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Rectovaginal fistula risk doses in patients with cervical cancer

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Summary

Purpose: To evaluate the incidence and risk factors, both clinical and physical, of the development of a postradiation recto-vaginal fistula in cervical cancer patients.
Materials and methods: A retrospective analysis of 222 consecutive patients receiving radical treatment for invasive cervical cancer at the Regional Oncology Centre in Bydgoszcz between 1993 and 1995 has been performed, on 140 patients treated with radiotherapy alone and 82 patients who received radiotherapy combined with surgical treatment. The doses and dose rates of brachytherapy were specified at point A, the mean dose being 49 and 46 Gy for radiotherapy alone and combined treatment, respectively. External beam irradiation was applied in fractions of 1.8-2 Gy, up to a total dose of 44.6 Gy (36 - 50 Gy). The dose and dose rate in the rectum (point R_1) were determined according to the protocol 38th ICRU, the biological extrapolated dose (BED), using a LQ model, was calculated as a sum of a dose from external beam irradiation and brachytherapy.
Results: A total of 17 (7.6 %) recto-vaginal cases of fistulae were found; 13 (9,2%) in patients treated with radiotherapy alone, 4 (4,8%) in patients treated with combined treatment. The median latency time was 11.8 months (range 7 to 24). There is a strong association between the risk of developing a fistula and the biological extrapolated dose (BED) at point R_1. Addition of surgical treatment results in a higher risk of complications. Age, clinical stage, hemoglobin level, performance status and the overall treatment time, type and size of applicators were not found to have a significant effect on the risk of developing recto-vaginal fistula.
Conclusions: The biological extrapolated dose (BED) at point R_1 is an important predictive factor relevant for postradiotherapeutic rectovaginal fistula incidence risk. Surgery is an important factor modifying the postradiotherapeutic rectovaginal fistula incidence risk. No significant influence on the fistula incidence risk of such parameters as age, FIGO stage, physical activity, haemoglobin level, overall treatment time, type and size of applicators has been demonstrated.
Key words: late effect, radiation injury, dose-effect relationship, brachytherapy, cervix uteri.

Ocena dawek ryzyka popromiennej przetoki pochwowo-odbytniczej u chorych na raka szyjki macicy

Streszczenie

Cel: Identyfikacja klinicznych i fizycznych czynników ryzyka popromiennej przetoki pochwowo - odbytniczej u chorych na raka szyjki macicy.
Materiał i metodyka: Materiał obejmował grupę 222 kolejnych chorych na inwazyjnego raka szyjki macicy poddaną radykalnej radioterapii w latach 1993-1995. Pacjentki podzielono na 2 grupy w zależności od sposobu leczenia, samodzielną radioterapię zastosowano u 140 chorych, u 82 radioterapię w skojarzeniu z leczeniem chirurgicznym. Dla każdej chorej wyznaczono biologiczna dawkę równoważną (BED) w punkcie R_1 (wg 38 raportu ICRU) wykorzystując model liniowo kwadratowy. Zastosowano metodę regresji logitowej jedno i wielokrotnej. Wyznaczono dawki i krzywe ryzyka popromiennej przetoki pochwowo-odbytniczej oraz iloraz szans dla analizowanych czynników ryzyka.
Wyniki: Wystąpiło 17 popromiennych przetok pochwowo odbytniczych (7,7%), 4 po leczeniu skojarzonym (4,9%) i 13 (9,3%) po samodzielnej radioterapii. Czynnikami ryzyka popromiennej przetoki pochwowo-odbytniczej były: biologiczna dawka równoważna w punkcie R_1 oraz zastosowanie leczenia chirurgicznego. Nie wykazano istotnego wpływu takich cech jak wiek, stopień zawansowania klinicznego, stopień sprawności klinicznej, całkowity czas leczenia, rodzaj i wielkość aplikatorów.
Wnioski: Biologiczna dawka równoważna (BED) w punkcie R_1 jest istotnym czynnikiem predykcyjnym ryzyka wystąpienia popromiennej przetoki pochwowo - odbytniczej a skojarzenie z leczeniem chirurgicznym istotnie modyfikuje tę zależność.
Słowa kluczowe: późny efekt radioterapii, uszkodzenia popromienne, zależność dawka-efekt, brachyterapia, szyjka macicy.

This paper is a shortened version of the PhD Thesis „Rectovaginal fistula risk doses in patients with cervical cancer"
Skrót rozprawy doktorskiej „Ocena dawek ryzyka popromiennej przetoki pochwowo - odbytniczej u chorych na raka szyjki macicy"

Introduction

The therapeutic ratio is the differential consideration of the dose dependence of tumour cure probability and risk of late complications. Whereas, local tumour control is well defined, late complications are much less so. Since in most cases, the severity and, sometimes, the latency vary between patients and depend on the radiation dose, grading systems have been developed to transform analogous data on severity distributions into digital data of severe complications frequency [1]. This, however, inevitably involves a large degree of subjectivity regarding the impact of severe complications on the treated patients' quality of life. In the end, the Holthusen concept of a therapeutic ratio as a differential dose dependence makes sense only if the clinical impact on an individual patient's quality of life is comparable, local tumour recurrence being such a grave consequence that it has to be balanced by similarly grave normal tissue damage.

A grave late complication after cervical cancer radiotherapy is a rectovaginal fistula. Moreover, it has, for the purpose of scientific analysis, the rare advantage (shared only by myelopathy and very few other types of late normal tissue damage in radiotherapy) of being a quantal, i.e. all-or-nothing effect, which, moreover, leaves little doubt as to its clinical diagnosis.

The clinical picture of a fistula is easy to identify in the retrospective analysis of case histories. Moreover, a postradiotherapeutic rectovaginal fistula is a late complication, and the risk of its possible occurrence is a crucial factor limiting the escalation of radiation doses in the effort of increasing therapeutic gain.

The relationship between radiation dose and clinical effect may be significantly affected by numerous factors. The modifying factors may be divided into three categories. The first comprises physical parameters of irradiation: dose per fraction, interval between fractions, dose rate, and overall treatment time. The second category contains biological factors which are less well characterized: intrinsic radiosensitivity, capacity of regeneration and repair of sublethal damage as well as degree of oxygenation and redistribution in the cellular cycle. These, in turn, are subject to the influence of concomitant diseases, mechanical injury, infections and age or various genetic syndromes. The last category of modifying factors is constituted by the interaction of radiotherapy with other treatment modalities

Table 1. Clinical characteristics of different radiotherapy schedules.

Variable		Radiotherapy alone	Radiotherapy and surgery	All
Number of patiens		140 (63%)	82 (37%)	222 (100%)
Age [year] (222 pts)		55 (24-80)	50 (27-77)	53 (24-80)
Zubrod (124 pts)	I°	64 (83%)	46 (97%)	110 (88%)
	II°	12 (15%)	1 (2%)	13 (10%)
	III°	1 (1%)	0	1 (1%)
	IV°	0	0	0
FIGO (222 pts)	I°	1 (0,5%)	80 (36%)	81 (36%)
	II°	82 (37%)	2 (1%)	84 (38%)
	III°	56 (25%)	0	56 (25%)
	IV°	1 (0,5%)	0	1 (0,5%)
Histology (222 pts)	Ca planoepitheliale	133 (60%)	82 (37%)	215 (97%)
	Adenocarcinoma	5 (2%)	0	5 (2%)
	Others	2 (1%)	0	2 (1%)
Haemoglobin level [mg%](222 pts)		11,7 (5,5-15,2)	12,8 (10,9-16,4)	12,1 (5,5-16,4)

for the same cancer such as surgery, hyperthermia or chemotherapy.

In the group of 222 patients treated for cervical cancer in Bydgoszcz between 1993-1995, we observed 21 patients who developed rectovaginal fistula, which is an unexpectedly high rate of this severe complication. For this reason, I investigated the whole cohort of patients who were treated in those 3 years for cervical cancer in order to determine the influence of potential risk factors such as dose distribution, dose fractionation, overall treatment time, age and interaction with surgery. The aim of this study was to assess incidence risk factors of the development of a postradiation recto-vaginal fistula in cervical cancer patients.

Materials and methods

Population

Out of patients admitted to the Department of Oncology in Bydgoszcz from 1993 to 1995, 222 consecutive patients (aged 25 to 80 years, mean 53 years) were diagnosed with cancer of the uterine cervix and included in the retrospective study. In every case, the diagnosis of carcinoma was based on pathological findings according to the current classification of the International Federation of Obstetricians and Gynecologists. Eighty-one patients had Stage IB disease, 84 Stage II, 56 Stage III and one Stage IV. One hundred and forty patients with Stage II, III, and IV were treated with radiation alone. Therapy consisted of intrauterine brachytherapy and additional external beam pelvic radiation (XRT) according to different schedules. In Stage III or/and in cases of vaginal neoplasmatic infiltration bigger than 4 cm, external beam RT was followed by brachytherapy (BRT) in 64 of the 140 patients. The mean follow-up of this group was 26 months. Eighty-two out of 222 patients (80 stage Ib and 2 stage II) underwent combined therapy of irradiation (XRT and BRT) and surgery. One woman with Stage IB cancer was unfit for surgical treatment due to concomitant diseases and was treated with RT alone (*Table 1*). Therapy consisted of preoperative brachytherapy followed by a Wertheim-Meigs operation (radical hysterectomy) conducted 6 weeks after the second brachytherapy fraction. On the basis of intraoperative findings (lymph nodes involvement, macroscopic residual tumour and/or neoplasmatic cells in the postoperative specimen) thirty-six patients were qualified for additional external beam pelvic irradiation. The mean follow up was 39 months.

Brachytherapy

Two hundred and fifteen patients were treated with low dose rate (LDR) brachytherapy using standard Fletcher applicators, and 7 patients using vaginal cylinders with intracavital tandem. The brachytherapy schedule consisted of two insertions, 10-14 days apart. Dose fractions at point A and the rectal point R_1 were calculated according to the report #38 of ICRU (*Table 2*).

External irradiation

External irradiation was delivered with megavoltage units (Co-60 machine or 9-MV linear accelerator) using a target dose of 1,8-2 Gy per fraction, daily, 5 fractions per week. The total dose varied between 36 and 50 Gy (mean 44,9 Gy). EBRT was applied with a four-field box technique; the planning target volume was the tumour, external, internal and common iliac lymph nodes. No shields were applied. Due to the proximity of point A and point R_1 the doses were considered to be equal.

Calculations of the biological extrapolated dose (BED) at point R_1, resulting from variable dose rates of continuous irradiation and variable fractionated doses of external

Table 2. Dosimetric characteristics of different radiotherapy schedules.

Variable	Radiotherapy alone	Radiotherapy and surgery	All
Average brachytherapy dose at point A [Gy]	49 (± 4,7)	46 (±5,9)	48,2 (±5,4)
Dose at point R_1 normalized to dose at point A [%]	84.8 (±36)	77 (± 20)	82 (±31)
Average external radiation dose at the reference point [Gy]	45.1 (±1,5)	42 (±6,5)	44.6 (±3,4)
Average external radiation and brachytherapy dose at point R_1[Gy]	82 (±18)	54 (±23)	72 (±24)
Overall treatment time [day]	76 (±34)	87 (± 73)	80 (±52)

irradiation, were carried out using a linear-quadratic (LQ) formula, taking a dose of 60 Gy of continuous irradiation delivered in a total time of 168 hours (0,357 Gy/h) as equal to the dose of 60 Gy of external irradiation delivered in 30 dose fractions in a total treatment time of 42 days. Calculations were based on the following formulas [2] and parameters: mono-exponential half time of repair ($T_{1/2}$) of 1.5h and an α/β ratio of 3.5 Gy for late complications.

$$BED_{EBRT} = D_{EBRT} \bullet (1 + d_f / (\alpha/\beta))$$
$$BED_{BTH} = D_{BTHatR1} \bullet (1 + D_{BTHatR1} * g / (\alpha/\beta))$$
$$g = 2 \bullet (\mu \bullet t - 1 + \exp(-\mu \bullet t)) / (\mu \bullet t)^2$$
$$\mu = 1n2 / T_{1/2}$$

t = exposure duration
d_f = dose per fraction
D_{EBRT} = total dose EBRT
$D_{BTHatR1}$ = total dose BTH at R_1 point

A postradiotherapeutic rectovaginal fistula was diagnosed if signs and symptoms of fistula occurred in a patient who had not been diagnosed with local relapse or absence of local tumour control. Due to the concomitant inflammatory process in the uterine system, tumour relapse was excluded in each case on the basis of the findings of a histopathological examination.

In order to evaluate risk factors, a uni- and multifactorial logistic regression analysis was employed. The occurrence of the complication was a dependent variable, and a biological extrapolated dose (BED) at point R_1 were independent explanatory variables, along with parameters such as age, FIGO stage, physical activity, haemoglobin level, overall treatment time, length of intracavital tandem, size of ovoids, and application of intravaginal cylinder combined with tandem. P values less than 0.05 were considered statistically significant. For each independent variable the odds ratio with lower and upper border of 95% confidence intervals was calculated. All calculations were made using maximum-likehood procedures with Statistica'99 software [3].

Results

Actuarial, an overall 5-year survival rate in the populations examined in stages I0, II0, III0 were 76.5%, 53.3% and 33%, respectively. One woman in stage IV0 died 20 months after treatment. Twenty-seven subjects (12%) were diagnosed with local relapse, whereas remote metastases were found in 19 (9%).

Rectovaginal fistulas were observed in 21 patients (9.5%). In 4 cases the presence of the fistula coincided with histopathologically confirmed failure of local tumour control and it was impossible to determine whether symptoms were due to a late postradiotherapeutic complication or to a recurrence of the neoplastic process. The remaining 17 cases were unambiguously classified as postradiotherapeutic complications. Complications occurred in 4 out of 82 patients (4.9%) treated by radiotherapy combined with surgery, and in 13 out of 140 (9.3%) subjected to radiotherapy alone. In every patient, the fistula developed suddenly without any prodromic symptoms. The actuarial 5-year risk of radiation-induced rectovaginal fistula was 12.3% (*Figure 1*). The median time to the development of this complication was 11.8 months, the latent period ranging from 7 to 24 months since the

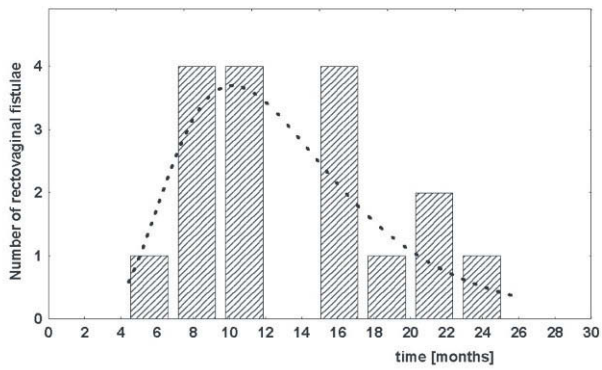

Figure 2. The histogram of latent period of rectovaginal fistula.

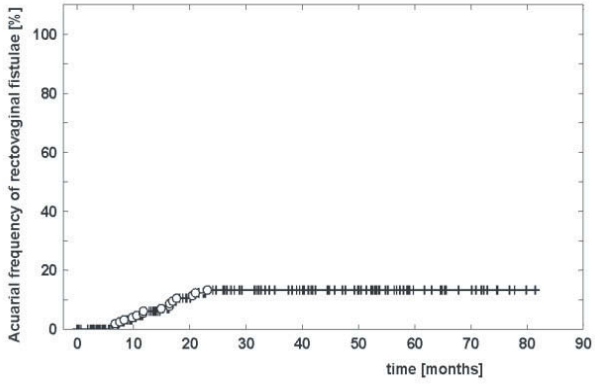

Figure 1. The actuarial frequency of rectovaginal fistula. (+ censored, o complete).

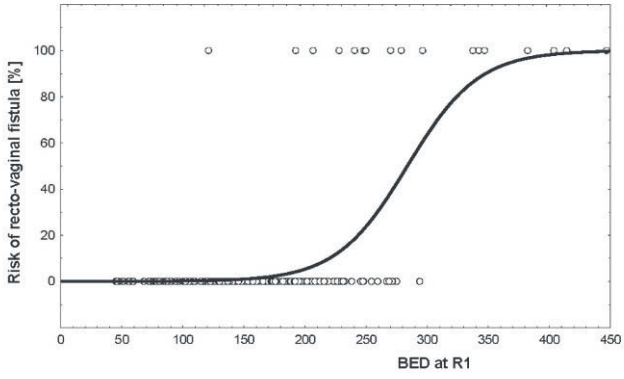

Figure 3. Dependence of rectovaginal fistula risk and biological extrapolated dose (BED) at point R_1.

Table 3. Physical and clinical risk factors of rectovaginal fistula multivariate analysis.

Variable	Odds ratio	-95%CI	+95%CI	p-value
BEDat R_1	1.1	1.0	1.1	0.005
Surgery	43.8	0.2	11116.7	0.03
Performance status	19.4	0.4	1053.6	0.14
FIGO stage	1.3	0.1	25.6	0.87
Age	1.0	0.9	1.1	0.98
Haemoglobin level	0.7	0.3	1.6	0.43
Tandem length	0.5	0.2	1.8	0.32
Ovoid size	0.6	0.1	2.6	0.48
Overall treatment time	1.0	1.0	1.0	0.55

start of the treatment (*Figure 2*). The probability density function had a log normal distribution.

Statistical analysis (*Table 3*) demonstrated a significant correlation between the risk of developing rectovaginal

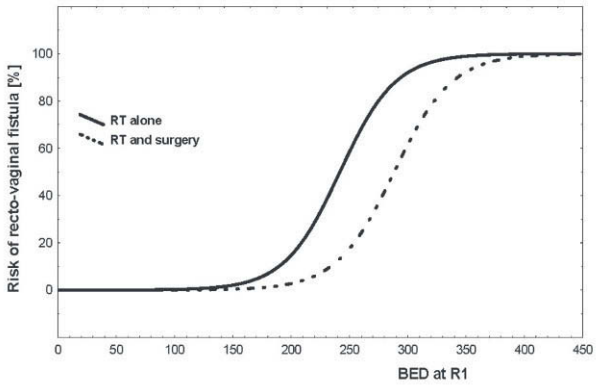

Figure 4. Dependence of rectovaginal fistula risk and biological extrapolated dose (BED) at point R_1 for radiotherapy alone and combined with surgery.

fistula and the biological extrapolated dose (BED) at point R_1. The risk of rectovaginal incidence relative to the normalized total dose at point R_1 is illustrated by the curve in *Figure 3*. Combined treatment with surgery followed by radiotherapy also significantly affected the dose-effect relationship as also illustrated in *Figure 4*.

No effect of factors such as age, FIGO stage, physica activity, haemoglobin level, overall treatment time, type and size of applicators on the fistula development risk was observed (*Table 2*).

Discussion

The incidence of severe sigmoidovaginal and rectovaginal fistulae after radiotherapy for cancer of the uterine cervix, as attested by the literature, varies from 0% to 9% [4-12]. In our study, the incidence of rectovaginal fistulae as a postradiotherapeutic complication was 7.6%. The group of our patients provided a basis for identifying clinical and physical risk factors.

The most important risk factor is the radiation dose at point R_1. There is some disagreement as to the relevance of the dose in this [13-16]. The advantage of using the dose at point R_1 is that it can easily be identified, precisely defined, and has widely been adopted in research on radiation-induced fistulae. Defining a dose rate at a point where the dose gradient from brachytherapy is high carries the risk of making errors in dose calculation estimated at about 10% [17,18]. That error was not taken into account in the calculations. The results in the form of dose effect curves showing the actuarial risk of a rectovaginal fistula in relation to the physical dose at point R_1 are illustrated in *Figure 5* and show a characteristic sigmoid shape. For comparison, a dose response curve in severe complications, which is a broader category, presented by Perez [7], is also shown. Although the curves were obtained using different methods, graphic evaluation of the risk, a logistic regression model and the segmental linear regression analysis suggest that the results, in fact, do not differ. Kottmeier [19], Pourquier [20], Yudelew [21] and Esche [14] also suggested that in the dose range from 75 to 85 Gy a rapid increase in the severe complication risk occurs. Unfortunately, statistical significance of curve fitting precision was not obtained for

those patients who had undergone combined treatment. This suggests that other factors, which modify the dose-effect relationship, should not be ignored.

By employing a linear-quadratic formula (LQ), allowance was made for the difference in the biological effectiveness resulting from a dose rate in brachytherapy and a fraction dose in external beam irradiation. No correction for repopulation was used. Variability of the total dose and dose per fraction in external beam radiation and variability of doses and dose rates, resulting from different physical dose distribution of brachytherapy in relation to point A resulted in a wide dispersion of the calculated effective biological radiation dose at point R_1 and well defined dose effect curves.

The complication risk following postoperative radiotherapy is higher and isoeffective doses are lower by approximately 10% compared to radiotherapy alone (*Figure 4*). But, in fact, we observed a lower rate of complications after the combined treatment schedule since a much lower mean biological dose at point R_1 was given.

On the other hand, Kucera reported a 7.4% incidence rate of fistula in patients subjected to a combined treatment versus 3.2% subjected to radiotherapy alone [6]. Thoms in his study presents a group of 244 uterine cervix carcinoma patients, homogeneous in terms of FIGO stage, IB, but undergoing different treatment regimens [11]. In the group subjected to the combined treatment the frequency of fistula was 9% compared to 4% after radiotherapy alone. Also Eifel and Frank noted that the fistula incidence was twice as high as a result of the combined treatment [22, 23]. Obviously, the increased risk of fistula as a consequence of radiotherapy after surgery of the cancer of the cervix can be prevented by decreasing the radiation dose at point A by 10 – 15%. The use of a biological effective dose for the combination of external beam and brachytherapy schedules resulted in a consistent relationship between BED and rectal late effect. The estimated BED below 115-135 Gy as a predictor of a low risk (<10%) rectal injury [24-30].

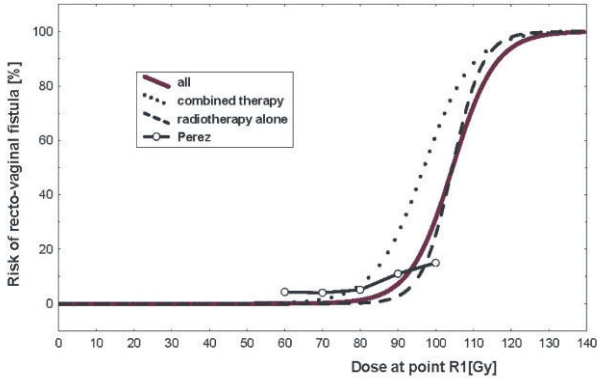

Figure 5. Dependence of rectovaginal fistula risk and total dose at point R_1 for radiotherapy alone and radiotherapy combined with surgery. Additionally severe rectal complication risk curve according to Perez.

Our evaluation of the clinical and physical factors modifying the postradiotherapeutic fistula incidence risk demonstrated no significant influence of such clinical factors as age, FIGO stage, physical activity, haemoglobin level, overall treatment time, type and size of applicators. Radiation dose and dose distribution are the main risk factors for the development of this rare but extremely severe complication.

Conclusions

1. The biological extrapolated dose (BED) at point R_1 is an important predictive factor relevant for postradiotherapeutic rectovaginal fistula incidence risk.
2. Surgery is an important factor modifying the postradiotherapeutic rectovaginal fistula incidence risk.
3. No significant influence on the fistula incidence risk of such parameters as age, FIGO stage, physical activity, haemoglobin level, overall treatment time, type and size of applicators has been demonstrated.

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