

Is 3D printing-guided three-dimensional brachytherapy suitable for cervical cancer: from one single research institute?

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Summary

Objective: To investigate the guidance value of 3D printing in brachytherapy for cervical cancer and its role in the doctor-patient communication. **Results:** The median follow-up time was 36 months (10-63); 3D models of 50 patients with cervical cancer were successfully printed out. Fifty patients underwent 255 times the source applicator. EQD 2 of HR-CTV D90, bladder D2cc, sigmoid colon D2cc, and rectal D2cc were 75.26 ± 6.31 , 67.84 ± 8.75 , 47.36 ± 7.62 , and 62.45 ± 8.68 Gy, respectively, and the overall score of the verisimilitude and usefulness of 3D printing models by five doctors was 8.0 ± 0.8 points. The score of patients' satisfaction to the use of 3D printing model for operation communication was 9.0 ± 0.5 points. During three months of follow-up, two patients were with rectal hemorrhage in later period (level 2), and the symptoms were improved after hemostasis, enema and other symptomatic treatments. Three-year local control (LC) was 92% (46/50), three-year progression-free survival (PFS) was 82% (41/50), and three-year overall survival (OS) was 84%. Three-year late toxic and side effects mainly include radiation proctitis, radiation urethritis, and vaginitis, and their level 3 incidence rates were: radiation gastroenteritis 10%, radiation urethritis 6%, and radiation vaginitis I: 8%, respectively. **Conclusion:** 3D printing model can well display relationship with the surrounding normal tissues and effectively guide doctors to conduct individualized brachytherapy for cervical cancer. It can also be used as a tool to communicate with patients, render doctor-patient communication more effective, and obtain a good curative effect and less toxic and adverse effects, which is worth further clinical practice.

Key words: 3D-printing; Cervical cancer; Brachytherapy.

Introduction

Cervical cancer is a common malignant tumor in female, and ranks only second to breast cancer. Early stage is surgical treatment-oriented, while middle-advanced stage is radiation therapy-oriented [1].

In vitro radiation + high dose rate (HDR) of brachytherapy is clinical standard treatment mode. Brachytherapy, as an important part of the cervical cancer radiotherapy, greatly reduces the radiation injury of normal tissue on the premise of obviously improving patients' local control [2]. In the last century, the clinical common traditional two-dimensional intracavitary after-loading radiotherapy has the defects of target volume blindness and insufficient individualized plan [3]. The imaging-guided three-dimensional intracavitary after-loading developed in recent years can exert CT-guided three-dimensional intracavitary brachytherapy for cervical cancer, which improves the tumor target area coverage, but for eccentric large tumor, severe parametrial invasion, pelvic wall and vaginal recurrence, as well as other refractory cases is difficult for ordinary source applicator alone to obtain ideal target area coverage and local control [4, 5].

In order to further improve the accurate coverage of tumor target dose, intracavitary brachytherapy is currently often combined with multiple-needle implantation radiother-

apy technique for tumor clinically, which is operated under CT positioning guide and can preliminarily exert implantation treatment of cervical cancer [6, 7], but its shortcomings are obvious as follows: 1) the resolution of the tumor under CT guidance is low and causes deficient accuracy of the tumor implantation 2) the stereoscopic structure and specific location of tumor can only be simply judged by the physicians' sense of space, 3) the spatial locations of surrounding normal tissues and tumor are still difficult to grasp, and the possibility of damage to normal tissue increases significantly [7]. In summary, the pelvic cavity and cervical cancer tissues vary in size and location, and it is very difficult for clinical routine brachytherapy and implantation to achieve the actual individualization [8].

The application of 3D printing is expected to change the process, the entity models from 3D printing turn the virtual reconstruction-based brachytherapy into direct planning on the entity models [9]. At present, 3D printing-assisted surgical planning has been successfully applied in the maxillofacial oral surgery and orthopedic surgery [10], but it is rarely reported in after-loading cervical cancer radiotherapy [11]. In the study, 3D printing was used to make 3D models for cervical cancer patients and effectively guide the selection of brachytherapy and the operations of doctors.

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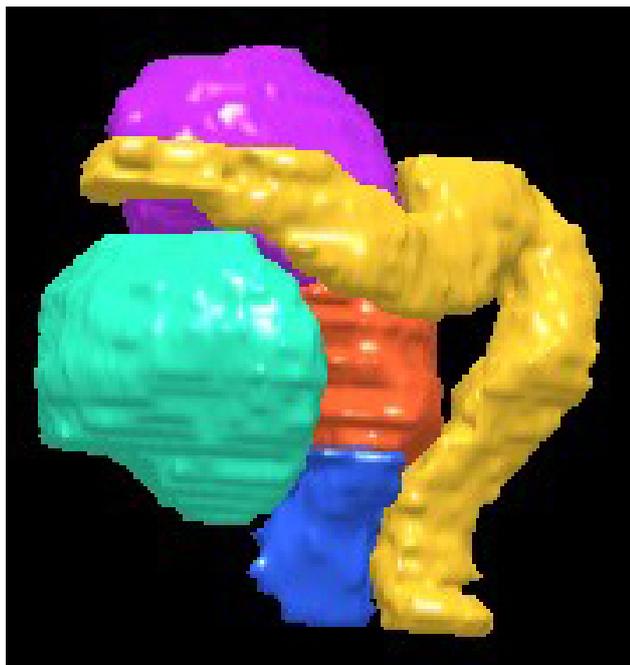


Figure 1. — 3D model image.

Materials and Methods

Fifty cases of cervical cancer patients who received initial treatment between June 2010 and December 2013 were selected. They were with complete clinical pathological data, all received radical three-dimensional conformal radiotherapy, and the intracavitary brachytherapy was conducted in accordance with the following methods. The staging criteria for cervical cancer of International Federation of Gynecology and Obstetrics (FIGO, 2003) were used for staging, and general data are shown in Table 1.

The patients were placed in the supine position and thermoplastic phantom was used to fix the position. Patients were instructed to hold urine in order to control the filling degree of bladder. CT simulator was used for positioning, the scanning range was from the 3rd lumbar to 2 cm under ischial tuberosity, and the layer thickness was 5 mm. The possible lymph node metastasis in abdominopelvic cavity was outlined as GTV-nd. Clinical target volume (CTV) included the pelvic lymph node area under common iliac, Stage IIIA included the groin superficial lymph area, and if there were metastatic lymph nodes in common iliac or around abdominal aorta, abdominal aortal lymph area was included, and the upper bound was at the renal venous superior border level. In addition, CTV also included the total uterus as well as the vaginal wall at 2 cm outside of parametrial area and vaginal lesions. The area 8 mm outside the CTV in all directions is was planning target volume (PTV). Outlined organs at risk included bladder, rectum, sigmoid colon, small intestine, two femoral heads, etc. Oncentra master treatment planning system (v3. 3SP3) was used for planning design and operation. Four-field conformal radiotherapy was conducted in the United States var-

ian 600C/D linear accelerator, total external exposure dose was 50 Gy/25f, and GTV-nd and GTV-P reloading was 10 Gy/5 times to the total amount 60 Gy. During the same period, 40 mg/m² cisplatin mono-chemotherapy was conducted one time/week for a total 5~6 times.

Table 1. — *Clinical information*

Projects	n = 50
Age	47 ± 3.4
FIGO staging	
IIb	22
IIIa	19
IIIb	9
Tumor volume	59.2 ± 4.4
Tumor types	
Exophytic	11
Endogenous	23
Ulcerative	16
Tumor diameter	
≥ 4cm	39
< 4cm	11
Lymph node metastasis	
Positive	13
Negative	37

MRI scanning + enhancement: 3.0 MR was used for scanning and enhancement examination of all patients. Patients were fasting, emptied the bladder, and drank 200 ml of water before scanning to fill the intestinal tract, so that gas artifacts were reduced and the contrast agent damage to the kidney was reduced. Scanning range was from the upper pole of kidney to the symphysis pubis, and the scanning was from the side of head to the foot.

Image post-processing: DICOM-formatted files of MR enhancement examination were extracted, medical imaging tool kit and three-dimensional medical image data processing platform 3DDOCTOR were used for post-processing of data, and different colors were used to outline cervical cancer tissue, uterus, vagina, bladder and rectum. Standardized 3D printing STL-formatted files were finally output.

Printing 3D models: Conventional 3D printing technology was used to print cervical cancer and normal tissue models with a 0.2-mm thickness. Printing materials were thermoplastics. After different tissues were printed with different colors, 3M double-sided tape was used to adhere, fix, and reshape them into 3D models.

Medical professionals were openly evaluated for the model. Evaluation mainly included 5 problems: 1) the overall evaluation, 2) the selection of parametrial tumor implantation location and depth, 3) the presentation of tumor and surrounding normal relational position, 4) the selection of intracavitary source applicator angle and depth, 5) the scientificity as the overall individualized brachytherapy plan. Score was 1~10 points from low to high in turn, 1

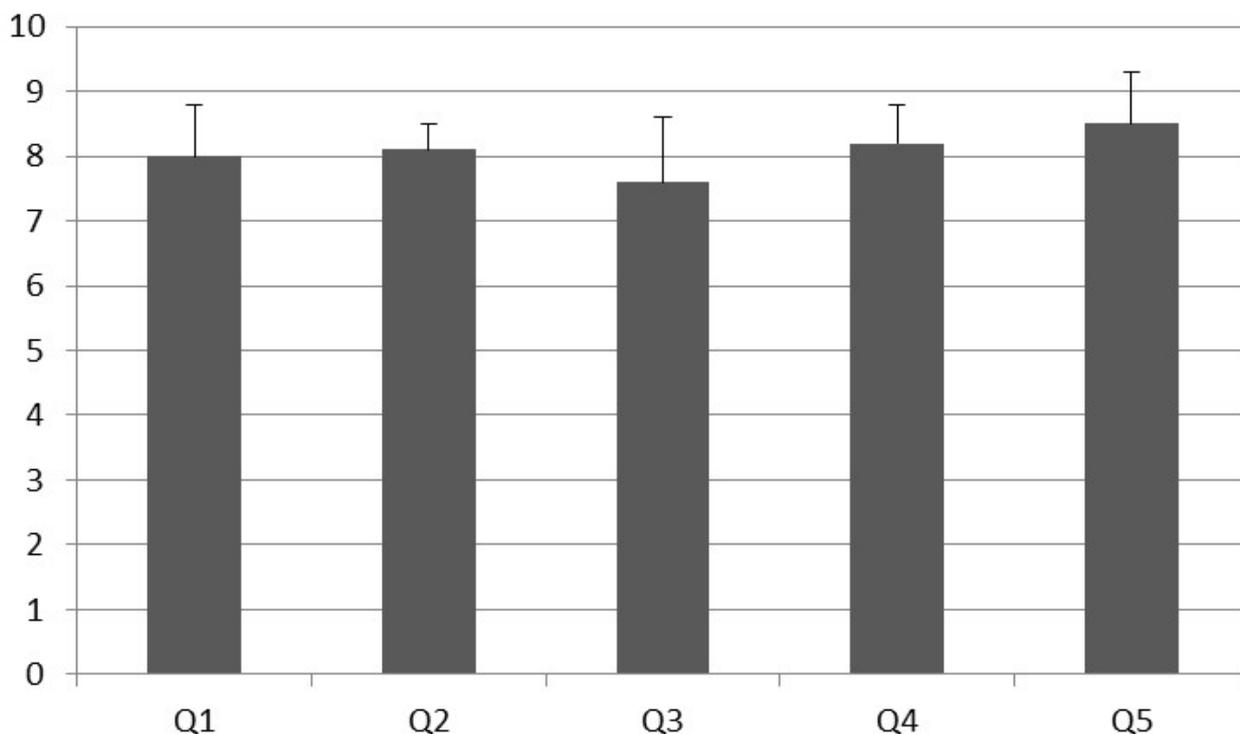


Figure 2. — Face validation of the cervical cancer models. Q1 = overall usefulness, Q2 = choice of location and depth of the plant needle, Q3 = details of normal tissues around the tumor, Q4 = choice of angle and depth of the applicator, and Q5 = usefulness in treatment planning

point indicated useless/not lifelike at all/very poor, and 10 points indicated very useful/very lifelike/very good.

The questionnaires for patients and non-medical professionals were designed to assess the conversation before radiotherapy. Questionnaires included four open questions: 1) your overall evaluation of this conversation, 2) whether the model was helpful to know the condition, 3) the usefulness of model to understand radiotherapy, and 4) whether you wanted a doctor to use 3D models to communicate with you. Score was 1~10 points from low to high in turn, 1 point indicated useless/not lifelike at all/very poor, and 10 points indicated very useful/very lifelike/very good.

Radiotherapy doctors used 3D printing models to inform the patients or specified family members about the illness and make them understand the tumor size, location, and characteristics, as well as the brachytherapy implantation way, the possible complications of treatment, and so on.

3D-guided intracavitary brachytherapy: The bladder was emptied before brachytherapy and 100 mL of 0.9% sodium chloride solution was injected via catheter. The corresponding uterine cavity and vaginal vault source applicators and implantation needles were selected according to the 3D models, the source applicators were placed and fixed, and then CT scanning was conducted. **Target area outlining:** the CT image was transmitted to Oncentra after-loading treatment planning system via the network, and the target areas [gross tumor volume (GTV) and HR-CTV] as well

as organs at risk (bladder, rectum and sigmoid colon) were outlined. HRCTV: all cervix + tumor extension area identified before afterloading treatment, including parametrium, vault, and corpus. Bladder, rectum, and sigmoid colon were outlined in CT image step by step. Oncentra master treatment planning system (v3.3SP3) was used for reverse treatment plan design and optimization, HR-CTV single prescription dose was 6 Gy, the dose was 24-36 Gy/4-6 times, the target area outlined by doctors were referred for plan design and the dose optimization in three-dimensional direction, $D_{90} \geq 90\%$ of prescription dose, and the bladder, rectum, and sigmoid colon D_{2cc} had to be less than 450 cGy/f as much as possible. Finally the source applicator was connected to high-dose-rate ^{192}Ir after-loader for treatment.

Patients with greater than Stage IIb received concurrent radiochemotherapy and received cisplatin 40 mg/m² during the same period of radiotherapy, and each patient received 4~6 times of concurrent chemotherapy within treatment cycle. Thirteen cases with lymph node metastasis received cisplatin 40 mg/m²d2-4 + paclitaxel 1350 mg/m² d1 one month after radiotherapy. Twenty-one was a cycle, a total of 2~4 cycles.

Patients were followed with gynecological examination every three months the first year, every six months in years 2-3, and every 12 months in years 4-5. All patients were scanned with MRI at three-month follow-up and again at

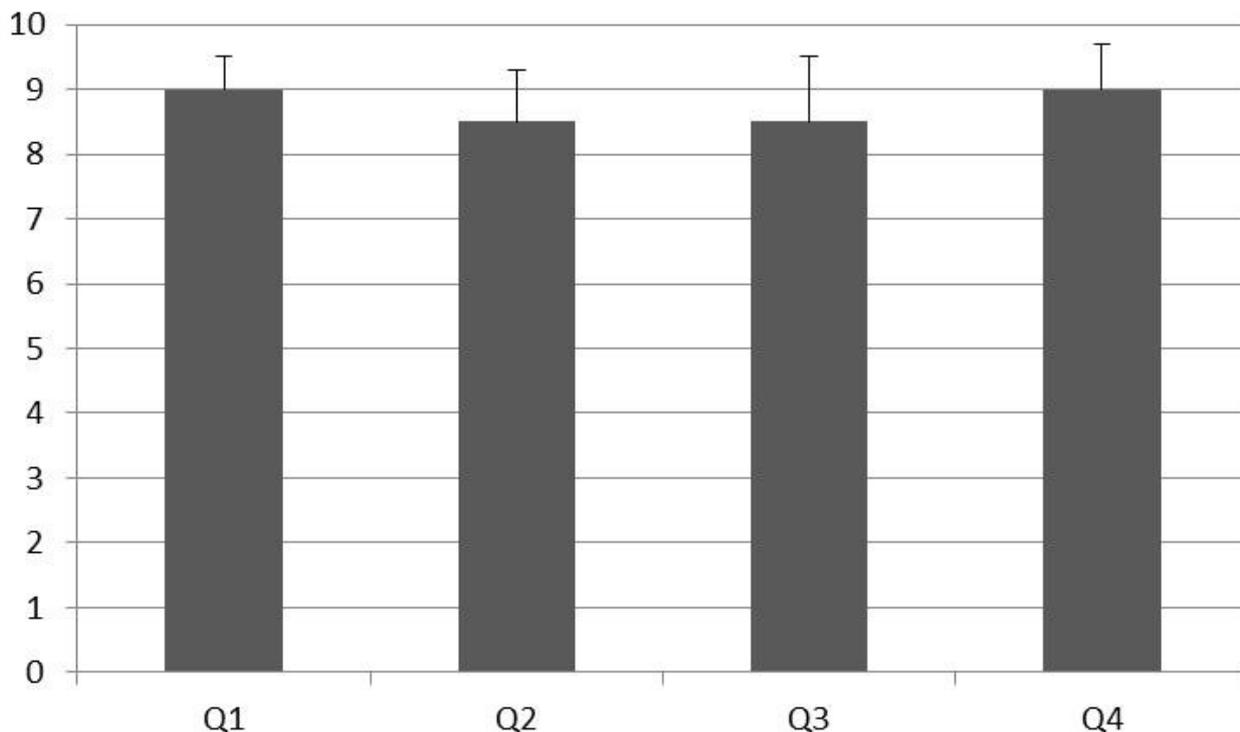


Figure 3. — Patient's acceptance survey of the cervical cancer models. Q1 = overall satisfaction of the conversation, Q2 = the model is useful to understand the disease, Q3 = the model is useful to understand the procedure of radiotherapy, and Q4 = whether the model is liked and open to discuss with the radiation therapist.

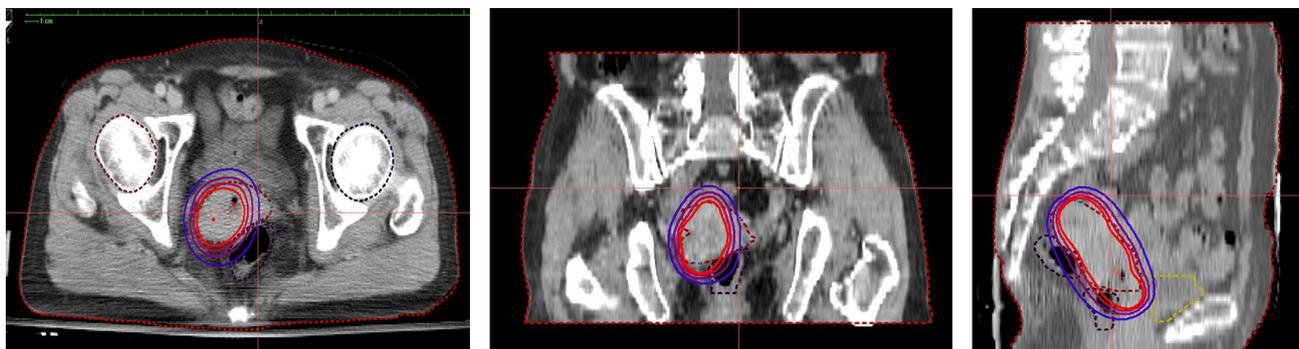


Figure 4. — Tumor target area dose is effectively guaranteed under the 3D printing guidance.

12-month follow-up. MRI was also performed if a recurrence was clinically suspected. Late morbidity was calculated at three years. SPSS 18.0 version statistical software was used for analysis, and Kaplan-Meier method was applied to draw local control, progression-free survival, and overall survival curves.

Results

3D doctor software was used for digital modeling of the collected MRI images, and then weedo printer was used to print cervical cancer models in different colors. Four colors of polymers were used for printing with 16- μ m thickness step-by-step. Corpus was white, bladder was blue, rectum

was yellow, and solid tumor was red, which was conducive to the analysis of the lesions.

A total of five experienced radiation experts were surveyed and the results of questionnaire 1 showed that the mean overall evaluation score was 8.0 ± 0.8 points, the mean score of the selection of parametrial tumor implantation location and depth was 8.1 ± 0.4 points, the mean score of the presentation of tumor and surrounding normal relational position was 7.6 ± 1.0 points, the mean score of the selection of intracavitary source applicator angle and depth was 8.2 ± 0.6 points, and the mean score of the scientificity as the overall individualized brachytherapy plan was 8.5 ± 0.8 points, as shown in figure 2..

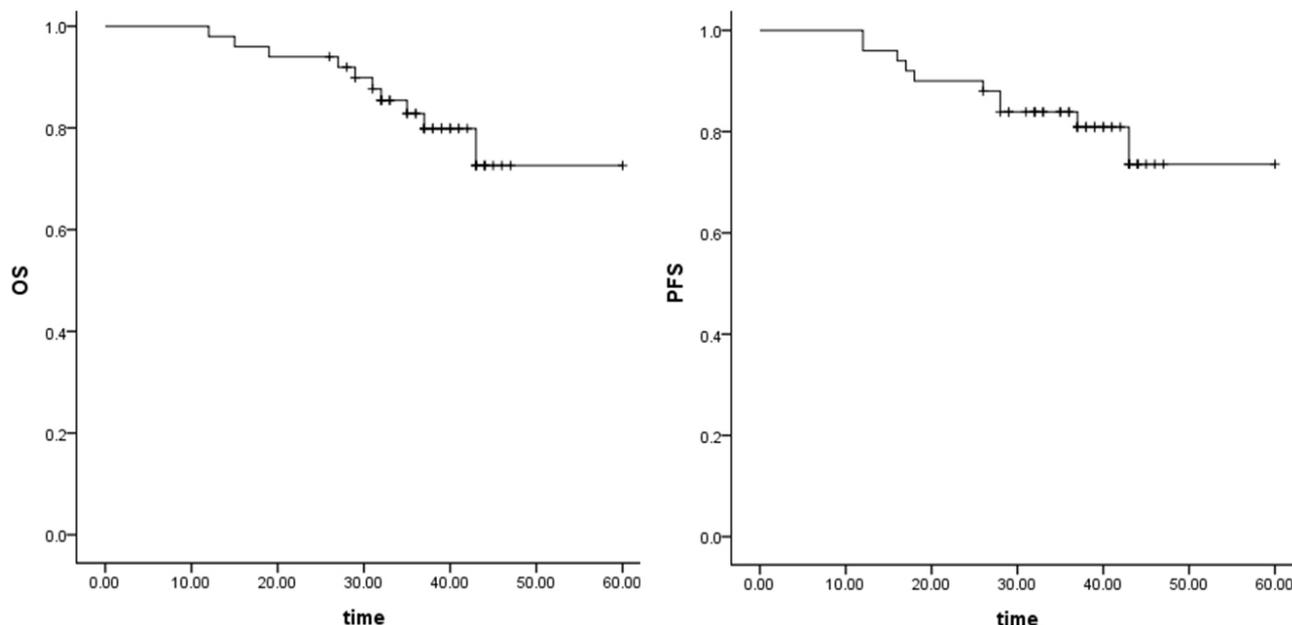


Figure 5. — Progressionfree and overall survival of cervical cancer.

The results of questionnaire 2 showed that 1) the mean score of your overall evaluation of this conversation was 9.0 ± 0.5 points, 2) the mean score of whether the model was useful to know the condition was 8.5 ± 0.8 points, 3) the mean score of the usefulness of model to understand radiotherapy was 8.5 ± 1.0 points, and 4) the mean score of whether you wanted a doctor to use 3D models to communicate with you was 9.0 ± 0.7 points. Patients and/or families had higher satisfaction to the use of 3D printing models of cervical cancer for condition explanation and preoperative communication modes.

DHV of three-dimensional after-loading treatment plan was analyzed, HR-CTV D90, bladder D2cc, sigmoid colon D2cc and rectum D2cc were recorded, and the biological equivalent dose was converted according to cervical cancer tissue $\alpha/\beta = 10$ and organs at risk $\alpha/\beta = 3$. EQD 2 of HR-CTV D90, bladder D2cc, sigmoid colon D2cc and rectum D2cc were 75.26 ± 6.31 , 67.84 ± 8.75 , 47.36 ± 7.62 , and 62.45 ± 8.68 Gy, respectively.

All patients successfully completed brachytherapy, a total of 109 case-times of after-loading brachytherapy were completed, 11 case-times were with single intracavitary source applicator, 58 case-times were with intracavitary source applicator + vault source applicator, and 40 case-times were combined with needle implantation treatment based on the above. Figure 4 shows that the tumor target area brachytherapy isodose curve was significantly optimized and parametrial tumor dose increased significantly.

Among 50 patients, six patients completed four cycles of concurrent chemotherapy, five cases completed six cycles of concurrent chemotherapy, and the remaining all completed five cycles of concurrent chemotherapy, 13 patients with positive lymph nodes received adjuvant chemother-

apy, and among them, three cases completed four cycles, four cases completed three cycles, and six cases completed two cycles of adjuvant chemotherapy. One case was with internal cervical orifice residual shown by MRI at three months after radiotherapy, one case was with left obturator lymph node residual shown by MRI at three months after radiotherapy, the remaining were without tumor via review at three months after radiotherapy, and the complete remission rate of tumor was 93.48 (48/50). The follow-up showed that three patients were with parametrial recurrence at 12, 18, and 28 months after the radiotherapy began respectively, and one case was with right internal iliac and right common iliac lymph node recurrence. The remaining 46 cervical cancer patients were without tumor recurrence within radiotherapy field, and the three-year LCR was 92% (46/50). The follow-up also showed three cases with mediastinal and left supraclavicular metastasis, one case with lung metastasis, one case with bone metastasis, and two cases with lung and bone metastasis. The three-year progression-free survival was 82% (41/50) and the three-year OS was 84% (42/50), as shown in Figure 5.

RTOG/EORTC standard for evaluation was used and included one case of acute reactions with three-level enteritis and five cases with two-level enteritis, and they were alleviated after symptomatic treatment. The symptoms were improved after enema and other symptomatic treatment. Three-year late toxic and side effects mainly included radiation proctitis, radiation urethritis and vaginitis, and their level 3 incidence rate were: radiation gastroenteritis: 10%, radiation urethritis: 6%, and radiation vaginitis I: 8%, respectively, and the conditions of all patients were not affected by the complications.

Discussion

The present situation of the application of 3D printing technology in the medical industry and the essential characteristics of additive manufacturing technology is rapid and efficiently and accurately reproduces the 3D calculation models [12]. From the perspective of the medical industry, 3D printing and medical industry is a “natural match”, and therefore, the market favors the application of 3D printing technology [13]. Lee *et al.* report indicates that 3D printing technology has been widely applied in the medical model, in surgery, as well as represents a surgical guide for orthopaedic implants and in other fields [14]. As for the doctors, the application of 3D printing technology is more precise [15, 16]. The simulation model can find a large amount of hidden information, the doctor can conduct pretreatment evaluation and choose intracavitary brachytherapy path and precise implantation radiotherapy plan, and can early exercise the given complete tumor volume and dose in radiotherapy, avoiding the surrounding tissue and other complex situations. Thus, every cervical cancer patient could receive individualized radiotherapy as far as possible, and the tumor dose could be maximized within the safety range.

Current clinical common 3D brachytherapy for cervical cancer is a CT positioning-guided treatment, it can preliminarily exert implantation and intracavitary cavity treatment of cervical cancer tumors, but its shortcomings are obvious [7, 8, 17]: 1) the low resolution of the tumor under CT guidance causes deficient accuracy of the tumor implantation, 2) the stereoscopic structure and specific location of tumor can only be simply judged by the physicians' local spatial thinking, 3) the spatial locations of surrounding normal tissues and tumor are still difficult to grasp, and the possibility of damage to normal tissue increases significantly. In summary, the pelvic cavity and cervical cancer tissues vary in size and location, and it is very difficult for clinical routine brachytherapy and implantation to achieve actual individualization. The application of 3D printing technology is expected to change the process, achieve a higher degree of individualized brachytherapy for cervical cancer, and improve patients' survival and quality of life [18].

In this study, 3D printing technology was applied in individualized brachytherapy for cervical cancer. After the cervical cancer models were printed, radiotherapy doctors and patients conducted different aspects of validation for the models. The radiotherapy doctors participating in the study gave high recognition to the fidelity of the models, 3D printing adopted MRI image data, the resolution of MRI to cervical cancer tissue, and the surrounding tissue was significantly superior to that of CT images [19], the reconstructed 3D model could reflect the actual situation of the tumor and was more valuable for guidance of radiotherapy, and the professionals' score of the overall evaluation of cervical cancer model was 8.0 ± 0.8 points [20]. At the same time, the entity models from 3D printing turn the virtual reconstruction-based brachytherapy into direct planning on the entity models. The questionnaire survey results show

that 3D printing has the following obvious advantages: 1) improving the conformality and dose distribution of cervical cancer brachytherapy, and Figure 3 shows that the iso-dose curve is obviously optimized, 2) it can more protect normal tissue, and the grasp of implanted needle quantity and depth is more accurate, and 3) the doctors' operation of the source applicator is smoother, and the selection of source applicator is clearer. In another part of the study, the individualized cervical cancer models were used to explain their conditions to the patients and communicate with them before radiotherapy; hence the patients or families had a more profound understanding regarding the technique and risk of radiotherapy, their cooperation degree and comfort increased significantly, and the overall evaluation reached 9.0 ± 0.5 points. In terms of clinical curative effect, 3D-printed cervical cancer models effectively guided the 3D brachytherapy, and through the DVH image evaluation of brachytherapy, the EQD2 of HR-CTV D90, bladder D2cc, sigmoid colon D2cc and rectum D2cc were 75.26 ± 6.31 , 67.84 ± 8.75 , 47.36 ± 7.62 , and 62.45 ± 8.68 , respectively, and both tumor and normal organ doses were satisfied [6, 21, 22].

Nonetheless, there are also some shortcomings in the study. Normal and tumor tissues in the models are outlined in the software step by step and the different organs cannot be automatically generated. The formed 3D models are still different from the actual images to a certain degree, the difference is closely related to the doctors' subjective outlining levels, and the outline of uterine cavity, in particular, is still not satisfactory [23]. In addition, printing materials in the study are hard in texture, are unable to simulate the soft structure of human tissue, and cannot perform simulation operation directly on the models [24]. To solve these problems, on the one hand, suitable image post-processing procedure for 3D printing has to be developed to make it more easily to reconstruct the fine anatomic structures of cervical cancer, on the other hand, suitable materials for soft tissue printing need to be explored to print out the models with similar texture to human tissue and have the radiotherapy physicians directly perform planning and preview on the models [25]. On this basis, it is necessary to design randomized controlled trials to validate the curative effect of 3D printing-guided individualized brachytherapy for cervical cancer.

In summary, digital modeling and 3D printing technology help to improve the cervical cancer patients' understanding of radiotherapy, which is helpful in planning before radiotherapy, precise source application during radiotherapy, and curative effect is ensured after radiotherapy of medical workers of intracavitary brachytherapy for cervical cancer, but the long-term efficacy of radical radiotherapy for cervical cancer has yet to be observed with a longer follow-up.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee Fuzhou General hospital.

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Conflict of interest

The authors declare no conflict of interest.

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