treatment courses during the whole radiotherapy session. According to National Comprehensive Cancer Net-

work (NCCN guidelines [2015,  $V_2$ ]), the coverage of a microscopic nodal disease requiring an RT dose was 45 Gy (40–50 Gy), and generally, an additional 10–15 Gy was given for LNs that were significantly enlarged and unresectable by either simultaneous integrated boost (SIB) or sequential boost. An SIB gross target (positive lymph node) was boosted up to 2.2 Gy/fraction, and CTV was 2.0 Gy/fraction. And conventional fractionations (1.8 Gy or 2.0 Gy/fraction) used for all patients by sequential boost. The same fraction dose was used for the patient before and after repositioning. For patients with two courses, the RT-structure, RT-dose, and RT-plan files for each course were transferred from the Pinnacle (Philips Healthcare), Eclipse (Varian), or Tomotherapy TPS (Accuracy) system to the MIM™ system for dose summation based on the actual fractionation schemes. Considering that the dose fractionations of patients with sequential radiotherapy or SIB were consistent before and after repositioning, dose accumulation workflow of MIM was directly used for dose summation, and the whole dose accumulation process includes the following steps: (1) to select the original CT (previous course) and the new CT (under designing course) of a case; (2) to perform the rigid registration on original CT/new CT; (3) to set the actual delivered fractionation times for original plan (e.g., 15 fractions) and new plan (e.g., 13 fractions) as the numerators, while set the planned times (e.g., 28 fractions) as the denominators, respectively (and then input “15/28” in origin dose and “13/28” in old dose to calculate the accumulated dose); and (4) to calculate the dose distribution on the postregistration image and to submit the dose. And then analyze the DVH statistics. The volume of the PBM receiving 1 to 65 Gy ( $V_0$ – $V_{65}$ ) was recorded.

In the treatment of cervical cancer, intracavitary brachytherapy was performed after external beam radiotherapy (EBRT) was completed or in the last week of pelvic EBRT. Given that the radioactive source is far enough from the pelvic bone, as well as the protective effect of gauze packing, the intracavitary radiotherapy dose to the bone from intracavitary radiotherapy was considered negligible.<sup>18</sup>

## 2.4 | Chemotherapy

All 232 cervical cancer patients received four cycles of paclitaxel combined with cisplatin-based CCRT, that is, paclitaxel ( $135 \text{ mg/m}^2$ ) on d1 and cisplatin (DDP,  $75 \text{ mg/m}^2$ ) on d2 every 4 weeks. For reference, Zhan-Zhao Fu<sup>19</sup> showed that CCRT (cisplatin) had potentially relatively low incidences of hematotoxicity among all CCRT regimens. In this research, all selected patients underwent chemotherapy with the same regimen as a baseline to balance the BM suppression caused by chemotherapy. Chemotherapy and radiotherapy were typically held if the white blood cell count (WBC)

was  $<2.0 \times 10^9/L$ , the absolute neutrophil cell count (ANC) was  $<1.0 \times 10^9/L$ , or the platelet (Plt) count was  $<50 \times 10^9/L$ . A total of 132 patients experienced treatment interrupted, after symptomatic treatment, then continued chemotherapy and radiotherapy as the blood cells were recovered, and all patients completed four cycles of chemotherapy.

## 2.5 | HT and scoring

All patients were required to undergo weekly routine blood examinations to assess acute HT. When one of the four indicators, namely, leukopenia (WBC), neutropenia (ANC), anemia (Hgb), and thrombocytopenia (Plt), was reduced, HT was defined at a certain time point, and the last radiotherapy marked the endpoint of observation. Toxicity was noted and graded per the criteria of the acute radiotherapy morbidity scoring of the Radiation Therapy Oncology Group (RTOG). Because the purpose of this study was to explore dosimetric parameters to predict HT and different radiation doses have different manifestations for different patients, a clinical intervention was carried out regardless of which index decreased. Therefore, the four indicators were not recorded separately.

## 2.6 | NTCP modeling

Lyman's concept of the sigmoid dose–response (SDR) integral model to describe the dose effect on healthy tissues as a whole or in parts after uniform dose irradiation is presented below:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp(-x^2/2)^d x, \quad (1)$$

$$t = \frac{(D - TD_{50}(v))}{(mTD_{50}(v))}. \quad (2)$$

Given the exposure of healthy tissues to nonuniform doses, Kutcher, Burman,<sup>14,20</sup> and Lyman built two successive simplified algorithms for DVHs: the effective volume reduction scheme ( $V_{\text{eff}}$ , (3)–(6), was used in this study) and the effective dose reduction scheme ( $D_{\text{eff}}$ ), and these improved the SDR model.

$$t_i = \frac{(D_{\text{max}i} - TD_{50i}(v))}{mTD_{50i}(v)}, \quad (3)$$

$$TD_{50i}(v) = TD_{50}(1) V_{\text{eff}i}^{-n}, \quad (4)$$

$$V_{\text{eff}i} = \sum_j v_{ij} d_{ij}^{1/n}, \quad (5)$$

$$d_{ij} = \frac{D_{ij}}{D_{\text{max}i}}, \quad (6)$$

where  $TD_{50}(1)$ ,  $m$ , and  $n$  denote the three parameters of the LKB model. Parameter  $TD_{50}(1)$  represents the cumulative dose with a 50% probability of complications to an organ when all volumes are irradiated. Parameter  $m$  represents the steepness of the dose–response at  $TD_{50}$ . Parameter  $n$  is the volume effect parameter. Based on the equations shown above,  $D_{\text{max}i}$  is the maximum radiation dose reaching the BM for the  $i$ th patient. For each patient  $i$ ,  $j$  represents the number of dose–volume bins for the patient's corresponding DVH (the  $j$  range is approximately 50–150).<sup>21</sup>  $V_{ij}$  and  $D_{ij}$  are the corresponding  $j$ th volume unit and cumulated dose, respectively, received by this volume unit after converting the integral DVH of patient  $i$  to the differential DVH. The sum of  $v_{ij}$  is equal to 1,  $d_{ij}$  is the normalization of each dose unit, and the sum of  $d_{ij}$  is equal to 1.<sup>22</sup>

The PBM DVH and follow-up outcomes (i.e., HT) of our 232 patients comprised the input data for the determination of the LKB model parameters using maximal likelihood analysis. Parameters  $TD_{50}(1)$ ,  $m$ , and  $n$  were adjusted to maximize the probability of predicting complications for patients who experienced complications and minimize the probability of predicting no complications for patients who were free of complications.<sup>22</sup> With the identified NTCP parameters, NTCP curve presenting the relationship between the volumetric effective dose and toxicity percentage was plotted.

## 2.7 | Statistical analysis

Tumor stage and pathological patterns were coded as categorical variates. Continuous variates consisted of age, prescription dose, and dose–volume parameters. Univariate logistic regression analysis was used to determine the correlation between the dose–volume parameters and  $\geq$ grade 2 HT, and the Mann–Whitney U test was used to confirm the correlation. Multivariate logistic regression analysis was performed using binary logistic regression models and included all statistically significant clinical and dosimetric parameters from the univariate logistic regression analysis ( $p < 0.05$ ).

The data of 185 patients were used as the training set and the data of 47 patients were used as the verification set to fit the model. Statistical analysis was performed using SPSS (version 24.0). A receiver operating characteristic (ROC) curve was used to assess the predictive abilities of the LKB–NTCP model and DVH parameters, which were quantified by the area under the curve (AUC) of the ROC curve.

**TABLE 1** Patient, tumor, treatment characteristics, and clinical factors

Characteristic	Number	<i>p</i> Value	<i>t</i>	95% CI*
Age (Y) [Mean±SD]	52.85 ± 9.45	0.35	0.59	[-0.03, 0.05]
Pathology		0.88	0.87	[-0.06, 0.15]
Squamous carcinoma	220			
Adenocarcinoma	9			
Adenosquamous carcinoma	3			
FIGO stage		0.14	-0.06	[-0.03, 0.04]
IIA	9			
IIB	55			
IIIA	7			
IIIB	159			
IVA	2			
RTOG grade		-	-	-
0 or 1	5			
≥2	227			
≥3	132			
≥4	29			
Radiotherapy technique		0.13	-1.49	[-1.27, 0.02]
IMRT	118			
Tomo	114			
Cumulated prescription dose[Mean± SD]	50.95 ± 2.96 Gy	0.001	4.08	[0, 0.01]
45 Gy	24			
50.4 Gy	157			
≥55.8 Gy	51			
Chemotherapy regimens				
Paclitaxel + cisplatin	232	0.52	0.86	[-0.04, 0.10]

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; IMRT = intensity modulated radiation therapy; RTOG = The Radiation Therapy Oncology Group; SD = Standard Deviation; Tomo = helical tomotherapy.

\*95%CI = 95% confidence interval.

### 3 | RESULTS

#### 3.1 | Clinical factors

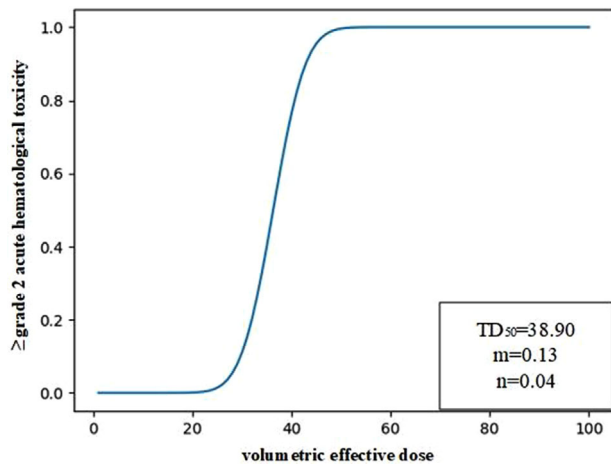
Both the univariate logistic regression analysis and the Mann–Whitney U test indicated no correlation between ≥grade 2 HT and the clinical factors analyzed, including age ( $p = 0.35$ ), FIGO stage ( $p = 0.14$ ), pathological type ( $p = 0.88$ ), chemotherapy regimen ( $p = 0.52$ ), and radiotherapy technique (Tomo/ff-IMRT) ( $p = 0.135$ ), the details presented in Table 1.

#### 3.2 | LKB-NTCP model parameters

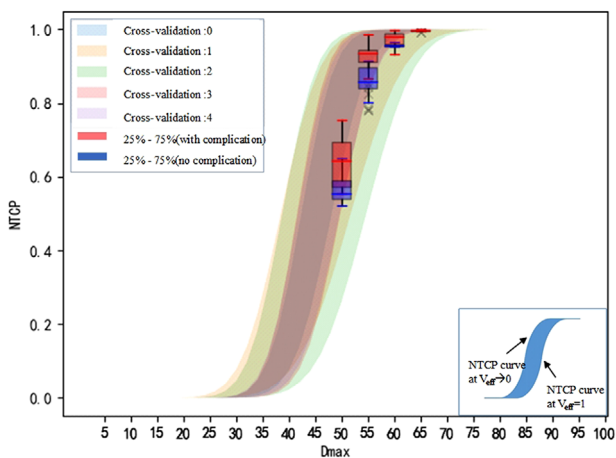
Maximum likelihood analysis was used to identify LKB-NTCP model parameters that could predict ≥grade 2 HT for all patients. The fitting LKB-NTCP model uses fivefold cross-validation, and each fold uses 20% of the

data as the validation set data. The model parameters were as follows:  $TD_{50}(1) = 38.90$  Gy (95%CI [36.94, 40.96]),  $m = 0.13$  (95%CI [0.12, 0.16]), and  $n = 0.04$  (95%CI [0.02, 0.05]).  $TD_{50}(1) = 38.90$  Gy indicated that the NTCP curve (predicting acute HT) exhibited a 50% toxicity probability mark at around the 38.90 Gy, as presented in Figure 1. Parameter “ $m$ ” represents the NTCP curve’s slope and denotes the extent of the response to dose sensitivity, and  $n = 0.04$  represents the PBM’s toxicity risk that is sensitive to “dosimetry hot spots” (small-volume effect, such as the spinal cord, and brainstem).

The NTCP parameters were identified, and the sigmoidal relationship between the volumetric effective dose and ≥grade 2 HT probability was plotted as shown in Figure 1. Figure 2 curve represents the predicted NTCP values for HT in patients, draw the parameter curves of the LKB NTCP model fitted by five cross-validation, respectively. And the average value of the five cross-validation was taken as the final result



**FIGURE 1** NTCP curve for  $\geq$ grade 2 acute hematological toxicity probability (%) related with volumetric effective dose



**FIGURE 2** The predicted and observed NTCP values for HT in patients using the  $V_{\text{eff}}$  (range: 0~1) and LKB NTCP model parameters via five cross-validation. Surfaces of five colors represent the results of five cross-validations. For surface of each color, the left border indicates the  $V_{\text{eff}}$  closer to 0, while right border indicates the  $V_{\text{eff}}$  equal to 1, and the area of surface represents that the range of  $V_{\text{eff}}$  is 0 to 1. In box-whisker plot, red indicates the patients with complication and blue indicates no complication. NTCP: normal tissue complication probability model,  $V_{\text{eff}}$ : effective volume

( $TD_{50} = 38.90$  Gy,  $m = 0.13$ ,  $n = 0.04$ ), then the NTCP value of each patient was calculated to draw the box-whisker plot. The box-whisker plot shows that the NTCP values were different due to different  $V_{\text{eff}}$  (the area of the NTCP curve represents that the range of  $V_{\text{eff}}$  is 0 to 1) under the same  $D_{\text{max}}$  (the patients were grouped in increments of 5 Gy in terms of  $D_{\text{max}}$ ), and the NTCP value of patients with complications was significantly higher than that of patients without complications, which demonstrated that the model effectively distinguished between patients with and without complications.

### 3.3 | Dosimetric parameters

The range and median relative percentage of the BM volume receiving 0–60 Gy and 5 Gy used as the observation point for all patients are presented in Table 2. Table 3 shows the significant dosimetric parameters. The median average dose to the PBM was 30 Gy. Per the univariate logistical regression analysis, there were significant associations ( $p < 0.05$ ) between  $\geq$ grade 2 HT and the following parameters: radiation dose,  $D_{\text{max}}$ ,  $D_{\text{mean}}$ ,  $V_{16-53}$ , and the NTCP (the use of LKB-NTCP with the set of model parameters found). Both low-dose and high-dose radiotherapy were associated with  $\geq$ grade 2 HT, which suggests that the PBM is not a typical “parallel” organ, such as the lung, liver, or kidney, nor is it a typical “serial” organ, such as the spinal cord, brainstem, or lens.

All the statistically significant clinical and dosimetric parameters in the univariate logistic regression analysis were input into the multivariate logistic regression analysis, yielding seven final factors that correlated significantly with  $\geq$ grade 2 HT:  $V_{16-18}$ ,  $V_{35,36}$  and  $V_{47}$ , and the NTCP (the use of LKB-NTCP with the set of model parameters found) ( $p$  value, AUC, 95% CI); cut-off values are present in Table 3. Figure 3 presents the ROC curves and corresponding AUC values of different dosimetric parameters to predict  $\geq$ grade 2 HT. The AUC for these parameters ranged from 0.66 to 0.87, which revealed that the dosimetric parameters showed excellent predictive ability for  $\geq$ grade 2 HT. Cervical cancer patients whose BM volume  $\geq 13.43\%$  receiving 47 Gy had higher rates of  $\geq$ grade 2 HT than those with  $V_{47} \leq 13.43\%$  ( $p = 0.045$ , AUC = 0.80, Figure 3b). The AUC of the LKB-NTCP was 0.87 (Figure 3d), and its prediction ability was better than that of  $V_{16-18}$ ,  $V_{35,36}$ , and  $V_{47}$ .

## 4 | DISCUSSION

### 4.1 | The NTCP model parameter interpretation

To our knowledge, this study cohort comprised the largest number of patients enrolled to date and used the higher prescription dose in the LKB-NTCP model to predict HT in cervical cancer patients receiving CCRT. As one of six NTCP models (LKB, Logit-EUD, Schultheiss, Poisson-EUD, Kallman and Parallel), the LKB model is the most widely used. Based on the clinical tolerance data of developed by Emami et al,<sup>23</sup> Burman et al.<sup>24</sup> applied the NTCP model proposed by Lyman to present the three parameters ( $m$ ,  $n$ ,  $TD_{50}$ ) that characterize the tissue response for 27 normal tissues under conditions of uniform irradiation to the whole volumes by curve fitting and observation. These results were adopted in the biological evaluation modules of

**TABLE 2** Distribution of dosimetric parameters

Parameters	Average	Median	Q1–Q3	$D_{\min} - D_{\max}$	SD*
$V_5$	96.3	97.09	94.19–99.26	84.67–100	3.45
$V_{10}$	90.93	92.17	87.09–95.30	76.89–100	5.34
$V_{15}$	81.83	81.69	76.58–87.05	64.96–100	6.74
$V_{20}$	69.84	70.74	64.24–75.71	48.91–100	7.93
$V_{25}$	56.77	58.03	49.90–63.36	30.2–100	9.69
$V_{30}$	43.49	44.16	35.63–49.96	18.6–100	10.51
$V_{35}$	32.27	32.81	25.30–38.45	11.65–100	10.48
$V_{40}$	23.17	25.53	16.78–27.84	6–100	9.76
$V_{45}$	15.36	15.47	9.66–19.72	0.84–99.39	9.05
$V_{50}$	8.18	7.66	3.57–10.96	0–98.37	7.99
$V_{55}$	1.46	0	0–0.15	0–17.21	3.32
$V_{60}$	0.08	0	0	0–8.52	0.69

Abbreviations: Max = maximum; Min = minimum; Q1 = 25th percentile; Q3 = 75th percentile.

Note:  $V_x$  indicates the relative percentage of BM volume receiving  $x$  Gy.

\*Indicate standard deviation.

**TABLE 3** Prognostic value of therapeutic factors associated with hemototoxicity in logistic regression analysis

Parameters	No hemoto- toxicity	With hemo- toxicity	Hemototoxicity <grade 2	Hemototoxicity ≥grade 2	$p$ Value	95% CI	AUC	Cut-off value
Radiation dose (Gy)	48.16 ± 2.58	50.16 ± 3.04	48.93 ± 3.94	51.2 ± 2.91	0.001	[0.57–0.84]	0.704	44.99
PBM $D_{\max}$ (Gy)	50.60 ± 2.94	54.19 ± 0.03	51.45 ± 4.08	54.32 ± 2.88	0.021	[0.56–0.85]	0.70	51.50
PBM $D_{\text{mean}}$ (Gy)	27.66 ± 1.62	30.03 ± 0.03	28.06 ± 3.64	30.16 ± 3.49	0.001	[0.57–0.82]	0.69	29.38
LKB-NTCP	NA	NA	NA	0.75 ± 0.05	0.023	[2.8E–29–0.05]	0.87	74.76
$V_{16}$	75.32 ± 0.04	79.65 ± 0.07	76.35 ± 6.17	77.55 ± 7.07	0.007	[0.54–0.78]	0.66	79.65
$V_{17}$	72.27 ± 0.04	77.31 ± 0.07	70.71 ± 6.51	77.55 ± 7.07	0.008	[0.55–0.80]	0.67	75.68
$V_{18}$	69.49 ± 0.03	74.9 ± 0.07	67.82 ± 6.85	75.17 ± 7.23	0.007	[0.56–0.81]	0.68	72.65
$V_{35}$	28.81 ± 0.05	32.35 ± 0.11	25.83 ± 7.79	32.88 ± 10.49	0.008	[0.60–0.82]	0.71	30.35
$V_{36}$	26.74 ± 0.05	30.38 ± 0.10	23.87 ± 7.79	30.91 ± 10.39	0.037	[0.60–0.82]	0.71	28.56
$V_{47}$	5.09 ± 0.05	12.62 ± 0.09	5.59 ± 5.15	13.10 ± 8.73	0.045	[0.72–0.89]	0.80	13.43
Radiation dose (Gy)	48.16 ± 2.58	50.16 ± 3.04	48.93 ± 3.94	51.2 ± 2.91	0.001	[0.57–0.84]	0.704	44.99

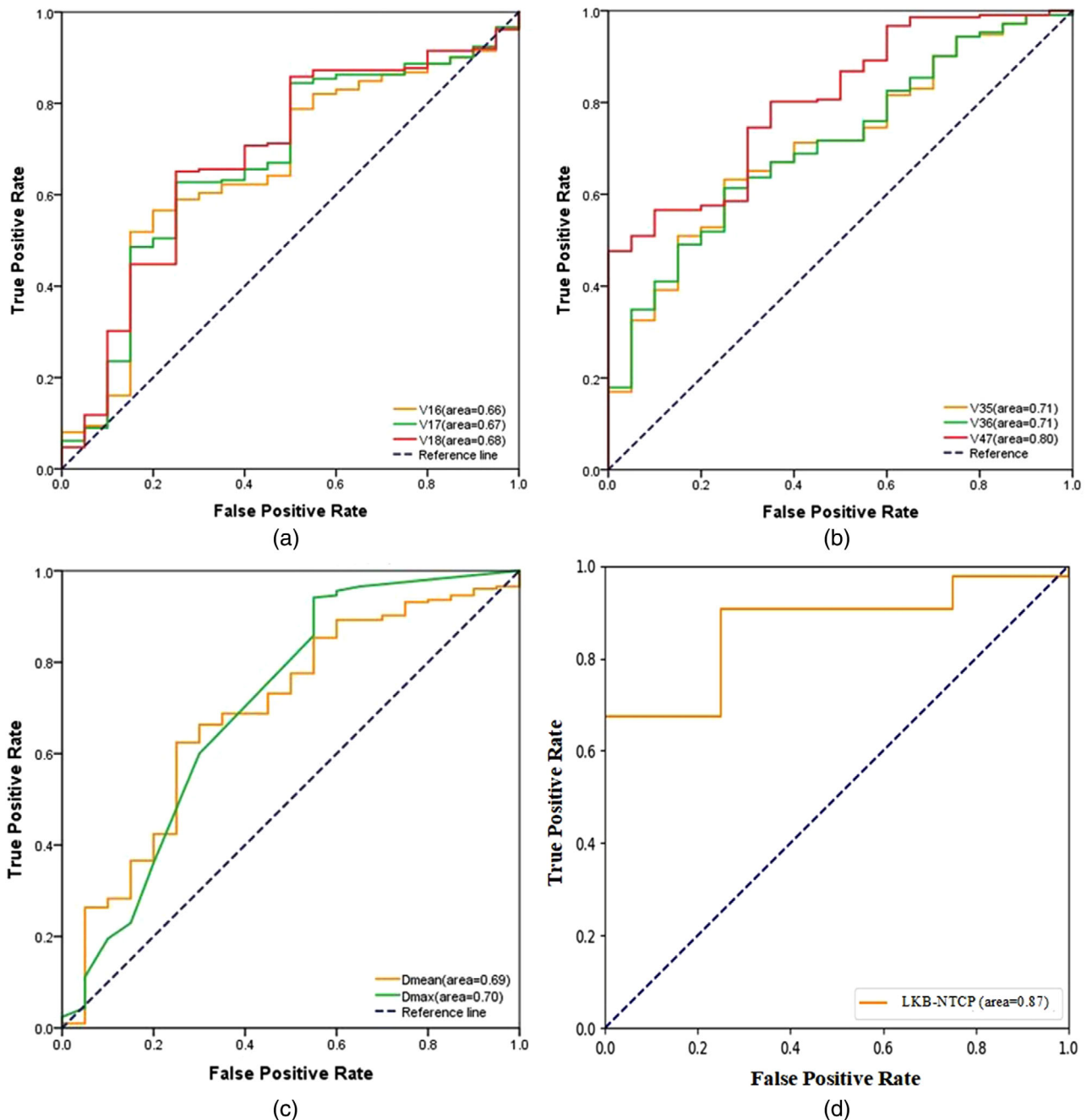
Abbreviations: 95%CI = 95% confidence interval; LKB-NTCP = the Lyman–Kutcher–Burman normal tissue complication probability (NTCP) model, the use of LKB-NTCP with the set of model parameters found; PBM  $D_{\max}$  = the maximum cumulated dose on pelvic bone marrow.

Note:  $V_x$  indicates the relative percentage of BM volume receiving  $x$  Gy.

commercial treatment plan systems such as Pinnacle.<sup>25</sup> However, with the development of precision radiotherapy, partial volume of most normal organs is exposed to nonuniform irradiation. In this case, the continued application of these parameters given by Burman will affect the accuracy of the complication assessment, so it is necessary to establish a group-specific model on the basis of clinical observation and DVH data analysis, that is, to fit new model parameters and make full use of NTCP model in predicting complications.

Bazan et al. identified the LKB model parameters during anal canal cancer radiotherapy-induced ≥grade 3 HT as  $TD_{50}(1) = 32.00$  Gy,  $m = 0.175$ , and  $n = 1.00$ .<sup>26</sup> Parameter “ $n$ ” from Bazan et al.’s result represents the

large-volume effect, which indicates the “parallel” organ behavior of the PBM, and the mean dose is a significant predictor of HT. However, the previous study examined 33 patients, and the mean prescription dose ranged from 40 to 54.4 Gy, and in this study, we examined 232 patients, and the prescription dose ranged from 45 to 60 Gy ( $51.30 \pm 3.17$ ); thus, we were able to correlate HT with high-dose regions on the PBM and, therefore, identified the parameter  $n = 0.04$ . The result of  $TD_{50}(1) = 38.90$  Gy is higher than but the same as that of Bazan (32 Gy). Parameter “ $m$ ” means that the curve is similar gradient at predicting ≥grade 2 HT ( $m = 0.13$  from this study) to gradient at predicting ≥grade 3 HT ( $m = 0.175$  from Bazan’s study).



**FIGURE 3** The ROC curve and AUC revealed that the volume–dose parameter for predicting  $\geq$ grade 2HT after radiation in cervical cancer. Normal tissue complication probability (NTCP) model;  $V_x$  = the relative percentage of BM volume receiving  $x$  Gy. AUC: area under the curve; LKB-NTCP: the Lyman–Kutcher–Burman (LKB).

LKB-NTCP model exhibits marked predictive ability and provides quantitative evaluation criteria for clinicians and physicists to compare different treatment schemes. The definition of gEUD (generalized EUD) is  $D_{\text{eff}}$  in the Lyman–Kutcher–Burman (LKB) model, with  $n = 1/a$ .<sup>27,28</sup> In order to transfer the two-dimensional DVH diagram into one-dimensional form, the effective dose ( $D_{\text{eff}}$ ) or effective volume ( $V_{\text{eff}}$ ) must be defined. Kutcher et al.<sup>29</sup> and Hamilton et al.<sup>30</sup> proposed a method

to simplify two-dimensional DVH to one-dimensional form.  $D_{\text{eff}}$  refers to the damage caused by uniform dose ( $D$ ) radiation to part of the volume ( $V$ ) of organs or tissues, which is equivalent to the damage caused by uniform dose “ $D_{\text{eff}}$ ” irradiate to the whole organ or tissue, that is,  $\text{NTCP}(V, D) = \text{NTCP}(V = 1, D_{\text{eff}})$ . And the  $V_{\text{eff}}$  is equivalent to the damage caused by part of the volume “ $V_{\text{eff}}$ ” of organs or tissues irradiated by the maximum dose ( $D_{\text{max}}$ ) in the DVH diagram, that is,



NTCP ( $V, D$ ) = NTCP ( $V_{\text{eff}}, D_{\text{max}}$ ). Compared with  $D_{\text{eff}}$  and  $V_{\text{eff}}$ , Moiseenko et al.<sup>21</sup> found that the equivalent volume method was more sensitive to the change of dose distribution in organs. However, the application of simple mathematical methods to solve complex biological problems will lead to deviations; therefore, the NTCP model has some limitations, especially in the field of individualized radiotherapy. On the one hand, the traditional NTCP model can only describe the relationship between organ dose and complications for a certain group of patients, instead of reflecting the idea of “tailored” individualized radiotherapy. With it, it is impossible to distinguish and predict the probability of complications between conventional and unconventional fractionation, whereas different fractionation schemes will significantly affect the probability of complications according to the clinical experience. On the other hand, the impact of the individual factors on the performance of complications failed to be considered in the traditional NTCP model. In view of the above limitations, model parameters were introduced to improve the ability to predicting the complications. For the different dose fractionation, the NTCP model and the linear quadratic model (L-Q)<sup>31</sup> were combined with the introduction of the  $\alpha/\beta$  factor as another model parameter to correct the Di. And Tucker et al.<sup>22</sup> proposed the generalized LKB-NTCP model, in which dose-modifying factor (DMF) was introduced into the existing three parameters of the traditional model. Therefore, the nondosimetric factor “smoking history” was introduced into NTCP model. The DMF corresponding to “smoking history” was obtained by analyzing the follow-up data of radiation pneumonia in patients with nonsmall cell lung cancer. This approach allows for predicting the probability of individual complications depending on personal circumstances, which expand the application field of NTCP model. The clinical factors were demonstrated to be no correlation with HT; therefore, no individual factors were introduced to NTCP model as DMF in this study. However, when it comes to the prediction of complications by other tumor NTCP models, DMF can be selected and introduced.

## 4.2 | The PBM dose–volume effects

The results of this study demonstrated that both low-dose and high-dose irradiation were associated with HT, which was inconsistent with Mell, Jutzy, and Albuquerque’s results but consistent with Fajardo and Julie’s results. Mell et al.<sup>32</sup> reported that BM  $V_{10}$  (volume of the BM receiving  $\geq 10$  Gy)  $\leq 90\%$  and  $V_{20} \leq 75\%$  could reduce the incidence of HT, while Jutzy et al.<sup>33</sup> reported BM  $V_{15} \leq 85\%$ , and Albuquerque et al.<sup>34</sup> reported  $V_{20} \leq 80\%$ . The above three studies show that the BM acts as a “parallel organ” and is sensitive to low doses in large volumes. However, some authors described the BM as a “serial-parallel organ,” meaning that it is

sensitive to both low and high doses. Fajardo et al.<sup>35</sup> revealed that active BM stem cells are highly sensitive to radiotherapy, with pathological changes occurring at doses  $< 4$  Gy and hypoplasia occurring at doses  $> 50$  Gy. Similarly, Julie et al.<sup>36</sup> advised that  $V_{10} \leq 87\%$  and  $D_{\text{max}} \leq 57$  Gy could reduce the incidence of HT. However, in this study,  $V_{16-18}$ ,  $V_{35,36}$ , and  $V_{47}$ , rather than  $V_{10}$ ,  $V_{15}$ , and  $V_{20}$ , were associated with clinically significant  $\geq$  grade 2 HT. The difference between this study and those by Mell, Jutzy, and Albuquerque was that the median prescribed dose was 50.4 Gy (45–60 Gy) rather than 45 Gy, and the higher prescribed dose revealed the effect of a high dose on HT. The sufficiency of small volume and high-dose region exposed the relationship between HT and the high-dose region. Previous studies<sup>32,33,35,36</sup> demonstrated that low-dose region ( $V_{10}$ ,  $V_{15}$ ,  $V_{20}$ ) or high-dose region ( $D_{\text{max}} \geq 50$  or 57 Gy) were correlated significantly with  $\geq$  grade 2 HT; in order to avoid omitting any dosimetric parameters related to HT, the interval of the extracted dosimetric parameters was set to 1 Gy in this study. Considering the low-dose-induced toxicity should relate to wide volume, it may be assumed that the OAR under about 16–18 Gy coverage presents sensitive to the toxicity.

Past studies have provided different accounts on this relationship, which suggests that the PBM is not a typical “parallel” organ, such as the lung, liver, or kidney, nor is it a typical “serial” organ, such as the spinal cord, brainstem, or lens. The same biological characteristic of irradiation on the PBM can also be found on the bladder during pelvic cancer radiotherapy. Marks et al. indicated that the majority of the bladder can be irradiated by approximately 30–50 Gy.<sup>37</sup> Therefore, if small volumes of the bladder receive 60–65 Gy, the incidence of serious complications would most likely be fairly low. Harsovia et al. also revealed that several points in the bladder wall DVH ( $V_{10-82}$ ) correlated with chronic toxicity.<sup>38</sup> Both studies above<sup>37,38</sup> showed that the bladder is an organ sensitive to a wide range of dose–volume factors, suggesting parallel-like behavior. However, prevalent serial behavior has also been reported for late mild-to-severe toxicity, indicating that a small fraction of the bladder receiving more than 78–80 Gy is highly predictive of late genitourinary toxicity.<sup>39</sup>

Some studies<sup>40,41</sup> have showed that at least one of the primary mechanisms of urinary function impairment relies on the irradiation of a small volume (i.e., the caudal portion of the bladder unavoidably included in the PTV) with a high dose, again suggesting serial-like behavior. In our study, we also observed “serial-parallel” behavior on the PBM, which is HT-sensitive to both  $V_{16-18}$  and  $V_{35,36,47}$  according to the multivariate analysis. So far, we can only speculate why the PBM presents different dose–volume behaviors: when HT is caused primarily by damage to the marrow in the PTV high-dose area, serial characteristics will be observed; however, there is also a much larger part of the PBM located in the

low-dose area (out of the PTV). If HT is caused largely by damage to the marrow by a low dose on a large volume, parallel characteristics will be observed. Regarding this feature, Jian Zhu's investigation showed that an IMRT biological optimization scheme with two groups of different equivalent uniform dose parameters yielded improved organ protection.<sup>42</sup> In this study, analysis of the data of all patients showed that HT was sensitive to  $D_{\text{mean}}$ ,  $D_{\text{max}}$ ,  $V_{16-53}$ , and NTCP, especially sensitive to  $V_{16-18}$ ,  $V_{35,36,47}$ , and the NTCP. Given the level of PBM protection during cervical cancer radiotherapy, it has been suggested that both hot spots in the PTV overlapping with the PBM and large areas with low doses outside the PTV should be avoided to spare more of the PBM, which means that a "tight" dose distribution should also be considered during planning.

### 4.3 | PBM delineation

The volume of active pelvic bone marrow (APBM) may predict the level of BM reserve better than the whole PBM, and it is easier to spare the volume of the APBM than to spare the entire PBM while maintaining target coverage.<sup>43</sup> However, the best method for defining active BM is unclear, and there are great inter- and intrasubject variabilities depending on the window level.<sup>26</sup> There are currently no ready-made imaging studies that can accurately define the boundary of the APBM and the further studies to define the boundary by MRI or PET-CT are under way. Therefore, as a limitation of this research, the pelvic bone was delineated instead of the active BM, and prospective confirmatory studies should be conducted in the future.

### 4.4 | The effect of radiotherapy technologies

Tomo is considered an advanced radiotherapy technology with high-intensity modulation capabilities for flexible delivery angles and fine beamlets. Therefore, we assumed that patients who received Tomo would experience fewer HTs than those who received ff-IMRT. However, the follow-up results in this study revealed no significant difference ( $p = 0.135$ ) between each of the radiotherapy delivery technologies (Tomo/ff-IMRT) and  $\geq$ grade 2 HT. This finding is consistent with those of previous studies by Lian et al.<sup>44</sup> and Renard-Oldrini et al.,<sup>45</sup> who presented the benefit of Tomo in sparing the bladder, rectum, and bowel but not the pelvic bones. The following inference can be made based on the fact that the majority of pelvic bones overlapped with the PTV; high-dose irradiation to the PBM is not avoidable by any delivery technology. Nevertheless, based on anatomical structures, ff-IMRT could enhance the intensity of bilateral beams to avoid irradiation of the anterior bowel,

which, as a result, unavoidably includes more of the PBM in the beam field. This, perhaps, is the reason why the  $p$  value between ff-IMRT and Tomo according to HT risk is not significant (0.135) but close to 0.1. Furthermore, unlike rotatory irradiations, such as Tomo or volumetric-modulated arc therapy, ff-IMRT covers part of the bowel structure during irradiation and, therefore, brings a higher risk of irradiation-induced ileus and intestinal fistula. Compared to ff-IMRT, the existence of a wide range of low-dose areas in Tomo causes skin and intestinal side effects. Nevertheless, Tomo remains viable for cervical cancer radiotherapy.

### 4.5 | The benefit of the NTCP factor to IMRT biological optimization

Most commercial TPSs support the use of biometric indicators in biological IMRT optimization. Li et al. compared biological IMRT optimization strategies with physical IMRT optimization strategies using three TPSs and concluded that although biological IMRT spares normal organs better, it is easier to reach the target dose coverage standard with physical IMRT than with biological IMRT.<sup>46</sup> We proved previously that optimizing the objective function of IMRT under different biological constraints with various biological parameters may specifically reduce dosimetry-related toxicities.<sup>42</sup> Therefore, based on the "serial-parallel" behavior of the PBM during irradiation-induced HT, biological IMRT with various specific parameters can be used.

## 5 | CONCLUSIONS

For cervical cancer patients treated with EBRT, both low-dose ( $V_{16-18}$ ) and high-dose ( $V_{35,36}$  and  $V_{47}$ ) irradiation were associated with hemototoxicity, depending on the fractional volumes receiving the variable degree of dosage. The LKB NTCP (with  $TD_{50}(1) = 38.90$  Gy,  $m = 0.13$ ,  $n = 0.04$  parameters),  $V_{16-18}$ ,  $V_{35,36}$ , and  $V_{47}$  of the PBM were strong predictors of HT. These results indicate that the potential to optimize the IMRT plan to avoid radiation hot spots on the PBM may reduce the incidence of  $\geq$ grade 2 HT. Both hot spots and large low-dose areas on the PBM should be avoided, which means that a "tight" dose distribution should be considered during planning. Long-term follow-up and the enrollment of significantly more patients are required in future investigations to ascertain the proposed predictive factors.

### ACKNOWLEDGMENTS

No applications.

### FUNDING

This work was supported by the National Natural Science Foundation of China (82172072), the

Shandong Provincial Natural Science Foundation (ZR2020LZL001), Focus on research and development plan in Shandong province (grant number 2018GSF118237), the Taishan Scholars Program of Shandong Province (Young Taishan Scholars, No. tsqn201909140), and the National Key Research and Develop Program of China (2016YFC0105106).

## CONFLICT OF INTEREST

The authors have no relevant conflicts of interest to disclose.

## REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
- Cervical Cancer, Version 2.2015 Featured Updates to the NCCN Guidelines.
- Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358(9284):781-786.
- Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340(15):1154-1161.
- Barney CL, Scoville N, Allan E, et al. Radiation dose to the thoracic vertebral bodies is associated with acute hematologic toxicities in patients receiving concurrent chemoradiation for lung cancer: results of a single-center retrospective analysis. *Int J Radiat Oncol Biol Phys*. 2018;100(3):748-755.
- Fyles AW, Dembo AJ, Bush RS, et al. Analysis of complications in patients treated with abdominopelvic radiation therapy for ovarian carcinoma. *Int J Radiat Oncol Biol Phys*. 1992;22(5):847-851.
- Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys*. 1995;32(5):1301-1307.
- Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC, Aydogan B. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1504-1510.
- Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys*. 2005;63(2):354-361.
- Ellis RE. The distribution of active bone marrow in the adult. *Phys Med Biol*. 1961;5:255-258.
- Mauch P, Constine L, Greenberger J, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1319-1339.
- Chitapanarux I, Tharavichitkul E, Nobnop W, Wanwilairat S, Vongtama R, Traisathit P. A comparative planning study of step-and-shoot IMRT versus helical tomotherapy for whole-pelvis irradiation in cervical cancer. *J Radiat Res*. 2015;56(3):539-545.
- Lyman JT, Wolbarst AB. Optimization of radiation therapy. III: a method of assessing complication probabilities from dose-volume histograms. *Int J Radiat Oncol Biol Phys*. 1987;13(1):103-109.
- Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method gerald. *Int J Radiat Oncol Biol Phys*. 1989;16(6):1623-1630.
- Taylor A, Rockall AG, Reznick RH, Powell MEB. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1604-1612.
- Lim K, Small W, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys*. 2011;79(2):348-355.
- Wang W, Liu X, Meng Q, Zhang F, Hu K. Nomogram for predicting para-aortic lymph node metastases in patients with cervical cancer. *Arch Gynecol Obstet*. 2018;298(2):381-388.
- Chang Y, Yang ZY, Li GL, et al. Correlations between radiation dose in bone marrow and hematological toxicity in patients with cervical cancer: a comparison of 3DCRT, IMRT, and RapidARC. *Int J Gynecol Cancer*. 2016;26(4):770-776.
- Fu ZZ, Li K, Peng Y, et al. Efficacy and toxicity of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer: a network meta-analysis. *Med (United States)*. 2017;96(2):e5853.
- Roberts SA, Hendry JH. The delay before onset of accelerated tumour cell repopulation during radiotherapy: a direct maximum-likelihood analysis of a collection of worldwide tumour-control data. *Radiother Oncol*. 1993;29(1):69-74.
- Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Haken RKT. Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int J Radiat Oncol Biol Phys*. 2002;53(4):810-821.
- Zhu J, Zhang ZC, Li BS, et al. Analysis of acute radiation-induced esophagitis in non-small-cell lung cancer patients using the Lyman NTCP model. *Radiother Oncol*. 2010;97(3):449-454.
- Emami B. Tolerance of normal tissue to irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21:109-122.
- Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys*. 1991;21(1):123-135.
- Hardemark B, Liander A & Rehbinder H et al. P3IMRT Biological optimization and EUD[EB/OL]. Pinnacle3 White Paper. www.edudoc.com/ebook/hardemark. Html, 2004 /2013-05-11.
- Bazan JG, Luxton G, Mok EC, Koong AC, Chang DT. Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with intensity-modulated radiation therapy for squamous cell carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys*. 2012;84(3):700-706.
- Liu F, Yorke ED, Belderbos JSA, et al. Using generalized equivalent uniform dose atlases to combine and analyze prospective dosimetric and radiation pneumonitis data from 2 non-small cell lung cancer dose escalation protocols. *Int J Radiat Oncol Biol Phys*. 2013;85(1):182-189.
- Lin H, Jing J, Xu L, Wu D, Xu Y. Combining the LKB NTCP model with radiosensitivity parameters to characterize toxicity of radionuclides based on a multiclonogen kidney model: a theoretical assessment. *Austr Phys Eng Sci Med*. 2012;35(2):165-176.
- Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys*. 1991;21(1):137-146.
- Hamilton CS, Chan LY, McElwain DLS, Denham JW. A practical evaluation of five dose-volume histogram reduction algorithms. *Radiother Oncol*. 1992;24(4):251-260.
- Miah AB, Gulliford SL, Clark CH, et al. Does-response of parotid gland function dose-response analysis of parotid gland function: what is the best measure of xerostomia? *Radiother Oncol*. 2013;106(3):341-345.
- Mell LK, Kochanski JD, Roeske JC, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with

- concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;66(5):1356-1365.
33. Jutzy J, Arya R, Kothari R, et al. Predictors of acute hematologic toxicity in women receiving extended-field chemoradiation for cervical cancer. *Gynecol Oncol*. 2019;154:150.
34. Albuquerque K, Giangreco D, Morrison C, et al. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT. *Int J Radiat Oncol Biol Phys*. 2011;79(4):1043-1047.
35. Berthrong M, Fajardo LF, Anderson RE. Hematopoietic tissue. In Fajardo LF, ed. *Radiation Pathology*. Oxford University Press; 2001:379-388. Published online 2001:2001.
36. Julie DAR, Oh JH, Apte AP, et al. Predictors of acute toxicities during definitive chemoradiation using intensity-modulated radiotherapy for anal squamous cell carcinoma. *Acta Oncol (Madr)*. 2016;55(2):208-216.
37. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1257-1280.
38. Harsolia A, Vargas C, Yan D, et al. Predictors for chronic urinary toxicity after the treatment of prostate cancer with adaptive three-dimensional conformal radiotherapy: dose-volume analysis of a phase II dose-escalation study. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1100-1109.
39. Cheung MR, Tucker SL, Dong L, et al. Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007;67(4):1059-1065.
40. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1124-1129.
41. Cahlon O, Zelefsky M, Shippy A, et al. Intensity modulated radiation therapy to a dose of 86.4 Gy for localized prostate cancer: toxicity data and preliminary biochemical outcomes. *Int J Radiat Oncol Biol Phys*. 2008;71(2):330-337.
42. Zhu J, Simon A, Haigron P, et al. The benefit of using bladder sub-volume equivalent uniform dose constraints in prostate intensity-modulated radiotherapy planning. *Onco Targets Ther*. 2016;9:7537-7544.
43. Zhou YM, Freese C, Meier T, et al. The absolute volume of PET-defined, active bone marrow spared predicts for high grade hematologic toxicity in cervical cancer patients undergoing chemoradiation. *Clin Transl Oncol*. 2018;20(6):713-718.
44. Lian J, Mackenzie M, Joseph K, et al. Assessment of extended-field radiotherapy for stage IIIC endometrial cancer using three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and helical tomotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(3):935-943.
45. Renard-Oldrini S, Guinement L, Salleron J. Comparaison entre arthrothérapie volumétrique modulée et tomothérapie pour le cancer du col utérin, avec irradiation lombo-aortique. *Cancer/Radiothérapie*. 2015;19(8):733-738. <https://doi.org/10.1016/j.canrad.2015.05.031>
46. Allen Li X, Alber M, Deasy JO, et al. The use and QA of biologically related models for treatment planning: short report of the TG-166 of the therapy physics committee of the AAPM. *Med Phys*. 2012;39(3):1386-1409.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Wang D, Yin Y, Zhou Q, et al. Dosimetric predictors and Lyman normal tissue complication probability model of hematological toxicity in cervical cancer patients with treated with pelvic irradiation. *Med Phys*. 2022;49:756–767. <https://doi.org/10.1002/mp.15365>