A comparative dosimetric study of cervical cancer patients with para-aortic lymph node metastasis treated with volumetric modulated arc therapy *vs*. 9-field intensity-modulated radiation therapy

Yaqin Wu[1#], Biqing Zhu[1#], Jingjing Han[1], Hanzi Xu[1], Zhen Gong[2], Yongqin Yang[1], Jian Huang[1], Emei Lu[1]

[1]Department of Radiation Oncology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing 210009, China; [2]Department of Gynecology, The Affiliated Obstetrics and Gynaecology Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing 210004, China

Contributions: (I) Conception and design: E Lu, J Huang; (II) Administrative support: E Lu; (III) Provision of study materials or patients: Y Wu, J Han; (IV) Collection and assembly of data: H Xu, Z Gong, Y Yang; (V) Data analysis and interpretation: Y Wu, B Zhu, J Han; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Emei Lu; Jian Huang. No. 42, Baiziting Road, Nanjing 210009, China. Email: luemei07@163.com; huangjian7107@163.com.

Background: To compare the dosimetric characteristics between volumetric modulated arc therapy (VMAT) and 9-field intensity-modulated radiation therapy (9F-IMRT) for cervical cancer patients with para-aortic lymph node (PALN) metastasis.

Methods: We selected 20 patients who had received extended-field radiotherapy for cervical cancer with PALN metastasis. IMRT and VMAT plans were compared in terms of target, organs at risk (OARs), homogeneity index (HI), conformity index (CI), the number of monitor units (MUs) and treatment time (s).

Results: The CI and HI of VMAT plans were superior to those of IMRT plans (P<0.05). As for OARs, the mean maximum doses (Dmean) to the kidneys in the VMAT plans were all lower than those in IMRT plans (P<0.001). V40, V50 of the rectum, and V40 of the bladder in VMAT plans involved fewer doses than IMRT plans (P<0.001). Compared with IMRT plans, VMAT reduced the average number of MUs by 51% and the average treatment time by 31%.

Conclusions: Both VMAT and IMRT plans can satisfy clinical dosimetric demands and protect OARs. VMAT has the best performance on CI and HI and can better protect the OARs. VMAT plans have fewer MUs and improve treatment efficiency.

Keywords: Cervical cancer; para-aortic lymph node metastasis (PALN metastasis); radiotherapy; intensity-modulated radiation therapy (IMRT); volumetric modulated arc therapy (VMAT)

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Introduction

Cervical cancer, which is a serious threat to women's life and health, is a common gynecological malignant cancer and currently ranks second in female cancer mortality rates. In addition, approximately 85% of cases occur in developing countries (1). Lymph node metastasis is the main pathway of cervical cancer metastasis. It generally proceeds from the primary tumor through the nearby lymphatic vessels and onwards to the uterus, obturator, and iliac and external iliac lymph nodes, finally metastasizing in the abdominal aortic lymph node (2). A study of the American Gynecologic Oncology Group (GOG) showed that 5% of the patients with stage Ib cervical cancer, 16% with stage II, and 25% with stage III had para-aortic lymph node (PALN) metastasis (3). PALN metastasis is one of the main prognostic factors for cervical cancer, and the PALN metastatic rate increases with the progression of disease stage (4). For the cervical cancer patients with PALN metastasis, extended-field radiotherapy should be considered (5). It is important for cervical cancer patients with PALN metastasis to choose an appropriate treatment plan.

Formerly, 3-dimensional conformal radiation therapy (3D-CRT) was the standard treatment for cervical cancer; however, this technique did not appreciably reduce radiation exposure to organs at risk (OARs) (6). The development of technology has led to the establishment of intensity-modulated radiation therapy IMRT (7), which can increase the gain ratio of radiotherapy and better protect the OARs (8-10). However, the treatment delivery time for IMRT is prolonged (9,10). Volumetric modulated arc therapy (VMAT) is a newer intensity-modulated arc therapy technique (11) that has been investigated in a variety of malignant tumors (12-14). Several studies on advanced cervical cancer have demonstrated reduced OAR doses with IMRT compared to 3D-CRT (15-17). There are also many studies that have focused on dosimetric differences between IMRT and VMAT in cervical cancer (18,19), but there are no reports comparing IMRT and VMAT in cervical cancer patients with PALN metastasis.

Thus, the current study was designed to compare the dose difference between IMRT and VMAT in the target area and in terms of organ dose. Additionally, it was designed to explore the optimal radiotherapy regimen for patients with cervical cancer with PALN metastasis.

Methods

Patient selection

A total of 20 patients who had received extended-field radiotherapy using the 9F-IMRT plan for cervical cancer with PALN metastasis were retrospectively selected for this study. The diagnosis of PALN metastasis was confirmed by PET-CT, which showed a standardized uptake value (SUV) ≥2.5, or lymph node diameter ≥10 mm. Every patient received concurrent chemotherapy with paclitaxel 135 mg/m^2 and cisplatin 50 mg/m^2. Patients were 39–72 years old, with a median age of 50.5 years. According to FIGO staging, 11 cases were stage II b, 9 cases were stage III b, and the pathological types were all squamous cell carcinoma. The maximum diameter of the abdominal aortic lymph nodes was 11–34 mm, and the average diameter was 15 mm.

CT simulation

Before the CT positioning was performed, the patients were required to empty their bowels and fill their bladders. All patients underwent CT scans in the supine position with a slice thickness of 3 mm, which is from the upper edge of T12 to 5 cm below the lower edge of the obturator foramen. After the simulation, the CT images were transferred into the Pinnacle treatment planning system (V9.2).

Delineation of target volumes and OARs

The target volumes were delineated by the same experienced radiation oncologist and radiologist (20). According to Report 83 by the International Commission on Radiation Units and Measurements (ICRU) (21), the clinical target volume (CTV) of extended-field radiotherapy for cervical cancer patients with PALN metastasis included the cervical mass, parametrial tissue, upper vagina, and uterus, along with the pelvic and PALNs of each patient. The planning target volume (PTV) was generated by adding 0.7 cm margins from the CTV in all directions except in the anterior and posterior directions (22) (*Figure 1*). The OARs included the kidneys, rectum, bladder, small intestine, pelvis, and bilateral femoral head.

9F-IMRT planning for cervical cancer patients with PALN metastasis

9F-IMRT plans were designed with Elekta Medical Systems, with a 6-MV beam linear accelerator. A total of 9 fields were used to generate the plans. The gantry angles of each field were 40°, 80°, 120°, 160°, 200°, 240°, 280°, 320°, and 0° (*Figure 2*). The prescription doses were 50.4 Gy in 28 fractions (daily dose of 1.8 Gy). All 9F-IMRT plans were normalized to cover 95% of the PTV with 100% of the prescription dose. The mean dose (D_{mean}) to the kidneys was limited to <12 Gy. The V50 of the small bowel was limited to less than 10%. The V50 of the rectum was limited to less than 50%, the V50 of the bladder was limited to less than 30%, and the V50 of the femoral heads was limited to less than 5% (23,24).

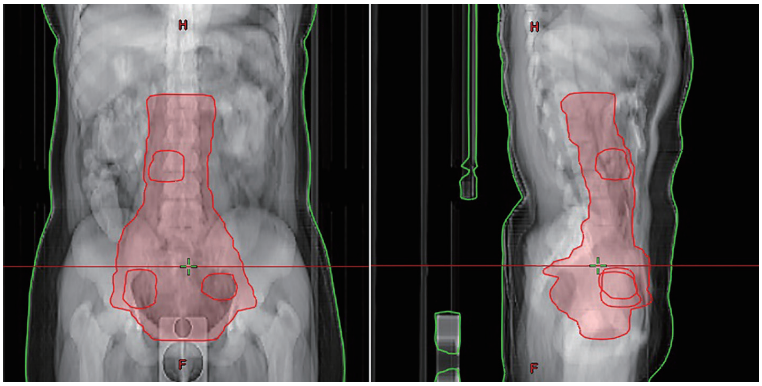

Figure 1 PTV of one cervical cancer patient with PALN metastasis. PTV, planning target volume; PALN, para-aortic lymph node.

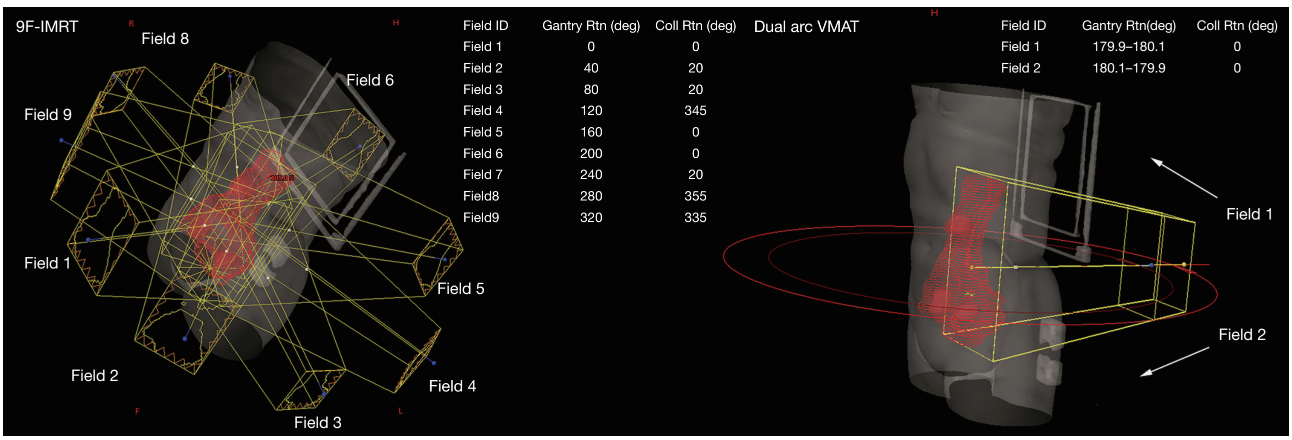

Figure 2 Beam-on fields of 9F-IMRT and beam-on fields of dual arc VMAT for one patient. 9F-IMRT, 9-field intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.

VMAT planning for cervical cancer patients with PALN metastasis

The prescription dose for the VMAT plans was the same as the 9F-IMRT plans (50.4 Gy in 28 fractions). The VMAT plans were performed using two coplanar arcs (clockwise rotation from 181° to 179° and counterclockwise rotation from 179° to 181°) (*Figure 2*). The 6-MV photon beam of Elekta Medical Systems was used. The VMAT plans were optimized in the Pinnacle treatment system (V9.2) by following the RTOG 0724 protocol, the same as for the 9F-IMRT planning (22). After dose calculation, all VMAT plans were normalized to cover 95% of the target volume, with 100% of the prescription dose.

Plan evaluation

ICRU 83 states that the quality of the radiotherapy program should be assessed by the target index (conformity index, CI) and the homogeneity index (HI).

$$CI = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \quad [1]$$

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad [2]$$

Description: TV_{RI} is the target volume of the prescription dose line, TV is the target volume, V_{RI} is the total volume of the prescription dose line, $D_{2\%}$ represents the approximate maximum dose, $D_{98\%}$ represents the approximate minimum

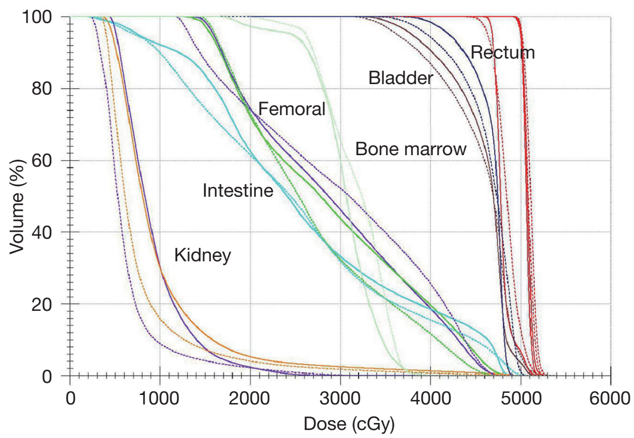

Figure 3 Comparison of DVH between dual arc VMAT and 9F-IMRT plans (the curve with represents the 9F-IMRT plan, and the curve with represents the dual arc VMAT plan). DVH, dose-volume histogram; 9F-IMRT, 9-field intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.

Table 1 Dosimetric parameters comparison between 9F-IMRT and dual arc VMAT

Item	VMAT	IMRT	t	P
$D_{2\%}$ (Gy)	50.4±1.9	53.1±3.7	3.055	0.007
$D_{50\%}$ (Gy)	47.2±0.8	46.9±0.9	–0.943	0.358
$D_{98\%}$ (Gy)	46.7±1.8	45.3±0.9	–3.161	0.005
$V_{95\%}$	98.7±0.9	97.7±0.8	–3.759	0.001
$V_{105\%}$	55.3±3.0	51.2±0.5	–5.855	<0.001
HI	0.08±0.03	0.10±0.03	2.262	0.036
CI	0.84±0.08	0.77±0.11	–2.657	0.016

$D_{2\%}$, the approximate maximum dose; $D_{50\%}$, the median dose; $D_{98\%}$, the approximate minimum dose; $V_{95\%}$, volume receiving 95% of the prescription dose; $V_{105\%}$, volume receiving 105% of the prescription dose; HI, homogeneity index; CI, conformity index. IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy. When 9F-IMRT *vs*. VMAT, P<0.05.

dose, and $D_{50\%}$ is the median dose. The CI value is between 0 and 1, and the larger CI values indicate a better dose of coverage in the target. Additionally, the lower the HI value is, the better the dose uniformity of the target (21).

Monitor unit (MU) and treatment time

Statistical analysis of MU was performed, and the treatment time of the two radiotherapy techniques was recorded (treatment time is the time taken for the first irradiation field to reach the end of treatment after completion of position and position verification).

Statistical analysis

SPSS 20.0 (IBM Corp, Armonk, NY, USA) statistical software was used to analyze the measurement data with ±s, between the two groups using the *t*-test. A P value <0.05 was considered a difference in statistical significance.

Results

Comparison of dose distribution

As shown in *Figure 3*, the dark yellow kidney volume was less than 1,200 cGy. Additionally, *Figure 3* shows that the kidneys on the 9F-IMRT and dual arc VMAT plans are well protected, but the dual arc VMAT plans could achieve a better dose distribution of the target. At the same time, the bladder and rectum doses in the dual arc VMAT were typically less than 9F-IMRT. Therefore, the OARs and the PTV dose-volume histogram (DVH) of the dual arc VMAT plan was superior to the 9F-IMRT plan.

Dosimetric comparison

Table 1 shows that the dose received by the target volume, D2% and D98% of the PTV in dual arc VMAT, was better than that in the 9F-IMRT plan, which was a statistically significant difference (P<0.01). The PTV volume receiving 95% and 105% of the prescription dose in dual arc VMAT was better than that in the 9F-IMRT plan, which was also a statistically significant difference (P<0.001). The CI for PTV was better in dual arc VMAT than in 9F-IMRT, while the HI for PTV in dual arc VMAT was lower than that in 9F-IMRT, which was a statistically significant difference (P<0.05).

Comparison of the irradiation dose of OARs

As for the OARs, the mean doses (D_{mean}) of the kidneys in the dual arc VMAT plans were all lower than those in the 9F-IMRT plans (P<0.001). The V40 and V50 of the rectum and V40 of the bladder in the dual arc VMAT plans carried fewer doses than IMRT (P<0.001). However, the V10, V20, and V30 of the rectum, V10, V20, V30, and

Table 2 Comparison of dose parameters for OARs between 9F-IMRT and dual arc VMAT

OAR	Dose of volume	VMAT	IMRT	t	P
Rectum	$V_{10\,Gy}$ (%)	98.2±1.3	97.9±1.2	−0.943	0.358
	$V_{20\,Gy}$ (%)	97.5±0.7	97.7±0.4	0.887	0.386
	$V_{30\,Gy}$ (%)	90.8±1.4	91.4±1.2	1.429	0.169
	$V_{40\,Gy}$ (%)	48.6±3.7	60.8±4.4	12.087	<0.001
	$V_{50\,Gy}$ (%)	42.7±1.7	37.1±1.2	15.582	<0.001
Bladder	$V_{10\,Gy}$ (%)	100±0.0	100±0.0	0.000	1.000
	$V_{20\,Gy}$ (%)	98.3±0.5	98.1±0.6	−1.418	0.172
	$V_{30\,Gy}$ (%)	76.7±2.9	76.3±2.8	−0.568	0.577
	$V_{40\,Gy}$ (%)	45.8±4.2	47.6±6.2	2.720	0.014
	$V_{50\,Gy}$ (%)	25.7±2.2	25.4±2.5	−0.419	0.680
Intestine	$V_{10\,Gy}$ (%)	81.8±1.1	81.1±1.6	−1.530	0.143
	$V_{20\,Gy}$ (%)	55.5±2.2	57.7±5.9	1.721	0.101
	$V_{30\,Gy}$ (%)	35.3±3.3	39.3±8.2	1.998	0.06
	$V_{40\,Gy}$ (%)	23.7±3.5	25.9±7.1	1.676	0.110
	$V_{50\,Gy}$ (%)	6.2±0.4	6.3±0.3	2.012	0.059
Femoral	$V_{10\,Gy}$ (%)	91.8±2.5	92.6±1.1	1.423	0.171
	$V_{20\,Gy}$ (%)	80.4±4.7	81.7±5.1	1.004	0.328
	$V_{30\,Gy}$ (%)	49.2±4.6	48.7±4.5	−0.626	0.539
	$V_{40\,Gy}$ (%)	30.1±1.6	30.7±0.8	1.513	0.147
	$V_{50\,Gy}$ (%)	3.4±0.6	3.2±0.5	−1.674	0.111
Kidney-L	Mean (Gy)	8.6±1.2	10.6±1.1	9.721	<0.001
Kidney-R	Mean (Gy)	8.4±1.3	10.6±0.9	5.741	<0.001

V_{xGy}, volume receiving at least X Gy dose; IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy. When 9F-IMRT *vs*. VMAT, P<0.05.

Table 3 Comparison of MU and treatment time between 9F-IMRT and dual arc VMAT

Item	VMAT	IMRT	t	P
MUs	812.5±218.1	1,670.7±182.2	16.628	<0.001
Time (s)	298.4±43.1	431.8±36.7	12.664	<0.001

IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy. When 9F-IMRT *vs*. VMAT, P<0.05.

V50 of the bladder,V10, V20, V30, V40, and V50 of the small intestine, and V10, V20, V30, V40, and V50 of the femoral heads all appeared the same as in the 9F-IMRT plans (P>0.05) (*Table 2*).

Comparison of MUs and treatment time

To evaluate the performance of dual arc VMAT and 9F-IMRT plans, the MU and treatment time were compared between the two plans and listed in *Table 3*. For the 20 patients, compared with 9F-IMRT, the dual arc VMAT plans reduced the average number of MUs by 51% (812.5±218.1 *vs.* 1,670.7±182.2). Compared with 9F-IMRT, the dual arc VMAT plans reduced the mean delivery time by 31% (298.4±43.1 *vs.* 431.8±36.7 s). Therefore, the dual arc VMAT plans reduced MU and treatment time, which means it had better treatment efficiency.

Discussion

Radiotherapy for cervical cancer was initially 2-dimensional whole pelvic radiotherapy (WPRT), which is associated with severe short- and long-term side effects. In recent years, with the continued improvement of radiotherapy technology, 3-dimensional conformal radiotherapy (3D-CRT) and fixed-field intensity-modulated radiotherapy (IMRT) have been extensively applied in the treatment of cervical cancer (25,26). IMRT possesses obvious superiorities over 3D-CRT technology because the dose distribution is more reasonable. In addition, IMRT can reduce the number of organs and normal tissues at risk, including the kidneys, rectum, bladder, and small intestine. Consequently, it can alleviate adverse reactions, thus improving the radiotherapy efficacy for cervical cancer (18,27). However, IMRT technology is associated with certain drawbacks, mainly in its efficiency (28).

Research has been carried out concerning dosimetric differences in radiotherapy using VMAT or IMRT for treating cervical cancer. Huang *et al.* (29) evaluated the dose distribution between VMAT and 7F-IMRT in 13 cervical cancer patients and found that VMAT regimen showed marked advantages over 7-IMRT in terms of target region dose homogeneity and protection of endangered organs. Meanwhile, Nguyen *et al.* (30) also found that, compared with a conventional IMRT regimen, VMAT could achieve a highly conformal target region dose distribution and greater protection of normal tissues.

IMRT-dominated radiotherapy remains the major PALN radiotherapy for cervical cancer. Osborne *et al.* (31) reported that using extended-field radiation therapy for patients with cervical cancer with PALN metastasis improved patient's condition in concurrence with advances in treatment. Portelance *et al.* (32) reported that, compared with 3D-CRT, IMRT reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. However, there is no research or report that compares IMRT and VMAT treatment plans for cervical cancer patients with PALN metastasis.

This study compared the dosimetric difference and the dosimetric parameters in 20 cervical cancer patients with PALN metastasis between 9F-IMRT and VMAT plans. The results in the current study indicate that the target region doses in both regimens can satisfy the dosimetric requirement. In terms of the target homogeneity and CI, the VMAT plan was superior to the 9F-IMRT plan, and the calculated treatment time of the 9F-IMRT was longer than that of the VMAT plan (431.8±36.7 *vs.* 298.4±43.1 s). VMAT can reduce the patient's discomfort caused by maintaining the same posture for a long time, reduce the errors caused by the body position during the treatment, and improve the accuracy of the treatment. The 9F-IMRT plans are delivered with the static IMRT technique, which needs more time to rotate the gantry and to move the MLCs between each beam-on (33). The 9F-IMRT plan has a disadvantage of relatively longer treatment times compared to VMAT; however, the expected real treatment time seems to be tolerable in the clinic.

Compared with the 9F-IMRT plan, the VMAT plan proved to be superior in the protection of OARs, because it reduced the irradiation dose they received. When a dose comparison of the kidneys was calculated, the observed mean dose for the kidneys in the VMAT plan was smaller than that in the 9F-IMRT plan, which could provide better protection for the kidneys. Meanwhile, V40 and V50 of the rectum and V40 of the bladder in the VMAT plans carried a smaller dose than that in the 9F-IMRT plan. VMAT was more conducive to the protection of normal tissues in the radiation field and in further reducing the adverse reactions patients experience during and after radiotherapy. In addition, the VMAT plan had lower MU than that of the 9F-IMRT plan, and the results are consistent with those in the international literature (34,35). Nevertheless, research results may be different in practical work, which can be attributed to the differences in planning systems such as single- or double-arc, radiation energy, optimization algorithm, and control of plan quality by operators. Therefore, a good VMAT plan needs to effectively control various influencing factors in the clinical environment and reduce unnecessary errors so as to obtain the optimization of the radiotherapy plan. For the same case, it requires a longer time to design a plan for VMAT in contrast with IMRT to meet the clinical requirements.

Conclusions

In summary, both plans could meet the requirements of OAR protection in cervical cancer patients with PALN metastasis. The VMAT plan is more ideal than 9F-IMRT plan in terms of target region conformity and can better protect OARs like the kidneys, rectum, and small intestine. In addition, VMAT contributes to reducing the exposure time and lowering the number of errors induced by position and organ movement during exposure. Therefore, the VMAT plan is a superior radiotherapy technique to

9F-IMRT plan in the radiotherapy treatment for cervical cancer patients with PALN metastasis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study is a retrospective analysis, only analyzing the patient's clinical data, not involving patient's privacy and treatment, so there is no informed consent was signed.

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