Acta Oncologica Vol. 31, No. 6, pp. 663–668, 1992

A CONTRIBUTION TO THE COMPARISON OF THE EFFICACY OF RADIOTHERAPEUTIC PROCEDURES IN CERVICAL CARCINOMA

TAČO TAČEV, JAROSLAV MICHÁLEK and JIŘÍ POLÁCH

This paper presents a new method in which the regression velocity of cervical carcinoma is measured by computer tomography and the results evaluated by two statistical methods: non-linear regression analysis and survival analysis. By means of this approach it was possible to compare the early effect of therapy in patients treated with intracavitary application of ^{226}Ra plus external radiotherapy with those treated with ^{252}Cf, ^{226}Ra and extended radiotherapy. In the latter group a higher efficacy of the therapy was demonstrated by both statistical methods. As the timing between external and intracavitary radiotherapy was different in the two groups and as ^{252}Cf contributed to a rather small part of the total radiation dose it could not be concluded that the difference in efficacy really was due to ^{252}Cf. Of essential interest was, however, that an obvious difference in efficacy could be found between two slightly different treatment techniques. The statistical procedure called survival analysis, used here parallelly with weighed regression analysis seemed to give better results than a classical regression analysis and can thus be recommended for processing of clinical data of the type which is discussed in this paper.

Methods allowing early comparison of the efficacy of various therapeutic approaches have always been of great interest for radiotherapy of malignant tumours. Long-term studies on survival and freedom from recurrence give the most adequate expressions for the overall value of a treatment method but are very time-consuming and may, moreover, too late reveal the fact that an applied therapeutic procedure may not have been optimal. Therefore, attention has been focused on early supplementary criteria for treatment efficacy as tumour regression rate (1, 2). This approach can be used only when the anatomy permits volumetric measurement of the tumour. The possibilities for such measurements have improved by modern diagnostic methods, such as sonograhy, computer tomography and nuclear magnetic resonance imaging.

In the present study the regression of cervical carcinoma was followed and statistically compared in two groups of patients with cervical carcinoma treated with different radiotherapy techniques.

Material and Methods

Regression curves for cervical carcinoma were compared in 58 patients treated in 1986–1987. The patients were randomly allocated into two groups. Randomization was performed on admission of each patient and was based on a random decision of type of treatment. Group 1 (33 patients) was treated with intracavitary application of ^{252}Cf followed by ^{226}Ra. Group 2 (25 patients) received intracavitary ^{226}Ra treatment. Only patients with advanced disease (stages II, III, IV according to the FIGO classification) were included.

The two treatment methods differed as follows: Group 1 patients received ^{252}Cf brachytherapy with a dose of 2 Gy (RBE = 6 (3)) in point A in the first week. In the 4th

Received 3 June 1991.
Accepted 12 June 1992.
From the Masaryk Memorial Cancer Institute (T. Tačev), Faculty of Sciences (J. Michálek) and Faculty of Medicine (J. Polách), Masaryk University, Brno, Czechoslovakia.
Correspondence to: Dr Jirí Polách, Computer centre, Medical School of Masaryk University, Jostova 10, 662 44 Brno, Czechoslovakia.

week this was followed by intracavitary application of ^{226}RA with a dose of 40 Gy in point A. Group 2 patients were treated solely with ^{226}Ra application in the 3rd and 5th weeks of therapy. The total radium dose was 55 Gy in point A. External radiation therapy in both groups was given with a Co Chisostat unit with extended fields adjusted according to the results of lymph node examination. The central pelvic dose from external radiotherapy was 40 Gy. The total dose in point A was equivalent to ~85 Gy in both groups when the high RBE of ^{252}Cf neutrons was taken into account. A detailed description of the treatment methods is given in Table 1.

Volumetric measurement of the enlarged cervix uteri was made with computerized tomography (4–7). The examination was performed with a Somatom 2 device. Before examination, a cylindrical swab immersed with saline solution was inserted into the vagina with its upper margin at the level of the isthmus uteri in order to distinguish the lower cervical margin from the surrounding healthy tissue. Images of cervical tissue in consecutive planes from the lower vaginal edge up to the uterine body were obtained which allowed calculation of the total cervical volume. Each examination was repeated three times and the arithmetic mean was calculated. The lower and the lateral outlines of the cervix were distinctly recorded in almost all cases. However, this was not always true for the junction of the cervix and uterine body and by this method a part of uterine body tissue may be included into the measurement of the cervical volume. To avoid an effect of this inaccuracy on the assessment of tumour regression, all measurements in a special patient were related to the definition of the junction between the cervix and the uterine body made at the first examination, i.e. before radiation therapy (Fig. 1). The uterine body tissue which may have been included in the volumetric measurements thus remained constant.

The regression of cervical carcinoma was followed till tumour clearance could be assessed macroscopically, i.e. when the cervical volume remained constant. The volumetric changes of the uterine cervix were in each patient estimate by 4–7 measurements. The intervals between the examinations were not regular and varied in each patient and within the whole sample.

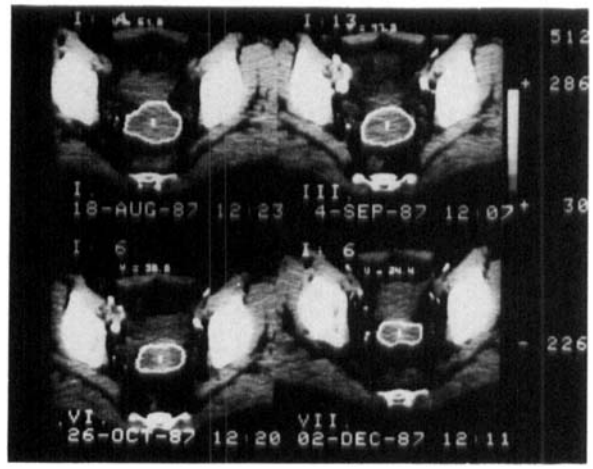

Fig. 1. Changes in volume of cervical carcinoma during and after radiation therapy.

Table 1

Treatment design

Group	Week of therapy 1	2	3	4	5	6	Total dose
1	^{252}Cf [1)] 12 μg uterovag. Point A 13.8 Gy-eq. Point B 4.5 Gy-eq	External irradiation full fields Point A–B 20 Gy Fractionation: 2 Gy/day		^{226}Ra 50 mg uterovag. Point A 40 Gy Point B 12 Gy	External irradiation split fields Point A 10 Gy Point B 20 Gy Fractionation: 2 Gy/day		Point A ~84 Gy-eq Point B ~57 Gy-eq
2	External irradiation full fields Point A–B 20 Gy Fractionation: 2 Gy/day 9 Gy		^{226}Ra 2 × 20 mg colpostat Point A 25 Gy Point B 10 Gy	External irradiation split fields Point A 5 Gy Point B 10 Gy	^{226}Ra 4 × 10 mg tandem Point A 30 Gy Point B 10 Gy	External irradiation split fields Point A 5 Gy Point B	Point A 85 Gy Point B 59 Gy

1) Dosimetric planning was performed in Gy-equivalents (Gy-eq.) by use of the following equation: D/Gy-eq. = Dn.RBE$_n$ + Dγ.RBEγ where D$_n$ and Dγ = physical doses from neutron and gamma components of ^{252}Cf irradiation; RBE$_n$ and RBEγ = relative biological effectiveness of the gamma and neutron components of ^{252}Cf irradiation

Statistical processing

Processing of a set of the determined statistical data was done by means of two statistical methods. The first one was classical non-linear regression analysis and the second one a modern statistical method called survival analysis (8). In order to avoid misunderstanding it should be mentioned that the survival analysis as a statistical method used here for data processing is not connected with the survival of treated patients.

First, we will deal with processing of a given data set by means of non-linear regression analysis. The decrease in the tumour volume after irradiation was modelled by the following regression relation (9):

$$Y_x = (1 + e^{\alpha})/(1 + e^{\alpha + \beta x}). \qquad \text{(Eq. 1)}$$

where x is the time of examination, measured from the start of medical treatment (in days) and Y_x is the relative tumour volume at time x, i.e.

$$Y_x = \frac{V_x - V_k}{V_0 - V_k},$$

V_x tumour volume at time x,

V_0 initial tumour volume.

V_k final tumour volume after recovery or at the last examination,

α, β are unknown parameters of which α describes the time of the response to medical treatment and β the decrease of the tumour volume during medical treatment.

The estimate of the unknown parameters was made by the method of least squares. For computation, the Gauss-Newton algorithm was used.

Statistical induction obtained by regression analysis was supplemented by statistical processing of the data set by survival analysis. For this analysis the decrease of the tumour size $V_0 - V_k$ (expressed as cm^3) during the period of medical care was determined for each patient. The treatment was regarded as a process leading to a decrease in volume units of the tumour until its complete clearance. The medical process could then be followed on a cumulative percentage curve of tumour persistence which, for time x, gave the percentage of volume units unaffected by the treatment. These curves are shown in Fig. 2. For each cumulative percentage value persisting tumour volume units the standard deviation was computed according to Greenwood's formula (10). The analysis implied the assumption that each tumour volume unit behaved homogeneously and independently during medical treatment both in an individual patient and in different patients.

To assess the significance of deviations in the two curves, Wilcoxon's statistics according to Breslow (11) or a test proposed by Mantel (12) were used. From our point of view, we laid stress on an evaluation by means of the Breslow test since it emphasizes the initial decrease in tumour volume and is less sensitive to the low decrease in volume that may occur in more radioresistent tumours. From a medical point of view it is important that neither of these two tests was sensitive to the choice of times at which the examinations were done. We have previously in detail described the statistical analysis (13). One assumption for this analysis is that the total number of tumour volume units is large.

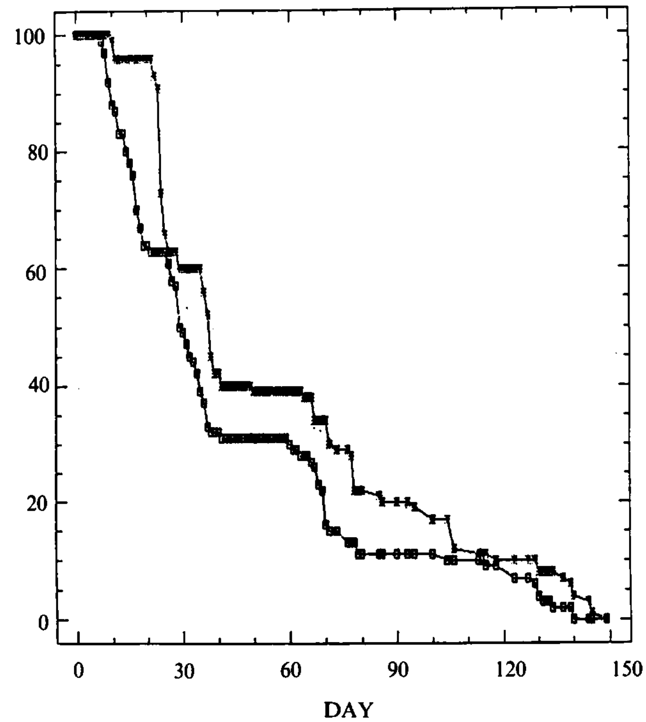

Fig. 2. Decrease in tumour volume units in relation to medical treatment. ∗: Group 1 (^{252}Cf + external RT + ^{226}Ra + external RT). ⊟: Group 2 (external RT + ^{226}Ra + external RT + ^{226}Ra + external RT).

Results

Estimates of the parameters α and β and their standard deviations s_α and s_β for the regression function (Eq. 1) were obtained for both groups of patients. The regression functions obtained are shown in Fig. 3. A preliminary estimation of the difference between the two regression curves based on an asymptotic normality of the obtained estimates showed a low level of statistical significance. However, the estimation of the tumour regression after the two medical procedures, even if it concerned the standardized data, did not sufficiently take into account the individual course of tumour volume decrease and considerable individual variability obscured the real curative effects of the applied treatment methods. It was therefore preferable to use the estimates of parameters of the regression function (Eq. 1) for each patient.

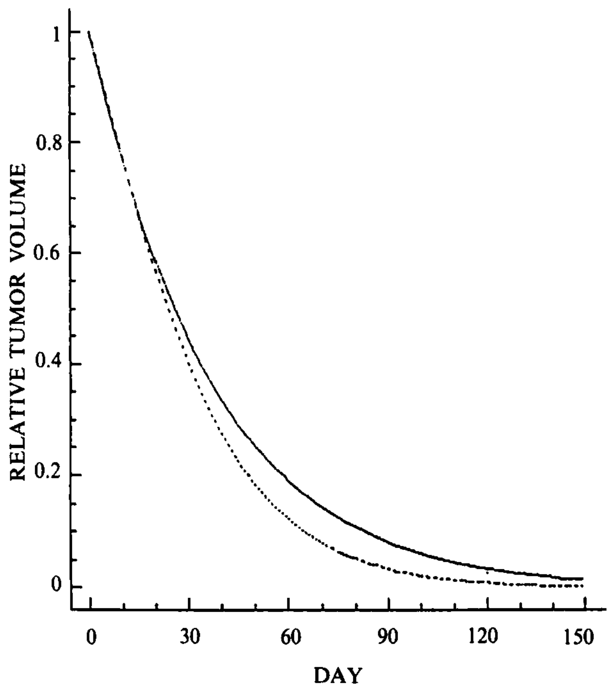

Fig. 3. Average decrease in the volume of cervical carcinoma. – – – – Group 1: patients treated with $^{252}Cf + ^{226}Ra$. n = 33, $\alpha = 0.116$, $s_\alpha = 0.753$, $\beta = 0.044$, $s_\beta = 0.009$. —— Group 2: patients treated with ^{226}Ra, n = 25, $\alpha = -2.206$, $s_\alpha = 5.212$, $\beta = 0.029$, $s_\beta = 0.009$.

A detailed analysis of the individual regression curves showed that several data were influenced by outlying observations and large measurement errors (for instance, there were individual curves where the tumour volume was estimated only during a part of the treatment period). After elimination of such outliers the small number of remaining measurements did not allow obtaining of estimates of parameters α and β (Eq. 1) which could be regarded as valid enough from statistical point of view. We therefore decided to exclude from this part of the statistical analysis all patients for whom it was not possible to reliably model the relative tumour volume decrease by means of the function (Eq. 1). By this procedure the original group of 58 patients was reduced to 37 patients, of whom 13 were treated with ^{226}Ra and 24 with ^{252}Cf. The causes of non-homogeneity and the deviations from the model (Eq. 1) in the excluded patients were not analysed in relation to individual reactions. The reduction in number of patients made it possible to use classical weighed regression analysis but conclusions based on such a small sample could lead to incorrect evaluation of the efficacy of the two treatment methods. To avoid this and to confirm or reject the results of weighed regression analysis we processed the data set from all patients by means of survival analysis.

In the whole group, made homogeneous in the way described above, individual estimates $\hat{\alpha}$, $\hat{\beta}$ of the parameters α and β were determined for each patient, together with standard deviations $s_{\hat{\alpha}}$, $s_{\hat{\beta}}$ and correlation coefficients $\rho(\hat{\alpha}, \hat{\beta})$. From the estimated regression function, the treatment time x_{50} necessary for a 50% decrease in relative tumour volume and its standard deviations were determined by means of inversion transformation. The detailed results are given in ref. 14, Table 2. They showed a considerable variability concerning the individual regression curves within each group, which obscured the therapeutic effects of the procedures used. Therefore, further processing involved assessment of the two therapeutic procedures by means of weighed regression based on standard deviations determined in the preceding analysis of the individual curves. The courses of the curves obtained by weighed regression are presented in Fig. 4. The values of the single parameters are shown in Table 3. By this processing the following hypotheses were tested:

1) $\alpha^{Ra} = \alpha^{Cf}$, i.e. there is no difference in the time of response to medical treatment between the procedures,
2) $\beta_{Ra} = \beta_{Cf}$, i.e. the decrease in relative tumour volume was equal in the two treatments,
3) $x_{50 \cdot Ra} = x_{50 \cdot Cf}$, i.e. the time needed for 50% decrease in relative tumour volume was equal after the two medical procedures.

The results of these analyses are given in Table 3. It is apparent that the test did not show any considerable difference between the parameters α_{Ra} and α_{Cf} at an acceptable significance level. The difference between the parameters β_{Ra} and β_{Cf} was disclosed by the test to be conclusive first on the 15% – significance level. A lower

Table 2

Average time (days) for regression of the tumour volume

Source of intracavitary radiation	Average time of survival of the tumour volume	SD	Time (days) for decrease in tumour volume to		
			25%	50%	75%
^{226}Ra	56.1	1.5	24	39	78
$^{252}Cf + ^{226}Ra$	43.2	1.2	17	29	68

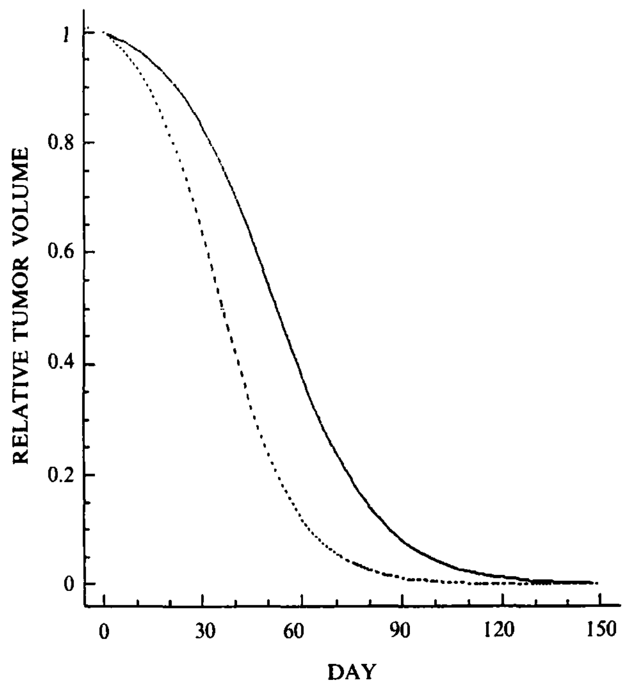

Fig. 4. Decrease in cervical carcinoma volumes. Parameters of regression curves, based on individual patient curves, were computed by weighed regression. - - - - Group 1 ($^{252}Cf + ^{226}Ra$). —— Group 2 (^{226}Ra).

value of the parameter α, describing the time of response to medical treatment, determined in the group of patients treated with ^{225}Cf, and a higher value of the parameter β, which indicates a steeper descent of the regression curve for the group of patients treated with ^{252}Cf, are evident in the course of the two weighed regression curves in Fig. 4. If we use the time x_{50} as one of the characteristics of this course, then Table 3 clearly shows a high statistical significance of the difference between the procedures concerning this characteristic. It can be concluded that the different courses of the regression functions are statistically significant, which is shown particularly concerning the time needed for a 50% decrease in relative tumour volume.

Further comparison of the two therapies was made by means of survival analysis. For the original non-homogenized groups of patients (group 1, n = 33; group 2, n = 25) the values were determined as follows: 73.1 for the Breslow statistics, 58.9 for the Mantel statistics, at one degree of freedom for comparison of cumulative percentage curves of persisting tumour volume units after irradiation with ^{252}Cf and with ^{226}Ra. The values were statistically significant on the 1%-significance level and provided evidence of the significant differences between the therapies compared. The results of evaluation shown in Table 2 were supplemented by the computation of the average time of survival of the tumour volume unit by its standard deviation and by estimates of the times for 25%, 50% (median) and 75% decrease in tumour volume. The comparison of these results with those obtained by means of regression analysis indicates a good agreement when comparing the two medical procedures. In the patients irradiated with ^{252}Cf there was a coincidence between the average time for obtaining 50% decrease of tumour volume ($x_{50} = 29.2$) and the estimate of the median time for a decrease in tumour volume (29 days) (Tables 2 and 3). In the 25 patients treated with ^{226}Ra, the variability was greater; the estimate x_{50} was 49.7 days and the estimate of the median time for a decrease in tumour volume was 39 days (Tables 2 and 3). This difference was largely caused by extending the group processed by weighed regression analysis by 12 patients treated with ^{226}Ra who, when processed by regression analysis, showed a strong non-homogeneity.

Discussion

The rate of regression induced by a certain therapeutic procedure is an important prognostic factor (15–17). When comparing the effectiveness of treatment in tumours which are similar in localization and biological type, the rate of tumour regression provides a convenient criterion for early evaluation of treatment efficacy. The possibility to follow the regression rate of a tumour or a tumour-enlarged organ is conditioned by the anatomic site of the

Table 3

Parameters of regression curves computed by weighed regression taking into account the course of the curve for each patient

	Group of patients		D.f.	F-test	Level of significance
	^{226}Ra	^{252}Cf			
Weighed estimate α	3.33	2.88	1 35	1.1	0.30
Standard deviation	0.10	0.46			
Weighed estimate β	0.065	0.082	1 35	2.1	0.16
Standard deviation	0.002	0.013			
Weighed estimate x_{50}	49.6	29.2	1 35	24.1	$<10^{-5}$
Standard deviation	2.2	2.7			

tumour and its relation to the surrounding tissues. In well-defined structures, such as the prostate, the recording of changes in volume with time by means of CT or sonography is convenient and easy to perform (1, 18, 19). Rather more difficult, however, is the volumetric assessment of the cervix, even though it can be directly studied by palpation and inspection. Evaluation of tumour regression by gynecological examinations during and after treatment is subject to bias and does not provide the information required. A more objective, though still inaccurate, approach is three-dimensional measurement of the cervical volume (9). The method presented here, which combines volumetric measurement of the cervix by computer tomography with mathematical and statistical evaluation of the results, shows a new way for early objective comparison of different therapeutic procedures. The main aim of this paper is to present a model for such studies. In the actual comparison the group treated by $^{252}Cf + ^{226}Ra$ brachytherapy supplemented by external radiotherapy showed a more rapid tumour regression than the group treated by ^{226}Ra and external radiotherapy alone. However, this does not necessarily mean that the difference was caused by the use of ^{252}Cf in one of the groups but also other factors may have played a role, such as the rather different timing of external and intracavitary radiotherapy in the two groups. Of essential interest is, however, that a significant difference in the regression curves was obtained after two slightly different treatment modalities.

REFERENCES

1. Aabo K. Prostate cancer: Evaluation of response to treatment, response criteria, and the need for standardization of the reporting of results. Eur J Cancer Clin Oncol 1978; 23: 231–6.
2. Maruyama Y, Muir W. Importance of tumor clearance rate. Int J Radiat Oncol Biol Phys 1984; 10: 321–2.
3. Maruyama Y, Beach JL, Feola J. Scheduling of hypoxic tumor therapy using neutron brachytherapy. Radiology 1980; 137: 775–81.
4. Brieman RS, Beck JW, Korobkin M, et al. Volume determination using computed tomography. AJR 1982; 138: 329–33.
5. Brenner DE, Whitley NO, Houk TL, Aisner J, Wiernik P, Whitley J. Volume determinations in computed tomography. JAMA 1982; 247: 1299–302.
6. Pilepich MV, Prasad SC, Perez CA. Computed tomography in definitive radiotherapy of prostatic carcinoma, part 2: definition of target volume. Int J Radiat Oncol Biol Phys 1982; 8: 235–40.
7. Staron RB, Ford E. Computed tomographic volumetric calvulation reproducibility. Invest Radiol 1986; 21: 272–4.
8. Fleming TR, Harrington DP. Counting processes and survival analysis, New York: Wiley & Sons Inc, 1991: 1–429.
9. Maruyama Y, Muir W. Human cervical cancer clearance after ^{252}Cf neutron brachytherapy versus conventional photon brachytherapy. Am J Clin Oncol 1984; 7: 347–52.
10. Greenwood M. The natural duration of cancer. Report on public health and medical subjects 33. London: H. M. Stacionary Office, 1926.
11. Breslow N. A generalised Kruskal-Wallis test for comparing samples subject to unequal patterns of censorship. Biometrica 1970; 57: 579–94.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50: 163–70.
13. Tačev T, Michálek J. Polách J, Prokeš B, Strnad V, Rašovská O. An assessment of regression of cervix uteri tumors using analysis of survival (in Czech). Clin Onkol 1991; 2: 54–7.
14. Tačev T, Michálek J, Polách J, et al. Monitoring regression of cervix uteri tumors during radiation therapy (in Czech). Clin Onkol 1989; 2: 141–8.
15. Dische S, Bennett MH, Saunders MI, Anderson P. Tumour regression as a guide to prognosis: a clinical study. Br J Radiol 1980; 53: 454–61.
16. Grossman I, Kurohara SS, Webster JH, George FW. The prognostic significance of tumor response during radiotherapy in cervical carcinoma. Radiology 1973; 107: 411–5.
17. Hardt N, van Nagell JR, Donaldson E, Yoneda J, Maruyama Y. Radiation induced tumor regression as prognostic factor in patients with invasive cervical cancer. Cancer 1982; 49: 35–9.
18. Fujino A, Scardino TP. Transrectal ultrasonography for prostatis cancer. II. The response of the prostate to definitive radiotherapy. Cancer 1986; 57: 935–40.
19. Wilmann P, Hancke S, Strange-Vongsen HH, Nielsen KK, Sorensen SM. The reliability of transabdominal ultrasound scanning in the determination of prostatic volume. Scand J Urol Nephrol 1987; 21: 5–7.