Biological effective dose evaluation and assessment of rectal and bladder complications for cervical cancer treated with radiotherapy and surgery

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Abstract

Purpose: This study aims to retrospectively evaluate dosimetric parameters calculated as biological effective dose in relation to outcome in patients with cervical cancer treated with various treatment approaches, including radiotherapy with and without surgery.

Material and methods: Calculations of biological effective dose (BED) were performed on data from a retrospective analysis of 171 patients with cervical carcinoma stages IB-IIB treated with curative intent, between January 1989 and December 1991. 43 patients were treated only with radiotherapy and 128 patients were treated with a combination of radiotherapy and surgery. External beam radiotherapy was delivered with 6-21 MV photons from linear accelerators. Brachytherapy was delivered either with a manual radium technique or with a remote afterloading technique. The treatment outcome was evaluated at 5 years.

Results: The disease-specific survival rate was 87% for stage IB, 75% for stage IIA and 54% for stage IIB, while the overall survival rates were 84% for stage IB, 68% for stage IIA and 43% for stage IIB. Patients treated only with radiotherapy had a local control rate of 77% which was comparable to that for radiotherapy and surgery patients (78%). Late complications were recorded in 25 patients (15%). Among patients treated with radiotherapy and surgery, differences in radiation dose calculated as BED10 did not seem to influence survival. For patients treated with radiotherapy only, a higher BED10 was correlated to a higher overall survival (p = 0.0075). The dose response parameters found based on biological effective dose calculations were D50 = 85.2 Gy10, and the normalized to total dose slope of the dose response curve γ = 1.62 for survival and D50 = 61.6 Gy10 and γ = 0.92, respectively for local control.

Conclusions: The outcome correlates with biological effective dose for patients treated with radiation therapy alone, but not for patients treated with radiotherapy and surgery. No correlations were found between BED and late toxicity from bladder and rectum.

Key words: BED, bladder complication, cervical cancer, radiotherapy and surgery, rectal complication.

Purpose

Radiotherapy (RT) is a well established method for treatment of cervical cancer. Definitive RT includes external beam radiation therapy (EBRT) to the pelvis and intracavitary brachytherapy (BT). RT in combination with surgery has been used for treatment of local disease, where RT has been added postoperatively to cases, showing unfavorable prognostic feature at surgery or has been given preoperatively [1-4]. Comparisons between treatment regimens with different fractionations, dose rates and treatment time as well as the evaluation of their effectiveness on tumor and normal tissues is possible through the use of bioeffect dose models that take into account the variation of the response with all the above-mentioned factors. The linear quadratic (LQ) model is currently the most used model for this purpose as it can account for differences in time, dose and fractionation with a relatively small number of parameters [5-7]. Several studies have investigated the predictive value of the LQ model in treatment of cervical cancer using BT [9-11], but there are very few reports on biological effective dose

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local control, overall survival and the risk for bladder and rectal complications for patients treated with RT combined with surgery or RT alone.

It is therefore the aim of this paper to explore the relationship between BED for various treatment schedules and local control, overall survival and the risk for bladder and rectal complications for patients treated with RT combined with surgery or RT alone.

Material and methods

Patients

A retrospective study was performed on 171 patients with cervical carcinoma FIGO stage IB-IIB treated with curative intent using RT combined with surgery or RT alone, between January 1989 and December 1991. One-hundred-and-thirteen patients were diagnosed in stage IB, 44 patients in stage IIA and 14 cases in stage IIB. Squamous cell carcinoma was diagnosed in 126 patients and adenocarcinoma in 34 cases (Table 1). Age at diagnosis varied between 22 and 87 years with a median of 43 years for patients treated with combination RT and surgery and 72 years for patients treated with RT only. Median follow up was 66 months (range 8-109 months). Outcome, in terms of survival and local control, were defined at five years. Late side effects were recorded until death or loss of follow-up. Late complications in bladder and rectum were recorded retrospectively according to the glossary of Chassagne [14] and were defined as complications persistent or occurring more than three months after radiotherapy. Complications grade 2 included symptoms resulting in intermittent or persistent interference with normal activity and/or requiring investigation such as rectoscopy or cystoscopy; grade 3 complications were defined as symptoms that affect the performance status of the patient and that require surgery or invasive procedures.

**Table 1. Patient characteristics**

| Characteristic          | Number of patients | %  |
|-------------------------|--------------------|----|
| Total                   | 171                |    |
| Stage                   |                    |    |
| IB                      | 113                | 66 |
| IIA                     | 44                 | 26 |
| IIB                     | 14                 | 8  |
| Histologic type         |                    |    |
| Squamous cell carcinoma | 126                | 74 |
| Adenocarcinoma          | 34                 | 20 |
| Others                  | 11                 | 6  |
| Treatment               |                    |    |
| BT + surgery            | 97                 | 57 |
| BT + surgery + EBRT     | 31                 | 18 |
| BT + EBRT               | 43                 | 25 |
| BT                      |                     |    |
| Manual                  | 91                 | 53 |
| After-loading           | 80                 | 47 |
| EBRT                    |                     |    |
| Pelvic alone            | 49                 | 66 |
| Pelvic + para-aortic    | 25                 | 34 |

**BT** – brachytherapy, **EBRT** – external beam radiotherapy

Treatment

During the period of this study, the treatment of choice at the Department of Gynecologic Oncology, Radiohemmet, Karolinska University Hospital, for patients with cervical cancer stage IB and IIA was intracervical preoperative brachytherapy. If lymph node metastases or unsatisfactory resection margins were diagnosed at surgery, postoperative external beam radiotherapy (EBRT) was added. Patients in stage IIB were treated with radiotherapy (RT) alone, as well as patients in stage IB and IIA not suitable for surgery due to medical reasons. For 128 patients, treatment included two BT fractions with a three-week interval, followed by radical surgery according to the Wertheim-Meig procedure four weeks after the second BT. Postoperative EBRT over a pelvic and a para-aortic field was added to cases with lymph node metastases, while patients with non-radical surgery received EBRT over the pelvis. Forty-three patients were treated with radiotherapy only, including two BT fractions with a three-week interval, followed by EBRT over the pelvis four weeks later (Table 1). EBRT was delivered by 6-21 MV linear accelerators using A-P fields with a daily fractionation of 1.6 Gy. The prescribed dose to the pelvis was 45 Gy (median 44.2 Gy; range 40-50 Gy) and to the para-aortic field 40 Gy (median 40 Gy; range 10.6-45.6 Gy). Central shielding was performed from the start of EBRT with an individualized shielding to the bladder and rectum depending on the dose already given by BT, and the dose to the organs at risk under the shielding was determined based on the computerized treatment planning system.

All patients received low dose rate brachytherapy. However, during the studied period, brachytherapy technique changed from manual radium technique to remote after-loading technique with cesium-137 (Selectron®). The manual technique was used in 39 cases (91%) in the group of patients treated by RT only and in 52 cases (41%) among patients treated by RT and surgery. In manual technique, the dose to bladder and rectum was estimated by measuring the dose rate by a gamameter at multiple points and the clinical dose to point A was retrospectively estimated to a median of 56 Gy (range 22-66 Gy). In the after-loading technique the rectal point dose was calculated at the anterior rectal wall five mm below the posterior level of the ring applicator and the dose to bladder was estimated at a point on the posterior surface of a catheter balloon according to the International Commission on Radiation Units and Measurements Report 38 recommendations [15]. The median dose to point A was 45 Gy (range 28-52 Gy). A detailed
description of the two BT techniques used has been reported elsewhere [16].

**Bioeffect dose calculations**

Comparison between the various treatment techniques was done based on biologically effective dose (BED) [6,7], which allows easy comparison and addition of the effects of various complete or partial treatment regimens, irrespective of method or pattern of delivery employed.

For EBRT, BED could be calculated according to equation 1.

$$BED_{EBRT} = nD \left[1 + \frac{d}{\alpha/\beta}\right]$$  \hspace{1cm} (1)

where $n$ is the number of fractions, $d$ is the dose per fraction and $\alpha/\beta$ is the ratio of the LQ parameters of the tissue investigated. When central shielding was used with an individualized shielding to the bladder and rectum, the dose to organs at risk determined under the shielding was used in the above formula for calculating the corresponding biologically effective dose.

For low dose rate BT where significant repair of damage takes place during the treatment duration, BED for each session is given by equation 2.

$$BED_{BT} = D \left[1 + \frac{2D}{(\alpha/\beta) \mu T} \left[1 - \frac{1}{\mu T \left(1 - e^{-1}\right)}\right]\right]$$  \hspace{1cm} (2)

where $D$ is the radiation dose, $T$ is the duration of the BT session and $\mu$ is a parameter characterizing the repair of sublethal damage in the irradiated tissues; $\mu = \ln(2)/T_{1/2}$ where $T_{1/2}$ is half-life of sublethal damage repair.

For combined treatment schedules, one could calculate the total BED as:

$$BED_{tot} = \sum_i BED_i$$  \hspace{1cm} (3)

where $BED_i$ are individual biologically effective doses from each session of RT.

Equation 3 gives the general BED expression that does not take into account the proliferation during treatment. However, tumor cell kinetic studies showed that proliferation of the cells after the start of treatment could be significantly higher than the proliferation before the initiation of irradiation, and therefore the biologically effective dose to the tumor could decrease to as much as about 1 Gy/day [8]. The effect of proliferation could be expressed through a supplementary term subtracted from $BED_{tot}$ (equation 4).

$$BED_{p orgy} = \sum_i BED_i - \frac{\ln(2)}{\alpha} \frac{T_{treat} - T_k}{T_P}$$  \hspace{1cm} (4)

where $T_{treat}$ is the overall treatment time, $T_k$ is the time for the onset of proliferation [17], $T_P$ is the effective doubling time during proliferation and $\alpha$ is the linear parameter of LQ model. Thus, the repopulation time $T_P$ describes the proliferation of tumors after damage has been inflicted through treatment. It is thought to describe the proliferation without inhibiting factors such as nutrient supply or even as the result of active processes as appear in the healing of normal tissues. The actual time available for accelerated repopulation is $T_{treat} - T_k$ and therefore no correction for proliferation is needed if the overall treatment time is shorter than $T_k$.

The expressions in equations 1-4 were used to calculate BED for tumors and normal tissues. The parameters used for calculations have been chosen in agreement with existing literature [8,12,17]. Generic values of 10 Gy and 3 Gy have been assumed for the fractionation sensitivities of tumors and normal tissues, respectively. The corresponding biologically effective dose for tumor was denoted $BED_{10}$ and for the organs at risk $BED_{3}$, respectively. The repair half-life for sublethal damage was 1.5 h resulting in a repair parameter $\mu = 0.46$ h$^{-1}$, the time for the onset of proliferation $T_k = 21$ days, the effective proliferation doubling time $T_P = 5$ days and $\alpha = 0.3$ Gy$^{-1}$.

The biological effective dose is further reported as $BED$ calculated as described above, but also as equivalent dose in 2 Gy per fraction, EQD$_2$, calculated as:

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$  \hspace{1cm} (5)

In this way the comparison of the results with previously reported studies using the BED concept could be easily performed, but also further comparison with studies following the new recommendations of the European Gynaecological Brachytherapy Group/European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) for dose reporting [19], which recommends the use of the EQD$_2$-formalism.

**Results**

**Tumor response**

The disease-specific 5-year survival rate (DSS) was 87% for stage IB, 75% for stage IIA and 54% for stage IIB. The corresponding overall 5-year survival rates (OAS) were 84%, 68% and 43%, respectively. Patients treated with radiotherapy and surgery had a local control rate at five years of 78%, while for patients treated with RT alone the five-year local control rate was 77%. Table 2 presents a summary of the overall survival data for all the patients in the study divided according to stage of disease and treatment type, together with the mean and median $BED_{10}$ without considering proliferation for each group. The data in the table shows that for the group of patients treated only with radiation therapy, the outcome appears to correlate with radiation dose. For the group of patients treated with BT and surgery, differences in irradiation dose calculated as $BED_{10}$ did not seem to influence overall survival. Among patients receiving a combination of both BT and EBRT together with surgery, the results diverge with an inverted correlation between $BED_{10}$ and survival for patients in stage IB, suggesting...
more complicated pattern of correlations. The remaining analysis will therefore focus on the group of patients receiving only RT.

Figure 1 shows the distribution of patients treated with RT only, according to BED$_{10}$ and their overall survival status at the follow-up time. The data show that the surviving patients had higher mean and median BED$_{10}$ than the patients that were deceased at the time of analysis. This indicates a positive correlation between BED$_{10}$ and treatment outcome for the patients receiving only RT. This is illustrated in Fig. 2 where BED$_{10}$ above the median value of 94 Gy$_{10}$, corresponding to an equivalent dose in 2 Gy per fraction (EQD$_2$) of 81 Gy, correlates with better overall survival ($p = 0.0075$). The same tendency is maintained if proliferation is taken into account for BED$_{10}$ calculation.

The dose dependence of overall survival for the 43 patients treated with RT alone is represented in Fig. 3. A logit fit of the data yields a D$_{50}$ of 85.2 Gy$_{10}$, the mean biological effective dose to the tumor that corresponds to a surviving fraction of 50% of the patients, corresponding to an EQD$_2$ of 71 Gy. The gamma slope was 1.62. A similar analysis was performed with BED$_{10}$ that includes the potential effect of proliferation, yielding D$_{50}$ = 55.7 Gy$_{10}$ (EQD$_2$ = 46 Gy) and $\gamma = 1.04$.

Figure 4 shows the correlation between BED$_{10}$ and local control among patients receiving RT only. As for overall survival, the data shows that higher BED$_{10}$ correlate with improved local control. The dose response relationship yielded D$_{50}$ = 61.9 Gy$_{10}$ (EQD$_2$ = 52 Gy) and $\gamma = 0.92$ for BED$_{10}$ without proliferation and D$_{50}$ = 36.0 Gy$_{10}$ (EQD$_2$ = 30 Gy) and $\gamma = 0.80$ for BED$_{10}$ that accounts for proliferation.

Table 2. Summary of the patient data on overall survival and BED to the tumour for the stage Ib, Ila and IIb patients treated with radiotherapy and surgery or with radiotherapy alone

| Total no. of patients | Treatment type |
|-----------------------|----------------|
|                       | Brachy + Surgery | Brachy + Surgery + EBRT | Brachy + EBRT |
| Stage Ib              |                |                          |               |
| No. of patients       | 82             | 14                        | 17            |
| Mean BED$_{10}$ (Gy$_{10}$) | 71             | 101                        | 100           |
| Median BED$_{10}$ (Gy$_{10}$) | 68             | 103                        | 104           |
| Surviving fraction of patients with BED$_{10}$ < Median BED$_{10}$ | 93%            | 43%                        | 63%           |
| Surviving fraction of patients with BED$_{10}$ > Median BED$_{10}$ | 90%            | 29%                        | 89%           |
| Stage Ila             |                |                          |               |
| No. of patients       | 13             | 14                        | 17            |
| Mean BED$_{10}$ (Gy$_{10}$) | 73             | 102                        | 96            |
| Median BED$_{10}$ (Gy$_{10}$) | 76             | 105                        | 97            |
| Surviving fraction of patients with BED$_{10}$ < Median BED$_{10}$ | 100%           | 29%                        | 44%           |
| Surviving fraction of patients with BED$_{10}$ > Median BED$_{10}$ | 100%           | 57%                        | 78%           |
| Stage IIb             |                |                          |               |
| No. of patients       | 2              | 3                         | 9             |
| Mean BED$_{10}$ (Gy$_{10}$) | 84             | 81                        | 72            |
| Median BED$_{10}$ (Gy$_{10}$) | 84             | 88                        | 79            |
| Surviving fraction of patients with BED$_{10}$ < Median BED$_{10}$ | 100%           | 0%                          | 20%           |
| Surviving fraction of patients with BED$_{10}$ > Median BED$_{10}$ | 0%             | 50%                        | 60%           |

Late toxicity

Late toxicity from bladder and rectum were recorded in 25 out of 171 patients (15%), of which five patients showed complications from both organs. Bladder complications were found in 12 patients and 18 cases showed complications from rectum. Grade 2 and grade 3 complications were found in 23 and 2 patients, respectively.

Figure 5 shows the distribution of patients on the dose intervals from the point of view of the complications to the rectum and the bladder for the patients undergoing RT only. The BED$_3$ has been calculated from the dose to the organ determined as described in the Materials and Methods section. The mean BED$_3$ was 86 Gy$_3$ (EQD$_2$ = 51 Gy) for rectum and 76 Gy$_3$ (EQD$_2$ = 46 Gy) for bladder. Late rectal complications were recorded in 30.2% (13/43) for a mean BED$_3$ of 83 Gy$_3$ (EQD$_2$ = 50 Gy) and bladder complications in 14% (6/43) for a mean BED$_3$ of 88 Gy$_3$ (EQD$_2$ = 53 Gy). No apparent dose correlation could be observed either for the rectum or the bladder.

Discussion

Radiation therapy is an important modality for the treatment of cervical cancers, alone or in combination with surgery. Several studies have investigated the outcome of RT
in relation to BED, but to our knowledge there are no reports on BED and outcome for patients treated with a combination of RT and surgery.

For treatment schedules including EBRT and BT it has been difficult to obtain a dose response relationship due to the diversity of combinations of treatment modalities and the composition of the analyzed patient populations. In a large patterns of care study Lanciano et al. [20] reported no dose response relationship in the results from 1558 pa-
tients treated with doses ranging from less than 75 Gy to more than 85 Gy in the clinical dose to Point A. Similarly, a review of 24 studies performed by Petereit and Pearcey [21] failed to find a correlation between BED in Point A and local control or survival in patients with cervical cancer stage I-III.

Evaluation of individual studies reporting various BEDs is very difficult due to the variation in the patient composition of the analyzed populations. In an analysis by Petereit et al. [22] comparing the outcome for stage I-III patients treated with HDR or LDR brachytherapy in combination with EBRT, BED varied in the range of 96-109 Gy10 and no dose-response relationship for pelvic control or relapse-free survival and BED10 was found. In a later study, Sood et al. [11] reported a mean BED10 of 87.3 Gy10 for patients with local control and 87.7 Gy10 for patients with local failure treated with RT alone. However, it should be noted, that Sood et al. [11] reported better local control for patients receiving treatments with BED10 above median than for patients with BED10 below the median.

Our results in terms of mean BED10 for the patients treated only with RT compare well with these reported studies. We found mean BED10 of 92 Gy10. Furthermore, we also found a positive correlation between the overall survival and BED in patients treated only with radiotherapy. The mean BED10 corresponding to a surviving fraction of 50% of the patients was $D_{50} = 85.2 \text{ Gy}_{10}$ and $\gamma = 1.62$. A similar analysis was performed with BED10 that includes the potential effect of proliferation, yielding $D_{50} = 55.7 \text{ Gy}_{10}$ and $\gamma = 1.04$. The latter analysis showed increased heterogeneity of the data, as supported by the lower $\gamma$, suggesting that proliferation may not be as important as recommended by the parameters used. Nevertheless, it has to be mentioned, that the observed trends were maintained even after the inclusion of a proliferation factor with generic parameters in the calculation of BED10. The size of the patient population available for this study does not however allow a more detailed analysis of the influence of proliferation. Though, investigating this aspect in the future is warranted.

Figure 4 shows the correlation between BED10 and local control in the investigated population. As for overall survival, data shows that higher BED10 correlate with improved local control. The dose response relationship yielded $D_{50} = 61.9 \text{ Gy}_{10}$ and $\gamma = 0.92$ for BED10 without proliferation and $D_{50} = 56.0 \text{ Gy}_{10}$ and $\gamma = 0.80$ for BED10 that accounts for proliferation. As for overall survival, the analysis of the data that included proliferation showed increased heterogeneity, supporting the hypothesis that the proliferation in the investigated population might have other characteristics than predicted by the parameters used.
The late rectal complication rate we have observed was 30% (13/43) and for the bladder complication rate was 14% (6/43) calculated as the rate of complications for RT patients only. These compare well with the findings of Chen et al. [23] who reported 30% and 5% late complications from rectum and bladder, respectively. However, Lanciano et al. [20] reported a late complication rate of 9.5%, but in that study only major complications were recorded. Sood et al. [11] in contrast reported only one late rectal complication among 26 patients treated with RT alone, but the definition of late complications it is not well described.

We found mean $BED_3$ of 86 Gy$^3$ for rectum and 76 Gy$^3$ for bladder, with mean $BED_3$ of 83 Gy$^3$ and 88 Gy$^3$ for patients with rectal and bladder complications, respectively. In a study of stage IB patients treated with RT by Lee et al. [10] mean rectal $BED_3$ was 125.6 Gy$^3$ for patients without rectal complications compared to 142.7 Gy$^3$ for patients with late complications, and the rectal complications increased when mean $BED_3$ was $\geq 131$ Gy$^3$. In our study we had only two patients with mean $BED_3 \geq 131$ Gy$^3$ and none of them were recorded with any late rectal complications.

In this study no correlation has been observed between the rate of complications and $BED_3$ to the organs at risk. This is in agreement with the studies by Clark et al. [24] and Chen et al. [23] who reported 125 Gy$^3$ and 110 Gy$^3$, respectively threshold $BED_3$ for the correlation between the dose and the rectal complications. Our median $BED_3$ for the rectum of 85 Gy$^3$ was lower than the reported threshold which could be one explanation to the lack of correlation. The low median $BED_3$ in our study might lead to low level of complication probability, which would not totally agree to our results. This may be explained by the rather high age among patients treated with RT only. Another factor of importance could be the large fraction of patients treated with manual technique generally associated with higher dosimetric uncertainties. However, the results of other studies might also be subject to dosimetric uncertainties. This stresses the difficulties in comparing studies from different institutions, from different time periods or with different stage compositions of the patient populations.

It has to be mentioned that the predictions of complication rates based on correlations with the biological effective dose for the organs at risk are subject of discussion due to the intrinsic limitations of the BED concept, which does not take into account the volume effects and the dose heterogeneity within the organ. While for the tumors, these are not a critical issues since they are typical parallel structures and their treatment outcome would correlate with the minimum dose, for rectum or bladder the volume effect and the distribution of the dose within the organ might be of high importance.
Conclusions

This study shows that the outcome of the treatment correlates with biological effective dose for patients treated only with radiotherapy, but not for patients treated with radiotherapy and surgery. The dose response parameters found based on BED\textsubscript{10} calculations were D\textsubscript{50} = 85.2 Gy\textsubscript{10} (EQD\textsubscript{2} = 71 Gy) and γ = 1.62 for overall survival and D\textsubscript{50} = 61.6 Gy\textsubscript{10} (EQD\textsubscript{2} = 52 Gy) and γ = 0.92 for local control. No correlations were found between BED and late toxicity from bladder and rectum.

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