

# Optimal dose for Stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose

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## Summary

**Purpose:** Prognosis of uterine cervical adenocarcinoma in locally advanced stage treated with radiation therapy has been considered to be much worse than that of squamous cell carcinoma because the optimal dose for the former one has not been determined. Thus, the current study was performed to investigate the optimal dose for Stage IIIB, locally advanced stage, adenocarcinoma of the uterine cervix on the basis of the biological effective dose (BED).

**Methods:** One-hundred and seventy-nine patients with Stage IIIB carcinoma of the uterine cervix were treated with curative intended therapy at Kitasato University Hospital between 1976 and 2000. Out of them, 13 patients had an adenocarcinoma component in pathological findings. Nine patients were diagnosed with adenocarcinoma and four patients were diagnosed with adenosquamous cell carcinoma. All patients were treated with external radiation therapy combined with intracavitary radiation therapy. The total BED<sub>10</sub> (T-BED<sub>10</sub>) was calculated from the BED of the external beam radiation therapy (E-BED<sub>10</sub>) plus the BED of the intracavitary radiation therapy (A-BED).

**Results:** Overall survival rate was 51%. Stratified by T-BED<sub>10</sub>, overall survival rate of the T-BED<sub>10</sub> ≥ 100 Gy group was 57% and that of the T-BED<sub>10</sub> < 100 Gy group was 30%. There was a trend toward a better survival rate of the T-BED<sub>10</sub> ≥ 100 Gy group than the T-BED<sub>10</sub> < 100 Gy group.

**Conclusion:** The current study suggested that the optimal dose for Stage IIIB adenocarcinoma of the uterine cervix might be T-BED<sub>10</sub> ≥ 100 Gy.

**Key words:** Radiation therapy; Adenocarcinoma of the uterine cervix; Biological effective dose.

## Introduction

Early stage invasive adenocarcinoma of the uterine cervix has been reported to achieve almost the same treatment results of radiation therapy as early stage invasive squamous cell carcinoma of the uterine cervix. Nakano *et al.* reported that the 5-year overall survival rates of Stage I and II adenocarcinoma of the uterine cervix treated with radiation therapy were 85.7% and 66.7%, respectively [1]. On the other hand, Arai *et al.* reported that the 5-year overall survival rates of Stage I and II squamous cell carcinoma of the uterine cervix were reported to be 83% and 71%, respectively [2]. However, advanced invasive adenocarcinoma of the uterine cervix has had much poorer treatment results than advanced invasive squamous cell carcinoma of the uterine cervix. Stage III and IV squamous cell carcinoma of the uterine cervix achieved 52.2% and 24.1% of the 5-year overall survival, respectively [1], however, Stage III and IV adenocarcinoma of the uterine cervix achieved 32.3% and 9.1% of the 5-year overall survival, respectively [2]. These outcomes might have resulted because both the prescribed doses and treatment regimens, consisting of a combination of external beam irradiation and intracavitary irradiation for squamous cell carcinoma and adenocarcinoma of the uterine cervix, were the same in

the previous studies. Thus, the optimal prescribed dose for advanced adenocarcinoma of the uterine cervix has not been established.

The purpose of the current retrospective analysis was to find the optimal dose for Stage IIIB, advanced stage, adenocarcinoma of the uterine cervix on the basis of the biological effective dose (BED).

## Materials and Methods

### Patients

One-hundred and seventy-nine patients with Stage IIIB carcinoma of the uterine cervix were treated with curative therapy at Kitasato University Hospital between 1976 and 2000. Out of them, 13 patients had an adenocarcinoma component in the pathological findings. Nine patients were diagnosed with adenocarcinoma and four patients were diagnosed with adenosquamous cell carcinoma. All 13 patients who were treated with radiation therapy, were investigated in the current study. The median age of these patients was 58 years (range; 39-83 years).

### Radiation therapy schedule

The radiation therapy treatment schedule was as follows. All patients were treated with a combination of external beam radiation therapy and intracavitary radiation therapy. As for external beam irradiation, anterior-posterior parallel opposed fields were adopted with 1.7-2.0 Gy per fraction, five fractions per week using 4-10 MV X-rays and the total dose of 38-60 Gy was prescribed with central shielding after 27-30 Gy. As for intra-

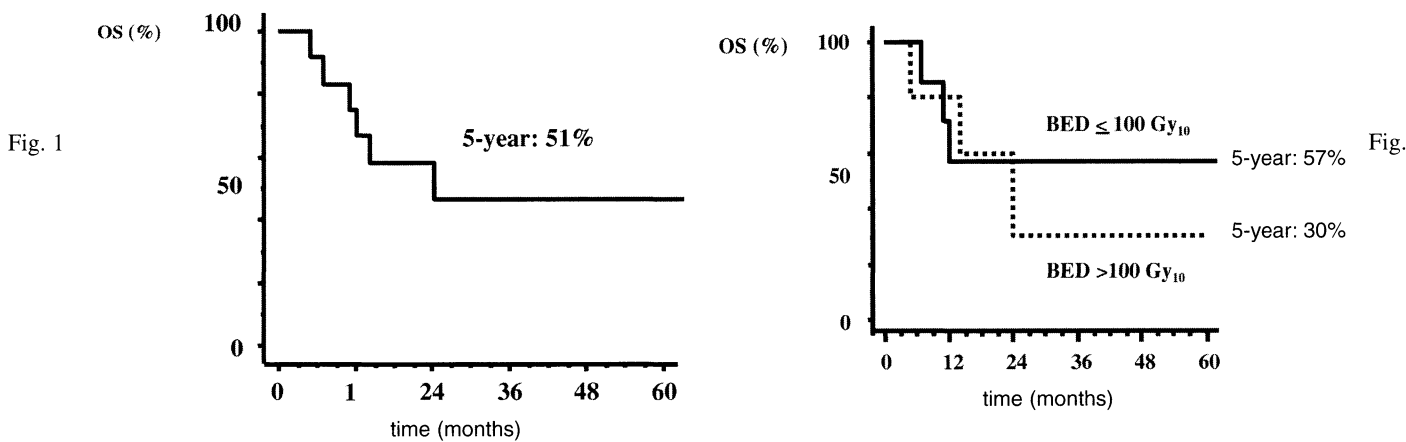


Figure 1. — Overall survival (OS) curve of Stage IIIB adenocarcinoma of the uterine cervix treated with radiation therapy.

Figure 2. — Overall survival (OS) curves of Stage IIIB adenocarcinoma of the uterine cervix treated with radiation therapy stratified by T-BED<sub>10</sub>. The overall survival rate of the T-BED<sub>10</sub> ≥ 100 Gy group was 57% and that of the T-BED<sub>10</sub> < 100 Gy group 30%.

caviatary radiation therapy, all patients were treated with <sup>60</sup>Co high-dose rate remote after loading system. The point A dose per fraction was 3.5-6.0 Gy and the total dose to point A was 15-30 Gy. Intracavitary radiation therapy was performed once a week totaling four to six times. The radiation treatment schedules listed in Table 1.

Table 1. — Radiation Therapy.

External beam radiation therapy	
X-ray	4-10 MV X-ray
Technical	anterior-posterior parallel opposed ports
Fraction size	1.7 Gy-2.0 Gy
Total dose	38-60 Gy
Initiation dose of central shielding	27-30 Gy

#### Calculation of biological effective dose (BED)

In the current study, calculation of the biological effective dose (BED) was performed to sum the dose of different fraction sizes. BED was calculated as the following formula.

$$BED = nd [1 + d/(\alpha/\beta)] [3]$$

n = number of fractionation, d = dose per fraction,  $\alpha/\beta$  = specific number

$\alpha/\beta$  was defined as 10 in most malignant tumor tissues and 2-5 in benign tumor or normal tissues. Thus, in the current study,  $\alpha/\beta$  was defined as 10. This BED was referred to BED<sub>10</sub> in as following this article.

Furthermore, we calculated BED<sub>10</sub> separately in the cases of external beam radiation therapy and intracavitary radiation therapy. The former was defined as E-BED<sub>10</sub> and the latter was defined as A-BED<sub>10</sub>. E-BED<sub>10</sub> was calculated from the dose to the following point. The half point between the isocenter of the anterior-posterior fields at the initiation of the treatment and the lateral side of the fields were used. A-BED<sub>10</sub> was calculated from the dose to point A. Moreover, T-BED<sub>10</sub> was defined as E-BED<sub>10</sub> plus A-BED<sub>10</sub>.

#### Statistics

Overall survival rate was calculated from the initiation of radiation therapy and overall survival curve was constructed by the Kaplan-Meier method.

#### Results

As for BED, E-BED<sub>10</sub> ranged from 45 to 72 Gy. A-BED<sub>10</sub> ranged from 22.5 to 48 Gy. T-BED<sub>10</sub>, E-BED<sub>10</sub> plus A-BED<sub>10</sub>, ranged from 75 to 112 Gy.

The median follow-up time of all patients was 35 months (range; 2-170 months). Overall survival rate was 51% (Figure 1). Stratified by T-BED<sub>10</sub>, overall survival rate of the T-BED<sub>10</sub> ≥ 100 Gy group was 57% and that of the T-BED<sub>10</sub> < 100 Gy group was 30% (Figure 2). There was a trend toward a better survival rate of the T-BED<sub>10</sub> ≥ 100 Gy group vs than that of the T-BED<sub>10</sub> < 100 Gy group.

Table 2 shows the late radiation morbidity. As for the small intestine, all four patients of the T-BED<sub>10</sub> < 100 Gy group were grade 0. However, one patient experienced grade 3, one patient experienced grade 4, and the other seven patients experienced grade 0 in the T-BED ≥ 100 Gy group. As for the rectum, all four patients of the T-BED<sub>10</sub> < 100 Gy group were grade 0. However, one patient experienced grade 2, one patient experienced grade 3, and the other seven patients experienced grade 0 in the T-BED<sub>10</sub> ≥ 100 Gy. As for the bladder, all 13 patients of both the T-BED<sub>10</sub> < 100 Gy group and T-BED<sub>10</sub> ≥ 100 Gy group experienced grade 0.

Table 2. — Late radiation morbidity.

Organ		Grade				
		G0	G1	G2	G3	G4
Small intestine	T.BED > 100	4	0	0	0	0
	T.BED < 100	7	0	0	1	1
Rectum	T.BED > 100	4	0	0	0	0
	T.BED < 100	7	0	1	1	0
Bladder	T.BED > 100	4	0	0	0	0
	T.BED < 100	9	0	0	0	0

Based on NCI-CTC ver 2-0.

## Discussion

BED is a useful tool to compare different treatments consisting of different fractionation schedules. In the case of advanced carcinoma of the uterine cervix, the combination of external radiation therapy and intracavitary radiation therapy is the standard method of radiation therapy. Actually, external radiation therapy usually adopts 1.8-2.0 Gy per fraction totaling 45-50 Gy and intracavitary radiation therapy usually adopts 5-6 Gy per fraction to point A totaling 15-30 Gy in advanced carcinoma of the uterine cervix. Thus, the calculation of BED to evaluate the optimal radiation therapy is very important. However, no previous studies have been performed to evaluate the optimal dose for adenocarcinoma of the uterine cervix on the basis of BED, although treatment results of advanced adenocarcinoma of the uterine cervix have not been satisfactory thus far. Nakano *et al.* reported that the 5-year survival rates of Stage III and IVA adenocarcinoma of the uterine cervix were 32.1 % and 9.1 %, respectively [2].

In the current study, a retrospective review was done of the treatment results of Stage IIIB adenocarcinoma of the uterine cervix by analyzing two recent reports in terms of BED [4, 5]. Toita *et al.* reported that the 5-year survival rate of Stage IIIB adenocarcinoma of the uterine cervix was 0%. Their study adopted median T-BED<sub>10</sub> was 98.4 Gy (range: 98.4-132 Gy). Suzuki *et al.* reported that the 5-year survival rate of Stage IIIB adenocarcinoma of the uterine cervix was 43% using a median T-BED<sub>10</sub> of 90.0 Gy (range: 88.5-98.4 Gy). On the other hand, the current study achieved 51% of the 5-year survival. The median T-BED<sub>10</sub> of the current study was 105 Gy (range: 75-112). Furthermore, the T-BED<sub>10</sub> ≥ 100 Gy group achieved 57% of the 5-year survival. The previous two reports adopted a median T-BED<sub>10</sub> < 100 and the current study adopted ≥ 100 Gy. The previous two studies adopted over 90 Gy of the median T-BED<sub>10</sub>, which meant only about 10 Gy of T-BED<sub>10</sub> more in the current study than the previous

studies. However, this 10 Gy of T-BED<sub>10</sub> had a much more significant impact on treatment results than the other 10 Gy of T-BED<sub>10</sub> such as a range of 110-120 Gy because the dose-response consisted of a sigmoid curve.

As for radiation morbidity, only two patients experienced grade 3 or more late radiation morbidity of the small intestine. Only one patient experienced grade 3 late radiation morbidity of the rectum. No patients experienced grade 1 or more of the bladder. These results suggest that late radiation morbidity of the current radiation therapy of T-BED<sub>10</sub> ≥ 100 Gy is acceptable.

In conclusion, the current study suggests that the optimal dose for Stage IIIB adenocarcinoma of the uterine cervix might be T-BED<sub>10</sub> ≥ 100 Gy.

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