Relative dose intensity and overall treatment time in older patients with cervical cancer treated with concurrent chemoradiotherapy

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Rie Nakamura *, Yuko Shimoji, Tadaharu Nakasone, Yusuke Taira, Yoshihisa Arakaki, Tomoko Nakamoto, Takuma Ooyama, Wataru Kudaka, Keiko Mekaru, Yoichi Aoki

Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

1. Introduction

Concurrent chemoradiotherapy (CCRT) using cisplatin (CDDP) is the standard treatment for locally advanced cervical cancer [1]. This standard treatment has been validated in a number of clinical trials, and CCRT is regarded as a standard treatment. However, older patients are often excluded from clinical trials, and there are few reports on the efficacy and safety of CCRT in older patients. Older patients have a high ratio of organ dysfunction and comorbidities, and many patients take multiple drugs; therefore, adverse drug reactions are more likely to occur. Furthermore, severe physical deterioration frequently occurs despite a mild adverse drug reaction. Thus, it remains controversial whether CCRT treatment should be indicated in patients aged 65 years or older with cervical cancer [2].

In this study, patients with cervical cancer treated with CCRT were divided into older patients (older group ≥65 years) and younger patients (younger group <65 years). The groups were compared, and the relationship between the relative dose intensity (RDI) and the overall treatment time (OTT) with progression-free survival (PFS) and overall survival (OS) were investigated.

2. Methods

We retrospectively analyzed patients with FIGO (International Federation of Gynecology and Obstetrics) stage IB1 to IVA cervical cancer treated with the first CCRT during the period 2009–2019 at the University Hospital of Ryukyus. The histological type was limited to squamous cell carcinoma. CCRT was indicated for cases in which the tumor diameter exceeded 40 mm or pelvic lymph node enlargement was observed. Cases with common iliac and/or para-aortic lymph node enlargement shown by CT or MRI were excluded. In addition, CCRT was selected for cases aged 64 years or younger with a tumor diameter of 25 mm or more [3].

The CCRT regimen consisted of CDDP 40 mg^{-2} weekly, administered concomitantly with radiation (RT). RT was administered as described in a previous study [4]. All patients were treated with whole-pelvic (WP) external beam RT (ERBT). A 50-Gy dose of ERBT was delivered in 25 fractions, and the center shield was set up after delivering 40-Gy. High-dose rate intracavity brachytherapy (HDR-ICBT) was delivered once per week at a fraction dose of 6 Gy administered one to three times at Point A, for a total dose of 6–18 Gy. A boost EBRT dose of 6–20 Gy in one to four fractions was applied to the pelvic walls and/or nodal metastases for patients with nodular parametrial involvement.

RDI is the ratio of the delivered dose intensity of chemotherapy to the standard (referenced) dose intensity [5]. It is said that keeping the RDI high can maximize the antitumor effect of the drug. In other words, it is necessary to minimize the dose reduction of drugs and postponement/discontinuation of the administration schedule due to adverse events [6].

OTT is the total treatment period of radiation, and is considered to be an important factor affecting the treatment outcomes. When treatment is discontinued, it is generally accepted that the treatment results will be reduced due to tumor re-growth. Consequently, the American Brachytherapy Society (ABS) recommends that OTT be contained within 8 weeks [7].

This retrospective study was approved by the Institutional Review Board of our University on 7 October 2019 (#1493) and all patients gave written informed consent.

3. Results

The patient characteristics and treatment outcomes are shown in Table 1. Of the 181 patients with squamous cell carcinoma treated with CCRT, 30 patients were classified into the older group, and 131 patients were classified into the younger group. With regards to FIGO staging, significantly more patients in the older group were stage III/IV compared to those in the younger group ($p = 0.022$). Pelvic lymph node enlargement was observed in 21 cases (70.0%) in the older group and 86 cases (57.0%) in the younger group, which was significantly higher in the older group ($p = 0.009$).

The median course of chemotherapy was significantly lower in the older group with 4 courses (range, 1–6 courses), and 5 courses in the younger group (range, 1–7 courses) ($p = 0.043$). The median RDI was also significantly lower in the older group at 0.62 (range, 0.20–1.00),

* Corresponding author at: Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, 207 Uehara Nishihara, Okinawa 903-0215, Japan.
E-mail address: h107649@med.u-ryukyu.ac.jp (R. Nakamura).

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Table 1
Patient characteristics and treatment outcome.

Clinical variables	Older group ≥65 years	Younger group <65 years	*p*-value
	$n = 30$	$n = 151$	
Median age (range) (years)	67 (65–73)	50 (30–64)	< 0.001
FIGO stage			
IB1	5 (16.7%)	24 (15.9%)	0.022
IB2	2 (6.7%)	40 (26.5%)	
IIA	1 (3.3%)	9 (6.0%)	
IIB	8 (26.7%)	39 (25.8%)	
IIIA	0	0	
IIIB	12 (40.0%)	35 (23.2%)	
IVA	2 (6.7%)	4 (2.7%)	
Performance status			
0	26 (86.7%)	143 (94.7%)	0.148
1	2 (6.7%)	6 (4.0%)	
2	2 (6.6%)	2 (1.3%)	
Pelvic lymph node enlargement			
Yes	21 (70.0%)	86 (57.0%)	0.009
No	9 (30.0%)	65 (43.0%)	
Median tumor size (range) (mm)	48 (25–102)	46 (16–110)	0.456
Median pre-treatment Hb (g dl^{-1})	13 (8–15)	12 (7–16)	0.171
Median pre-treatment SCC (ng ml^{-1})	6.4 (0.7–84.0)	7.3 (0.7–196.0)	0.810
Median course of chemotherapy (courses)	4 (1–6)	5 (1–7)	0.043
Median relative dose intensity	0.62 (0.20–1.00)	1.00 (0.04–1.00)	0.023
Median overall treatment time (days)	49 (35–74)	48 (9–69)	0.956
Median follow-up period (months)	40 (4–91)	22 (2–127)	0.448
Completion of radiotherapy			
Yes	27 (90.0%)	145 (96.0%)	0.172
No	3 (10.0%)	6 (4.0%)	

Student's *t*-test was used to analyze the distributed data, and Fisher's exact test was used to analyze the categorical data. A p-value of less than 0.05 was considered significant.
FIGO: International Federation of Gynecology and Obstetrics, Hb: Hemoglobin, SCC: Serum squamous cell carcinoma antigen.

and 1.00 (range, 0.04–1.00) in the younger group ($p = 0.023$). In contrast, there was no significant difference in the median OTT between the two groups, at 49 days (range, 35–74 days) in the older group, and 48 days (range, 9–69 days) in the younger group. Additionally, there was no significant difference in the completion rate of radiotherapy between the two groups, at 27/30 (90.0%) for the older group and 145/151 (96.0%) for the younger group. Furthermore, there were no significant differences in performance status (PS), tumor size, pre-treatment Hb (hemoglobin) level, pre-treatment SCC (serum squamous-cell carcinoma antigen) level, and follow-up period.

The survival rate is shown in Fig. 1. There was no significant difference in the 5-year PFS between the two groups, at 62.4% in the older group and 75.3% in the younger group ($p = 0.685$). Similarly, there was no significant difference in the 5-year OS between the two groups, at 71.6% in the older group and 83.0% in the younger group ($p = 0.791$).

Univariate and multivariate analyzes were performed on prognostic factors affecting PFS and OS (Supplementary Table S1). In terms of prognostic factors affecting PFS, multivariate analysis showed a significant difference in prognostic factors between RDI and tumor size; in other words, low RDI and increased tumor size were poor prognostic factors.

Supplementary Table S2 shows the adverse events. Grade 1 and 2 nausea and vomiting were significantly increased in the older group ($p = 0.023$). Regarding leukopenia, anemia, thrombocytopenia, and diarrhea, there were no significant differences between the two groups. No significant difference was observed in late radiation adverse events in the intestine and bladder. However, late radiation adverse events in the bones were significantly increased in older patients ($p = 0.009$).

4. Discussion

We aimed to compare the RDI and OTT in CCRT between the two groups. It is said that keeping the RDI high can maximize the antitumor effect of the drug. Indeed, by reviewing the relationship between the RDI and survival rate in advanced/metastatic solid tumors, it was reported that there was a favorable impact on survival by keeping the RDI ≥ 85% [8]. To date, many reports have examined the RDI and survival rates for chemotherapy for ovarian cancer. However, few reports have examined the RDI and survival rates of CCRT in cervical cancer. On the other hand, several studies were reported on the OTT and survival rates of CCRT. Currently, the ABS also recommends that OTT be contained within 8 weeks [7].

The results of our study show that the median RDI and the median number of chemotherapy courses were significantly lower in the older group than the younger group. In contrast, there was no significant difference in the OTT and completion rate of radiotherapy. Furthermore, when comparing the survival rates of the older group and the younger group, no significant difference was found between PFS and OS.

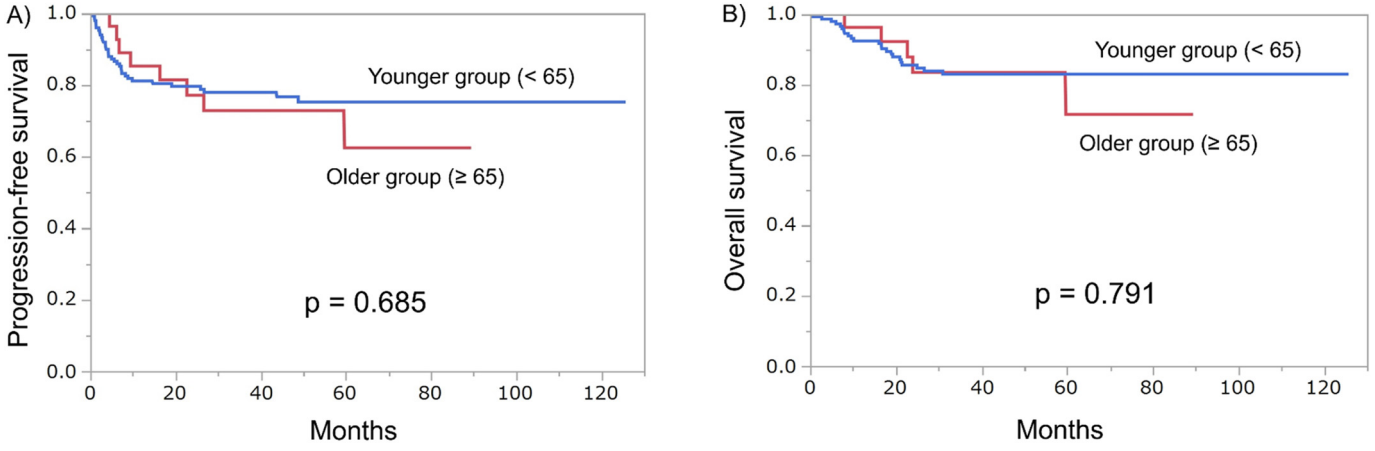

Fig. 1. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method, and differences were determined using the log-rank test. A *p*-value of less than 0.05 was considered significant. A) Kaplan-Meier curves for PFS. The 5-year PFS was 62.4% in the older group and 75.3% in the younger group, with no significant difference ($p = 0.685$). B) Kaplan-Meier curves for OS. The 5-year overall survival was 71.6% in the older group and 83.0% in the younger group, with no significant difference ($p = 0.791$).

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Whether age is a prognostic factor for cervical cancer remains controversial. Meanweal et al. reported that in stage IB disease of cervical cancer treated with definitive radiotherapy, the 5-year OS rate was 65% in patients between 25 and 29 years of age, compared to 71% in those between 65 and 69 years of age; thus, young age was a poor prognostic factor in cervical cancer as it rapidly progressed biologically or immunologically [9]. In contrast, Grigien et al. reported that age did not affect survival in 162 cases of stage IIA to IIIB cervical cancer treated with definitive radiotherapy when comparing three groups: under 50 years old, 50 to 64 years old, and over 65 years old. They consider factors other than age, such as tumor size, may have a strong impact on survival [10]. In our study, a low RDI was observed in the older group, and in multivariate analysis of PFS, low RDI was extracted as an independent poor prognostic factor. However, there was no significant difference in PFS and OS between the two groups. This may be because the previous reports are different in terms of radiation treatment and patient backgrounds. Therefore, it is still unclear whether age is a prognostic factor for cervical cancer.

Furthermore, there was no significant difference in the OTT between the two groups. In our study, the older group had a lower RDI than the younger group. However, radiotherapy, which is the main treatment, continued as far as possible if the protocol was satisfied, and in many cases, it was within the 8 weeks recommended by the ABS. Grigien et al. reported that OTT was an independent prognostic factor for OS, disease free survival, and local control [10]. Similarly, in our study, there was no significant difference in OTT between the two groups. As a result, it can be considered that OS and PFS showed no significant difference between the two groups. However, regarding PFS and OS, there are limitations such as the small number of cases in the older group and the retrospective nature of our study. Therefore, it is also suggested that a low RDI in the older group may be overestimated.

5. Conclusion

Although a low RDI was observed in the older group, it did not affect PFS and OS. Moreover, the OTT was not significantly different between the two groups. In CCRT in older patients, it was important to minimize the delay or discontinuation of the radiation treatment schedule.

Author Contributions

The work presented here was carried out in collaboration among all authors. RN, WK, and YA made substantial contribution to the study concepts and study design. RN, YS, TN, YT, YA, TN, TO, WK, KM, and YA engaged in data acquisition and data analysis. RN, WK, and YA engaged in data interpretation, and statistical analysis. RN presented and edited this manuscript. All authors have reviewed the manuscript and have approved the final article.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2020.09.007.

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