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FULL PAPER

Cervical cancer treated with reduced-volume intensity-modulated radiation therapy base on Sedlis criteria (NCCN VS RTOG)

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Objective: This study aimed to evaluate the clinical efficacy of different target volumes in pelvic radiotherapy in postoperative treatment of cervical cancer based on the Sedlis criteria.

Methods: Patients who admitted to our department for post-operative radiotherapy of cervical cancer from December 2001 to December 2011 and met the Sedlis criteria were retrospectively analysed. The incidences of acute and late radiation injuries, and overall, disease-free and tumour-specific survival with reduced-volume pelvic and whole-pelvis radiotherapy were evaluated and compared.

Results: A total of 371 patients were included in the study, including 239 receiving whole-pelvis radiotherapy and 132 receiving reduced-volume pelvic radiotherapy. The volume of contours for mean PTV volumes, bilateral femoral heads and small intestine volumes in reduced-volume pelvic radiotherapy were lower than whole-pelvis radiotherapy; the results were similar to the V10,

V20, V30, V40 and V45 for pelvic bone marrow and small intestine dose volume (both $p < 0.05$). The acute radiation injury observed in the two groups was mainly haematologic toxicity and upper and lower gastrointestinal symptoms. The incidences of acute radiation injury, and late radiation injury of gastrointestinal and urinary tracts were both significantly lower with reduced-volume pelvic radiotherapy than with whole-pelvis radiotherapy (both $p < 0.05$). Moreover, there was no significant difference in the incidence of lower extremity oedema, or 2-year or 5-year overall, disease-free or tumour-specific survival between groups (all $p > 0.05$).

Conclusion: Reduced-volume pelvic radiotherapy could relieve acute and late radiation injuries, especially myelosuppression, and did not affect long-term survival.

Advanced in knowledge: Our study shows that reduced-volume base on National Comprehensive Cancer Network 2016 is more fit for cervical cancer than others.

INTRODUCTION

Cervical cancer is a common gynecological malignancy worldwide.¹ The incidence of cervical cancer is on the rise in China. It caused approximately 98,900 new cases and 30,000 deaths in 2015.² The primary radical treatment of cervical cancer includes surgery and radiotherapy.³ The Sedlis criteria are newly included for intermediate risk factors in the 2015

National Comprehensive Cancer Network (NCCN) Guidelines to identify intermediate-risk indications for postoperative radiotherapy.⁴ The criteria are based on the risk factors of post-operative for the cervical cancer, such as lymphatic vascular space, deep stromal invasion and tumour size (the details were seen in Methods and Materials). Meanwhile, the target of radiotherapy was re-defined, it is suggested

that reduced-volume pelvic radiotherapy (including internal iliac lymph nodes, external iliac lymph nodes, and obturator lymph nodes only) can be given to patients with cervical cancer who have no lymph node metastasis detected during operation or by preoperative imaging, and meet the criteria after surgery. However, the clinical efficacy of reduced-volume pelvic radiotherapy has not been reported so far. In this study, postoperative cervical cancer patients who met the Sedlis criteria and received preventative pelvic radiotherapy were retrospectively analyzed to compare the clinical efficacy of reduced-volume pelvic and traditional RTOG whole-pelvis radiation.

METHODS AND MATERIALS

General clinical data

Patients given post-operative radiotherapy for cervical cancer from December 2001 to December 2011 in our department, with an Eastern Cooperative Oncology Group score of 0–1, no lymph node metastasis, parametrial invasion, no involvement of incisal edge and who met any of the following criteria (Sedlis criteria) were included: (a) lymphatic/vascular space invasion (LVSI), deep 1/3 stromal invasion, and any tumour size; (b) LVSI, middle one-third stromal invasion and ≥ 2 cm tumour size; (c) LVSI, superficial one-third stromal invasion, and ≥ 5 cm tumour size; or (d) no LVSI, middle or deep one-third stromal invasion and ≥ 4 cm tumour size. All patients had no history of malignancy and no contraindications to radiotherapy, and signed an informed consent before radiotherapy. They were divided into whole-pelvis [based on Radiation Therapy Oncology Group (RTOG)] and reduced-volume pelvic (based on Sedlis criteria) groups.

Radiotherapy protocol

CT simulation was performed with a scan range from the lower border of L4 to 2 cm below the end of the vagina. The CT images were transferred to the treatment planning system—Oncentra Master Plan v. 3.3 (Nucletron, BV, Veenendaal, Netherlands)—which made the localization CT and MR images to be fused. Target volumes were delineated by reference to Small.⁵ Pelvic lymph nodes were contoured with reference to Taylor et al.⁶ The inclusion of the whole group was outlined to endanger the organs, including the bladder, rectum, femoral head and intestine. Planning target volume was defined by expanding the CTV by 0.5 cm posteriorly and by 0.7 cm in the remaining directions. The three-dimensional conformal static-field intensity-modulated radiotherapy (IMRT) was used, 6 MV X-rays and 7 beams were applied. Dose calculation algorithms were employed by the methods of Collapsed Cone (Oncentra Master Plan v. 3.3 SP3). The radiotherapy plans corrected for tissue inhomogeneity. All the plans used 6 MV X-rays, 1.8 Gy per fraction, five times per week; the prescription dose was 45 Gy. The dose percentage of PTV should be above 95% to reach the prescription dose. Meanwhile, the dose was limited for organ at risk (OAR) as follows: rectum, V50 < 20% (V50 means the volume of tumour wrapped around 50 Gy isodose curve); bladder, V45 < 40%; small intestine, V30 < 40%; bilateral femoral heads, V50 $\leq$ 5%; pelvic bone marrow (including lumbosacral, iliac bone, ischio bone, pubic bone, proximal femoral and bilateral femoral heads), V30 < 50%.

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Efficacy evaluation

Side effects of radiotherapy were evaluated according to the acute radiation injury scoring criteria. Overall survival (OS) was defined as the time elapsed from the start date of radiotherapy to the date of death from any cause or the date of last follow-up. Disease-free survival (DFS) was defined as the time elapsed from the start date of radiotherapy to the date of disease progression (including local recurrence, regional metastasis, or distant metastasis) or death. Tumour-specific survival (TSS) was defined as the time elapsed from the start date of radiotherapy to the date of death from cervical cancer. The early side effects of radiotherapy were evaluated according to the RTOG acute radiation injury scoring criteria. The late complications of radiotherapy were assessed according to the RTOG/European Organization for Research and Treatment of Cancer late radiation injury scoring criteria.^{7,8}

Follow-up

The first follow-up visit was performed 1 month after the end of radiotherapy. Follow-up visits were scheduled every 3 months in the first 2 years, every 6 months in the third year and once a year thereafter. Patients who did not return to the hospital were followed up by phone.

Statistical analysis

Data were processed with SPSS 13.0 [v. 13.0; Chicago, IL (formerly SPSS Inc.)]. Enumeration data were analysed by χ^2 test. Means were compared with Student's *t*-test. Ranked data were analysed by Mann–Whitney *U* test. Survival analysis was performed using the Kaplan–Meier method. The dose to organs at risk was determined using Graphpad Prism [v. 5.0; La Jolla, San Diego, CA (Graphpad Software, Inc.)]. *p* < 0.05 was considered statistically significant.

RESULTS

Patient population

A total of 371 post-operative cervical cancer patients met the Sedlis criteria, with a median age of 53.7 years. Of them, 239 patients underwent whole-pelvis radiotherapy, and 132 had

Table 1. Comparison of clinicopathological characteristics between groups (n, %)

Clinicopathological parameters	Whole-pelvis radiotherapy (n = 239)	Small-field pelvic radiotherapy (n = 132)	p-value
Age (year)			0.211
<60	202	118	
≥60	37	14	
FIGO stage			0.944
IA1	99	53	
IA2	117	67	
IB1	23	12	
Hysterectomy			0.499
Type B	194	103	
Type C	45	29	
Pathological type			0.256
Squamous carcinoma	218	118	
Adenocarcinoma	9	2	
Adenosquamous carcinoma	12	3	
Sedlis criteria			0.973
A	62	33	
B	48	27	
C	81	43	
D	48	29	
ECOG score			0.325
0	148	92	
1	84	37	
2	7	3	

ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of Gynecology and Obstetrics.

Note. Hysterectomy Type B, modified radical hysterectomy; Type C, nerve sparing radical hysterectomy. See the "General Clinical Data section" for Sedlis criteria A, B, C and D.

reduced-volume pelvic radiotherapy. As of 31 December 2016, the overall groups of patients were followed up for 13.6–92.7 months, with a median follow-up of 68.9 months. A total of 17 patients were lost to follow-up, with a follow-up rate of 92.7%. The two groups were comparable in terms of age, The International Federation of Gynecology and Obstetrics staging, type of hysterectomy, pathological type and Eastern Cooperative Oncology Group score (Table 1).

Volume of contours

The mean PTV volumes were $747 \pm 98 \text{ cm}^3$ (NCCN), $958 \pm 82 \text{ cm}^3$ (RTOG); Mean PTV volume difference was $-167 \pm 41 \text{ cm}^3$ (NCCN vs RTOG). The mean bilateral femoral heads were $86 \pm 5 \text{ cm}^3$ (RTOG) and $81 \pm 7 \text{ cm}^3$ (NCCN). The mean small intestine volumes were $436 \pm 29 \text{ cm}^3$ (NCCN), $517 \pm 39 \text{ cm}^3$ (RTOG); Mean small intestine volume difference was $-74 \pm 16 \text{ cm}^3$ (NCCN vs RTOG). Similarly the average volumes of bladder were $454 \pm 36 \text{ cm}^3$ and $442 \pm 39 \text{ cm}^3$ for NCCN and RTOG, with rectum volumes of $35 \pm 4 \text{ cm}^3$ and $32 \pm 5 \text{ cm}^3$, respectively.

Dose volume to OAR

The pelvic bone marrow dose volumes V10, V20, V30, V40 and V45 were 97.8 ± 1.5 , 84.3 ± 5.3 , 52.4 ± 5.1 , 27.3 ± 4.1 and $12.3 \pm 5.2\%$ in RTOG plan, respectively; and 91.2 ± 3.6 , 63.3 ± 5.8 , 45.2 ± 5.3 , 22.7 ± 4.9 and $11.2 \pm 6.2\%$ in NCCN plan. When compared with the RTOG plan, the mean pelvic bone marrow dose volume was increased for NCCN plan ($p < 0.05$). Meanwhile, the small intestine dose volumes V10, V20, V30, V40 and V45 were 76.6 ± 13.8 , 52.4 ± 15.6 , 35.5 ± 11.2 , 30.9 ± 10.8 , $10.9 \pm 4.5\%$ in RTOG plan, respectively; and 61.6 ± 12.5 , 41.8 ± 13.1 , 16.9 ± 8.9 , 11.5 ± 9.7 , $4.7 \pm 2.2\%$ in NCCN plan. Concerning the small intestine dose volume, the group means of dose volume were the difference between RTOG and NCCN ($p < 0.05$). Similarly the dose volume for rectum, bladder and for two groups ($p > 0.05$) is calculated. Results are shown in Figure 1.

Acute radiation injury

All patients completed the radiotherapy. The median duration of whole-pelvis radiotherapy and reduced-volume pelvic

Figure 1. The dose of organ at risk (a) rectum; (b) bladder; (c) pelvic; (d) small intestine. RTOG, Radiation Therapy Oncology Group; NCCN, National Comprehensive Cancer Network.

radiotherapy was 23.7 ± 1.6 days and 24.2 ± 1.8 days, respectively, with no significant difference between groups ($p > 0.05$). The acute radiation injuries observed in the two groups were mainly haematologic toxicity, and upper and lower gastrointestinal symptoms. The incidence of decreased haemoglobin, thrombocytopenia and thrombocytopenia of $\geq$ Grade 3 toxicity with whole-pelvis radiotherapy was 7.1, 4.2 and 4.6%, respectively, which were significantly higher than the 2.3, 2.3 and 1.5% with reduced-volume pelvic radiotherapy ($p < 0.05$). The incidence of upper and lower gastrointestinal symptoms classified as $\geq$ Grade 1 with whole-pelvis radiotherapy was 94.5 and 96.6%, respectively, which were higher than the 71.2 and 81.8%

with reduced-volume pelvic radiotherapy ($p < 0.05$). Results are shown in Table 2.

Late radiation injury

The late radiation injuries observed in the two groups were mainly gastrointestinal and urinary tract symptoms. With whole-pelvis radiotherapy, gastrointestinal symptoms of $\geq$ Grade 3 were observed in 4 patients, and urinary tract symptoms of $\geq$ Grade 3 in 17 patients. Both symptoms were relieved after symptomatic treatment. No gastrointestinal or urinary tract symptoms of $\geq$ Grade 3 were observed with reduced-volume pelvic

Table 2. Comparison of acute radiation injuries between groups [case (%)]

	Whole-pelvis radiotherapy ($n = 239$)					Small-field pelvic radiotherapy ($n = 132$)				
	0	1	2	3	4	0	1	2	3	4
Decreased haemoglobin ^a	32	123	67	12	5	17	67	45	3	0
Thrombocytopenia ^a	18	137	74	9	1	27	68	35	2	0
Thrombocytopenia ^a	21	118	89	11	0	26	90	14	2	0
Upper gastrointestinal symptom ^a	13	174	52	0	0	38	76	18	0	0
Lower gastrointestinal symptom ^a	8	186	45	0	0	24	85	23	0	0

^aIndicates significant difference between groups ($p < 0.05$).

Table 3. Comparison of late radiation injuries between groups [case (%)]

	Whole-pelvis radiotherapy (<i>n</i> = 239)					Small-field pelvic radiotherapy (<i>n</i> = 132)				
	0	1	2	3	4	0	1	2	3	4
Gastrointestinal symptoms ^a	197	29	9	3	1	122	7	3	0	0
Urinary tract symptoms	188	34	12	5	0	112	16	4	0	0
Lower extremity oedema	232	6	1	0	/	129	3	0	0	/

^aIndicates significant difference between groups ($p < 0.05$).

radiotherapy. The incidence of lower extremity oedema with whole-pelvis and reduced-volume pelvic radiotherapy was 2.9 and 2.3%, respectively, with no significant difference ($p > 0.05$). Results are shown in Table 3.

Survival and prognosis

Eight deaths occurred in patients receiving whole-pelvis radiotherapy, including three from non-tumour causes (one from pneumonia, one from heart failure and one from diabetic ketoacidosis). One patient was diagnosed with primary lung cancer 4 years after radiotherapy. The 2-year and 5-year OS were 97.1 and 92.1%, respectively. The 2-year and 5-year TSS were 97.9 and 93.3%, respectively. The 2-year and

5-year DFS were 95.3 and 89.1%, respectively. A total of five deaths occurred in patients receiving reduced-volume pelvic radiotherapy including two from non-tumour causes (one from myocardial infarction and one from heart failure). The 2-year and 5-year OS were 97.7 and 91.6%, respectively. The 2-year and 5-year TSS were 98.4 and 93.9%, respectively. The 2-year and 5-year DFS were 96.2 and 89.3%, respectively. There was no significant difference in OS, PFS or TSS between groups ($p > 0.05$). Survival curves of the two groups are shown in Figure 2.

Figure 2. The survival of two groups (a) free disease survival; (b) disease special survival; (c) overall survival.

DISCUSSION

Concurrent radiochemotherapy combined with brachytherapy is the standard treatment of locally advanced cervical cancer. However, the treatment of early cervical cancer, especially post-operative radiotherapy indications in early cervical cancer, is still controversial. Conventionally, post-operative radiotherapy indications in patients with cervical cancer are high risk factors, *i.e.* positive lymph nodes, involvement of incisal edge and parametrial invasion. However, it is not clear whether radiotherapy should be given to patients with cervical cancer without high risk factors. At present, most studies on cervical cancer focus on the technological improvement of radiotherapy for intermediate and advanced cervical cancer, including adaptive IMRT and proton IMRT.^{9–13} There is only one ongoing study (GOG0263) on concurrent chemotherapy using the Sedlis criteria worldwide. However, post-operative radiotherapy field identified using the Sedlis criteria and the corresponding clinical efficacy have not been reported.

Obturator, internal iliac and external iliac lymph nodes (83.7%) are the most common sentinel lymph nodes in early cervical cancer, followed by common iliac (6.6%), para-aortic (2%) and inguinal lymph nodes (0.07%).¹⁴ This is consistent with the concept that reduced-volume pelvic radiotherapy should be given to post-operative cervical cancer patients who have no high risk factors and meet the Sedlis criteria. IMRT can reduce the side effects of radiotherapy for post-operative cervical cancer patients.¹⁵ All patients included in this study received IMRT. The incidences of acute and late radiation injuries were both lower than previously reported.^{8–10} It may be related to the early stage of cervical cancer of the patients included in this study. No patient developed intestinal obstruction in the overall group, which was not consistent with the findings of Wright et al.¹⁶ This may be associated with a low pre-operative tumour burden, a small post-operative target volume and early clinical stage in this study.¹⁷ Further research with large sample sizes is required.

According to the International Commission on Radiation Units 83 report, organs at risk are divided into serial, parallel and serial-parallel organs. High doses of D1cc, D2cc or D2 should be reported for serial organs, V_D and D_{mean} for parallel organs and all the above parameters for serial-parallel organs. Pelvis, as a parallel organ, is the most important haematopoietic tissue.¹⁸ In this study, the incidence of haematologic toxicity (decreased haemoglobin, thrombocytopenia and leukopenia) was shown to be significantly lower with reduced-volume pelvic radiotherapy than with whole-pelvis radiotherapy. Bone marrow-sparing IMRT was applied to reduce low dose radiation volume for all post-operative cervical cancer patients included in the study.¹⁹ Nevertheless, the incidence of bone marrow suppression was significantly decreased with reduced-volume pelvic radiotherapy because of a decreased CTV and significantly lower V10 and V20 as compared with whole-pelvis radiotherapy.²⁰ The planning target volume of bladder and rectum roughly overlapped with

the CTV. Hence, a dosimetric advantage was not seen in favour of the reduced-volume pelvic radiotherapy for the bladder and rectum. The incidences of acute and late radiation injuries of the upper and lower gastrointestinal tract were significantly lower with reduced-volume pelvic radiotherapy than with whole-pelvis radiotherapy. This further demonstrates that V15 for the small intestine is not only an important index to evaluate the gastrointestinal effects,²¹ but also an independent prognostic factor for evaluating late gastrointestinal effects.²²

Chemoradiotherapy of cervical cancer can lead to severe late intestinal and urinary tract radiation injuries in 6–23% of patients.²³ In the study, late radiation injury of $\geq$ Grade 3 was observed in 8.9% (21), 8.9% (21) and 0% (0) of the overall, whole-pelvis radiotherapy and reduced-volume pelvic radiotherapy groups. This may be closely related to the early cancer stage, absence of concurrent chemotherapy and a small radiation volume of the reduced-volume pelvic radiotherapy. It needs to be further investigated whether adjuvant radiotherapy provides better bladder filling, decreased mobility and higher protection of the intestinal tract in post-operative early cervical cancer patients to reduce radiation injury.²⁴ The incidence of lower extremity oedema with adjunctive radiotherapy using the Sedlis criteria in the 5-year follow-up was significantly lower than that reported by Ohba.²⁵ This may be related to the early cancer stage, and absence of distal external iliac lymph nodes, an independent factor of lower extremity oedema, in patients included in this study.^{26,27}

Patients with early cervical cancer receiving post-operative adjuvant radiotherapy had a good overall prognosis and a 10-year recurrence rate of 13–17%,²⁸ which was higher than that in this study. It may be related to the relatively short follow-up period of this study. Another study revealed 5-year recurrence-free survival of 93.8% in patients with no high risk factors who received post-operative concurrent radiochemotherapy,²⁹ which is similar to the results of whole-pelvis and reduced-volume pelvic radiotherapy in this study. The 2-year results of OS, TSS and DFS in both the whole-pelvis and reduced-volume pelvic radiotherapy groups are consistent with the findings of Folkert et al.³⁰ This shows that despite its larger radiation field, the whole-pelvis radiotherapy did not show a survival advantage in the 5-year follow-up period over the reduced-volume pelvic radiotherapy. This may be related to the biological characteristics of cervical cancer, as well as the low recurrence and metastasis rates of early cervical cancer.

CONCLUSIONS

This study retrospectively analysed the clinical efficacy of adjuvant radiotherapy in post-operative cervical cancer patients who met the Sedlis criteria. It was found that reduced-volume pelvic radiotherapy could relieve acute and late radiation injuries, especially myelosuppression, and did not affect long-term survival. However, the conclusions of this study require further consolidation.

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