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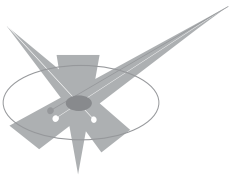

Original Paper

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Estimation of the α/β ratio for lower lip cancer treated with interstitial HDR brachytherapy

Andrzej Lebioda[1], Roman Makarewicz[1], Agata Rembielak[2], Brygida Bialas[2], Renata Kabacińska[1]

[1] Chair and Clinic of Oncology and Brachytherapy, University of Nicolaus Copernicus in Toruń, Collegium Medicum in Bydgoszcz, Poland
[2] Brachytherapy Deparment, Comprehensive Cancer Centre, Maria Skłodowska-Curie Memorial Institute Branch Gliwice, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background A standard linear-quadratic (LQ) model is now routinely used for clinical data analysis and the prediction of the clinical effect of radiotherapy. The typical α/β values suggested in the literature range from 10 to 20Gy for most tumours and early responding normal tissues, and from 2 to 5Gy for late responding tissues.

Aim The estimation of α/β ratio values for planoepithelial lower lip cancer.

Materials/Methods The clinical material is based on the records of 25 patients undergoing radical treatment with interstitial brachytherapy: 19 patients were administered brachytherapy exclusively and 6 patients were treated postoperatively. The following stage arrangement was applied: T_1 in 15 pts, T_2 in 9 pts, N_0 in 24 pts and N_1 only in one T_2 patient. Radiotherapy was based on HDR brachytherapy using the interstitial technique. Patients with positive margins after surgery were qualified for postoperative brachytherapy. The dose was either specified at the reference 80% isodose according to the Paris System or points calculated 3–5 mm from the macroscopic tumour. The average total dose was 38.3Gy, the number of fractions being 7 and the fraction dose 5.3Gy. The overall treatment time was 12 days. The average follow-up period was 30 months. A standard probit regression in conjunction with a linear-quadratic model was used.

Results The estimated value of the α/β ratio for lip cancer was 12Gy ($\pm 3.72*10^{-10}$ 95% CI).

Conclusions The estimated α/β ratio is consistent with α/β ratios published for squamous cell head and neck cancers.

Key words **lower lip cancer • LQ model • α/β ratio • brachytherapy**

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Author's address: Andrzej Lebioda Centre of Oncology, Romanowskiej 2 Str., 85-796 Bydgoszcz, Poland, e-mail: lebiodaa@co.bydgoszcz.pl

Background

A standard linear-quadratic (LQ) model is now routinely used for clinical data analysis and the prediction of the clinical effect of radiotherapy. Typical α/β values suggested in the literature range from 10 to 20Gy for most tumours and early responding normal tissues, and from 2 to 5Gy for late responding tissues [1–4].

Radical radiotherapy of lip cancer has a long tradition at our centre. Most of our patients, except those with T_3, T_4 stage and $N>_0$, were originally qualified for external beam irradiation. In the late 1990s we experienced limited access to external beam irradiation machines as a result of the exchange of the radiotherapy line at our centre, which led to a new group of patients qualified for interstitial brachytherapy schedules. Due to the lack of standards we had to apply a treatment schedule of a 6Gy fraction given once a week. In the presence of good implant tolerance and an acute reaction, we reduced the fraction dose to 3Gy and planned 17 fractions given once or twice per day for 14 days to give a 51Gy total dose. The wide range of fractions and total doses resulting from the new treatment schedule was the reason why we started to carry out the present analysis.

The discussion of α/β ratio values as they relate to prostate cancer [5–7] and the conclusions based on low α/β ratio values as well as the consequences of the benefit of high fraction doses were additional factors determining our work. Our discussion uses the same argument as Brenner and Martinez [8], firstly involving of high fraction doses using the interstitial technique far beyond the external beam radiotherapy range, and, as a consequence, pushing the high biological effectiveness of such fractionation schedules. Secondly we omitted the fact that the dose distribution in HDR brachytherapy interstitial technique was non-homogeneous.

Aim

The estimation of α/β ratio values for planoepithelial lower lip cancer.

Materials and Methods

Our clinical material is based on the records of 25 patients treated radically with interstitial brachytherapy at the Centre of Oncology in Bydgoszcz and the Cancer Centre – Institute of Oncology in Gliwice between May 1999 and December 2004. Nineteen patients were solely administered brachytherapy and 6 patients were treated post-operatively. All patients had pathologically confirmed squamous cell carcinoma of the lower lip. The following stage arrangement was applied: T_1 in 15 pts, T_2 in 9 pts, N_0 in 24 pts and N_1 only in one T_2 patient out of the 25. Patients with infiltration of the mouth corner were excluded from this study. One patient also had simultaneous lung cancer, two patients had previous cancer of the larynx and one patient had suffered a cerebral stroke. According to our recommendations post-operative brachytherapy was indicated in the cases of microscopic non-radical treatment or lack of information about the features of the margin.

Radiotherapy was based on ^{192}Ir HDR brachytherapy using the interstitial needle technique. Patients with positive or unknown margins after surgery (6 pts.) were eligible for post-operative brachytherapy. The dose was specified either at the reference 80% isodose according to the Paris System or points calculated 3–5 mm from the macroscopic tumour or tumour bed. The average total dose was 38.3Gy (range: 15 to 50Gy), the average number of fractions being 7 (range: 1 to 15), and the average fraction dose 5.3Gy (range: 3 to 15Gy). The average V_{100} was 4.8ccm, (range: 0.7–17ccm) and V_{200} 1.6ccm (range: 0.2–6.7ccm). The mean treatment time per fraction was less than 3 min, depending on the dose and source activity. The mean number of interstitial needles was 2 (range: 1 to 5). The overall treatment time (OTT) for brachytherapy alone was 12 days (range: 1 to 40). The mean follow-up period was 30 months (range: 24 to 43). Local control, defined as no evidence of the disease at the 24th month, constituted the clinical endpoint of our study.

All patients (25) showed a complete response and none of them experienced local recurrence. In all patients treated with brachytherapy as the sole method, epitheliolysis and oedema around the implant appeared. We did not observe late effects, i.e. fibrosis, skin retraction, hypo- or hyperpigmentation or ulceration. The only cosmetic defect was a little tissue loss at the place of the primary infiltration, and teleangiectiasis in two patients. No complications involving the implant (bleeding, infection) were noted.

Statistical analysis covered standard logistic regression in conjunction with a linear-quadratic model (LQ). The application of a logit regression model is based on the estimations of linear regression

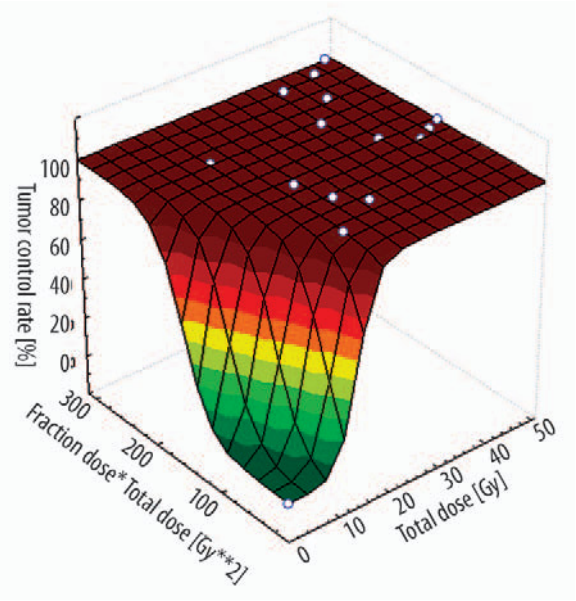

Figure 1. A surface plot of the local control probability as a function of the total dose and the product of the total dose and fraction dose.

parameters (independent variable) which influence local control probability (dependent variable) on the assumption that the variable has a normal distribution. The general form of the model may be described by the equation:

$$p = \exp(a_0 + a_1{*}x_1 + a_2{*}x_2 + \ldots + a_n{*}x_n) / (1 + \exp(a_0 + a_1{*}x_1 + a_2{*}x_2 + \ldots + a_n{*}x_n))$$

Where
p is the local control probability,
x_i is the independent variable i and
a_i is the parameter of item independent variable.

In one particular case, using the LQ model, the above equation assumes the form:

$$p = \exp(a_0 + \alpha{*}TD + \beta{*}TD{*}df) / (1 + \exp(a_0 + \alpha{*}TD + \beta{*}TD{*}df))$$

Where
α, β are the LQ equation parameters,
TD is the total dose,
df is the fraction dose and
TD*df is the product of the total dose and fraction dose.

Clinical data were presented in 3 columns, comprising total dose, total dose and fraction dose product, and clinical effect assessment. In our work tumour control at the 24th month was scored as "1" and lack of local control as "0". Using the maximal likelihood method the estimated coefficients were fitted. Additionally, standard errors were estimated. In order to obtain local control in 100% of patients the following parameters had to be introduced in the analysis: the total dose of 0Gy, the fraction dose of 0Gy, with no local control ("0" score). The confidence interval (CI) of the α/β ratio was calculated as the sum of the relative confidence interval of the α and β parameters and α/β value product. Cases weighting equal to the value of fraction dose was excepted. All the calculations were made using the maximum-likelihood procedures of the Statistica '99 software [9].

Results

The estimated α/β ratio was 12Gy ($\pm 3.72{*}10^{-10}$ 95% CI). The estimated α parameter was $0.587 Gy^{-1}$ ($\pm 9{*}10^{-11} Gy^{-1}$, 95% CI) and the β parameter was $0.05 Gy^{-2}$ ($\pm 7{*}10^{-12} Gy^{-2}$, 95% CI). Figure 1 is a surface plot of the local control probability as a function of the total dose (TD) and the product of the total dose and the fraction dose (TDxdf).

Discussion

By applying a linear-quadratic model in clinical practice we were able to estimate equivalent doses safely. The basic element of the LQ model is the α/β parameter. However, estimation of the basic and also the critical LQ model parameter which is the α/β ratio involves a wide, or even very wide, 95 percent confidence interval. The estimated α/β ratio of 12Gy is consistent with what is expected for the tumours investigated. Gordon Steel [10] presents six α/β ratios for head and neck cancers. The 95% confidence limit for two cancers (vocal cord and orpharyx) is not estimated; for the next two cancers (buccal mucosa and tonsil) it is between 3.6Gy and infinity; for larynx carcinoma it is 10–20Gy; and for nasopharynx cancer it is from 11 to 43Gy. Such a wide confidence interval depends on at least two factors. The first one is the method of analysis. The superiority of a nonlinear regression (logit or probit) over a reciprocal dose technique (Figure 2) is unquestionable [11]. We employed the former technique in our work using a method proposed by Howard Thames [12]. The logit transformation enables one to connect the biological effect, expressed as a percentage of local controls or complications, with fractionation parameters (TD, TD*df), preserving the simplicity of the LQ model.

The other factor is the clinical data set based on schemes characterized by little variability of

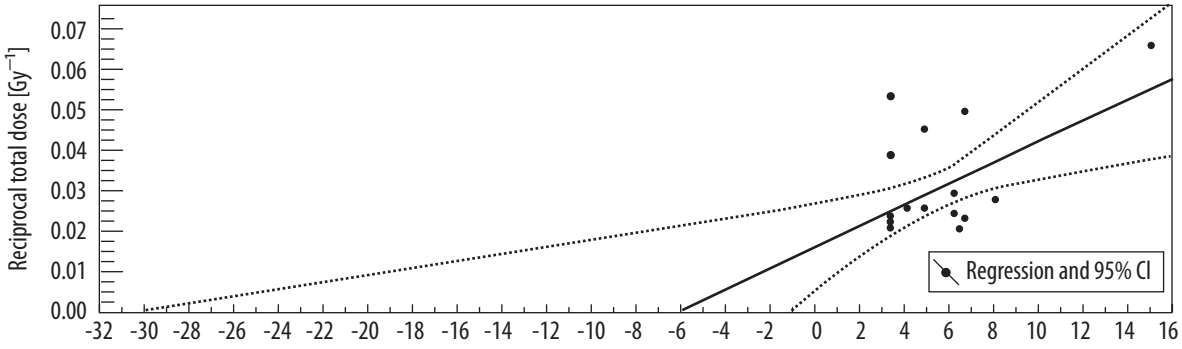

Figure 2. A linear plot of the local control probability as a function of the reciprocal total dose and the fraction dose, α/β value 6Gy, 95%CI 1–30Gy.

fractions and, in consequence, by the total dose. In our material, the ratio between the lowest and the highest fraction dose was 5× (3–15Gy) and 3× (15–50Gy) as regards the total dose. This was the result of the lack of HDR brachytherapy standards in the treatment of lower lip cancer. At the beginning we chose a treatment schedule of 6Gy per fraction given once a week. In the presence of good implant tolerance and acute reaction we reduced the fraction dose to 3 Gy and planned 17 fractions given once or twice daily over 14 days, expecting a lowering of late effect risks. A wide range of fractions and total doses due to the variability of treatment schedules enabled us to carry out this analysis.

A correction for repopulation was not introduced because of the short OTT and for incomplete repair due to the interval between those fractions being longer than 6 hours.

The disadvantage of our analysis is that the number of patients is small. The most important source of error may lie in the incorrect estimation of dose distributions or their specifications when using non-homogeneous dose distribution in contrast to external beam radiotherapy employing a homogeneous dose distribution.

Conclusions

We estimated the α/β ratio value to be 12Gy (±3.72*10^{-10} 95% CI), which is consistent with the previous estimation for squamous cell head and neck tumours.

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