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APPLICATION OF LINEAR PROGRAMMING TO DOSE OPTIMIZATION IN INTRACAVITARY IMPLANT THERAPY

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Intracavitary brachytherapy involves essentially the insertion of radioactive sources within an applicator into the uterus and vault. The loadings may be adjusted for the tolerance limits of normal tissues and for the tumor. Two questions are generally addressed in dose optimization: how to maximize the tumor dose, and how to minimize the radiation dose to critical organs or normal tissues.

The term optimization problem means the problem of finding the greatest possible numerical value (maximization) or least possible value (minimization) of some mathematic function of any number of independent variables, which are placed under certain constraints. These constraints can be expressed in the form of equalities or inequalities. Hence, in an optimization problem the search for the numerical solutions for the entire set of variables which do not violate the constraints must lead to an optimum (maximum or minimum) value of the function which is to be optimized. Such mathematic treatments are known as linear programming, and have been demonstrated to be successful in optimization of e.g. external beam radiation therapy (BAHR et coll. 1968, HODES 1974, REDPATH et coll. 1975, MCDONALD & RUBIN 1977).

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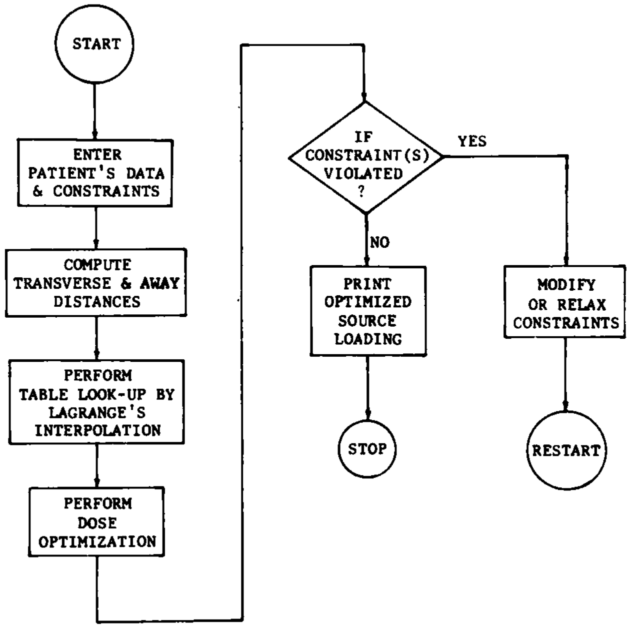

Fig. 1. Flowchart of the optimization algorithm.

The problems are generally expressed as:

Maximize (or minimize) $$z = \sum_{j=1}^{n} c_j x_j$$

Subject to $$\sum_{j=1}^{n} a_{ij} x_j \{\leqslant, =, \geqslant\} b_i$$

$$i = 1, 2 \ldots m$$

and also $$x_j \quad 0 \text{ for } j = 1, 2 \ldots n$$

It is understood in this mathematic statement that for each of the constraints, only one of the relations $\{\leqslant, =, \geqslant\}$ can be obtained at any one time.

Now consider the problem of dose optimization in intracavitary implant. The running index i stands for the anatomic point of interest, i, where a constraint is placed, and the running index j represents the jth line source. The matrix element a_{ij} is the specific dose rate in rad/mg-h which is contributed by the jth source to be optimized. The parameter, b_i, represents the radiation tolerance or the threshold dose required at the ith point. Finally the element c_j is the coefficient entering the so called profit or cost equation, and in the present case is the algebraic summation of a_{ij} over all the sources.

Method

A computer program written in FORTRAN has been developed to facilitate the computation. The input data, applicable to afterloading technique, requires the usual parameters, such as film magnification factors, number of sources and source co-

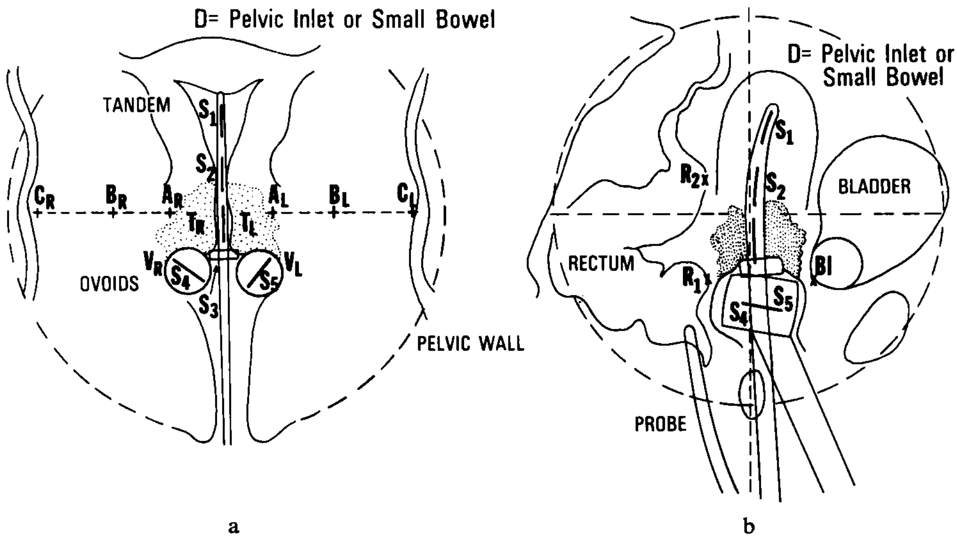

Fig. 2. Diagrammatic presentation of a set of reference points for dose constraints. a) Antero-posterior, b) lateral view. S = sources. A, B = Manchester reference points. T = ceryix tumor. V = vaginal surface. Bl = bladder. R1, R2 = rectum.

ordinates, location of anatomic points of interest where limiting doses are imposed. A flowchart outlining some of the major steps in the computer algorithm is presented in Fig. 1.

Specific dose-rate data were taken from KRISHNASWAMY (1972) since the experience in optimization during this development was limited to ^{137}Cs intracavitary implants. The 'transverse' and 'away' distances, as defined by KRISHNASWAMY, represent the parallel and vertical distances, respectively, from the point of interest to the center of the line source. Derivation of his analytical solutions are discussed in the Appendix. The specific dose-rate data have been published in a form of grid-table at an increment of 0.5 cm in the positive transverse and positive away distance; data points outside this quadrant can be easily related to this set of data by means of symmetry.

Except by chance, the coordinates of the transverse and away distances so computed do not fall onto the grid point. In those cases, data interpolation becomes necessary. Two standard techniques exist to handle data interpolation: one is Newton's Divided Difference Polynomials, and the other is Lagrange's Interpolating Polynomials. The latter was chosen for its simplicity in algorithm usage.

After all a_{ij} are calculated, the coefficients that enter into the cost or profit equation can be established. The approach in dose optimization was to maximize the dose difference between the tumor dose at all selected sites and the normal tissue dose at all healthy tissue locations. Mathematically,

$$c = \sum_{i=1}^{m} \begin{pmatrix} + \\ - \end{pmatrix} a_{ij}$$

Table

Summary of stepwise dose optimization for a ^{137}Cs intracavitary implant

Optimum	416+	60	71	71	No	87
'emitted	0	329	366	478	solution	426
radiation'	1 514	706	664	526		594
	0	92	131	165		187
	544 559	511 484	470 441	447 418		411 479
Bladder	13.0 ≤ 13.0	12.4 ≤ 12.5*	12.2 ≤ 12.4*	11.9 ≤ 12.2*	≤ 11.9*	11.9 ≤ 11.9*
Rectum	14.0 ≤ 14.0	12.5 ≤ 12.5*	12.0 ≤ 12.0*	11.5 ≤ 11.5*	≤ 11.0*	11.3 ≤ 11.3*
D	6.0 ≤ 10.0	4.0 ≤ 8.0*	4.0 ≤ 8.0	4.0 ≤ 8.0	≤ 8.0	4.0 ≤ 8.0
D	6.0 ≥ 6.0	4.0 ≥ 4.0*	4.0 ≥ 4.0	4.0 ≥ 4.0	≥ 4.0	4.0 ≥ 4.0
Rect. 1	6.2 ≤ 10.0	5.6 ≤ 7.0*	5.5 ≤ 7.0	5.3 ≤ 7.0	≤ 7.0	5.3 ≤ 7.0
Rect. 2	9.1 ≤ 10.0	8.1 ≤ 10.0	8.1 ≤ 10.0	8.0 ≤ 10.0	≤ 10.0	8.1 ≤ 10.0
T(R)	70.1 ≥ 48.0	59.3 ≥ 48.0	57.2 ≥ 48.0	50.8 ≥ 48.0	≥ 47.0*	53.9 ≥ 47.0*
T(L)	75.4 ≥ 48.0	63.1 ≥ 48.0	60.8 ≥ 48.0	53.4 ≥ 48.0	≥ 47.0*	57.0 ≥ 47.0*
V(R)	51.2 ≥ 45.0	45.0 ≥ 45.0	42.0 ≥ 42.0*	40.0 ≥ 40.0*	≥ 37.5*	37.5 ≥ 37.5*
V(L)	48.2 ≥ 45.0	45.0 ≥ 45.0	42.0 ≥ 42.0*	40.0 ≥ 40.0*	≥ 37.5*	37.6 ≥ 37.5*
V(A)	20.0 ≥ 20.0	20.0 ≥ 20.0	20.0 ≥ 20.0	20.0 ≥ 20.0	≥ 20.0	20.0 ≥ 20.0
V(P)	25.7 ≥ 20.0	23.0 ≥ 20.0	22.2 ≥ 20.0	21.0 ≥ 20.0	≥ 20.0	20.9 ≥ 20.0
A	20.0 = 20.0	20.0 = 20.0	20.0 = 20.0	20.0 = 20.0	= 20.0	20.0 = 20.0
	3 033	2 182	2 143	2 105		2 084

+ All these numbers are expressed in 10^8 Bq-h

* Dose constraints were altered from the preceding specifications

where positive sign is assigned to tumor dose and negative sign to normal tissue dose.

Constraints can be introduced by one of the three manners. They are less than or equal to, equal to, and greater than or equal to; and symbolically, these are $\leqslant$, $=$ and $\geqslant$, respectively. This was achieved, in the design of the present computer program, to which only one of the three integers (-1, 0 or $+1$, respectively) could be assigned according to the constraints specified.

With the cost equation established and with all constraints already initiated, optimization can then proceed. Into the computer program, a library subroutine was incorporated, known as ZX3LP, which is obtainable from the International Mathematical and Statistical Library, and actually performs the optimization.

Results

The input data required practically all usual parameters for afterloading intracavitary technique, such as film magnification factors, number of sources and source coordinates, and location of anatomic points of interest upon which dose constraints are placed. These reference points, referred to as Points A, B, C, T and V are defined elsewhere (MARUYAMA et coll. 1976), and are illustrated in Fig. 2. Three other points are also considered pelvic reference points: rectum (R), bladder (Bl) and pelvic inlet (D).

Table (*cont.*)

103	61	493	79	No solution	No solution
345	558	375	498		
704	411	481	506		
195	174	232	211		
340 383	529 372	375 340	378 406		
11.9⩽11.9	11.9⩽11.9	11.9⩽11.9	11.9⩽11.9	⩽11.9	⩽11.9
11.3⩽11.3	11.3⩽11.3	11.3⩽11.3	11.3⩽11.3	⩽11.3	⩽11.3
4.0⩽8.0	4.0⩽8.0	6.1⩽8.0	4.0⩽6.0*	⩽6.0	⩽6.0
4.0⩾4.0	4.0⩾4.0	6.1⩾4.0	4.0⩾4.0	⩾4.5*	⩾4.5
5.3⩽7.0	4.8⩽7.0	5.3⩽7.0	5.2⩽7.0	⩽7.0	⩽7.0
8.1⩽10.0	8.0⩽10.0	9.0⩽10.0	8.1⩽8.5*	⩽8.5	⩽8.5
59.2⩾47.0	47.3⩾45.0*	47.5⩾45.0	50.0⩾50.0*	⩾50.0	⩾50.0
62.8⩾47.0	47.3⩾45.0*	50.0⩾45.0	52.4⩾50.0*	⩾50.0	⩾50.0
32.5⩾32.5*	36.5⩾27.5*	35.0⩾27.5	39.4⩾35.0*	⩾40.0*	⩾40.0
38.3⩾32.5*	45.8⩾27.5*	35.0⩾27.5	35.0⩾35.0*	⩾40.0*	⩾40.0
20.0⩾20.0	20.0⩾20.0	20.4⩾20.0	20.5⩾20.0	⩾20.0	⩾20.0
21.3⩾20.0	20.2⩾20.0	20.0⩾20.0	20.8⩾20.0	⩾20.0	⩾20.0
20.0=20.0	20.0=20.0	20.0=20.0	20.0=20.0	=20.0	=20.0
2 076 T(R)	47.3⩽50.0*	47.5⩽50.0	50.0⩽55.0*	⩽55.0	⩽55.0
T(L)	47.3⩽50.0*	50.0⩽50.0	52.4⩽55.0*	⩽55.0	⩽55.0
	2 105 V(R)	47.5⩽50.0*	39.4⩽40.0*	⩽45.0*	
	V(L)	50.0⩽50.0*	35.0⩽40.0*	⩽45.0*	Removed
		2296	2 078		

A patient with cervical carcinoma required 4 ^{137}Cs sources in the tandem and one in each of the two ovoids. Two orthogonal, i.e. antero–posterior and lateral, films were exposed, and all reference points were identified and recorded. A series of steps in an attempt to achieve the dose optimization is illustrated in the Table.

The first column of the Table shows all the reference points of interest. Dose optimization results from the first attempt are tabulated on the left side of column 2 with the initial constraints given on the right side of the column. The optimum 'emitted radiation' in mg-h (i.e. $\times 10^8$ Bqh), also part of the computer output if optimization solutions do exist, are shown on the top part of the column. The first attempt indicated a loading of 416, 0, 1 514, 0 mg-h in the tandem and 559 and 544 mg-h for the right and left ovoids, respectively. The total mg-h, 3 033, is given at the bottom of the column.

The loading mentioned is not clinically useful, thus, a second attempt was followed with the first 5 constraints modified as indicated by those with asterisks; this resulted in disappearance of the two zeros in the tandem. Solutions from subsequent attempts are listed from left to right and are continued by the second half of the

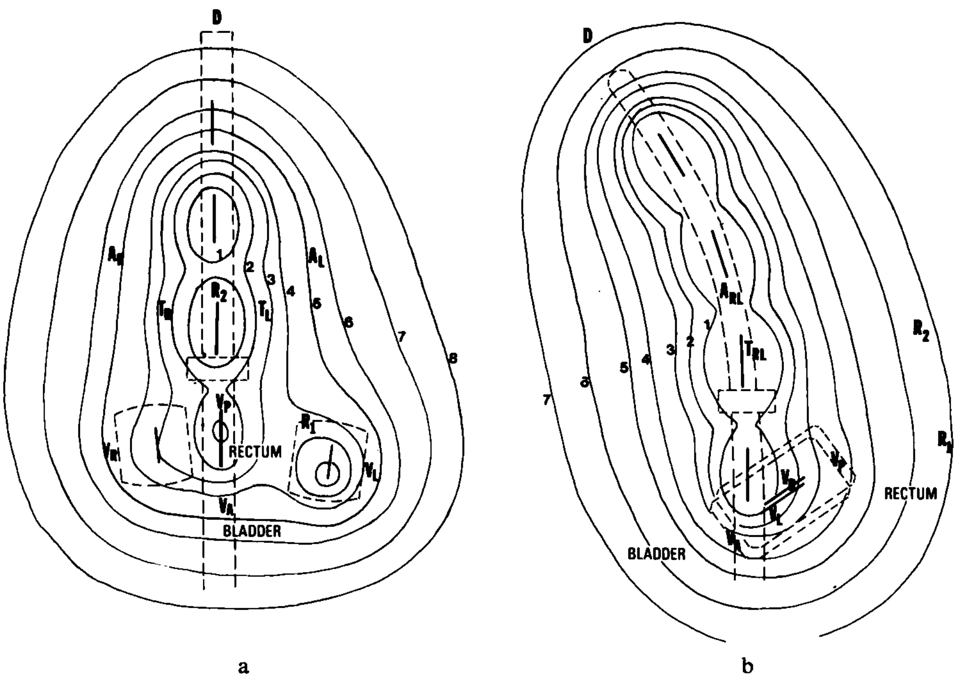

Fig. 3. Isodose rate distribution. a) Antero-posterior, b) lateral cervical view. 1 = 5 Gy/h, 2 = 3 Gy/h, 3 = 2 Gy/h, 4 = 1.5 Gy/h, 5 = 1 Gy/h, 6 = 0.75 Gy/h, 7 = 0.5 Gy/h, 8 = 0.35 Gy/h.

Table. Occasionally new constraints were added and are shown toward the bottom of the Table for the attempt. Sometimes no feasible solutions were encountered; these are illustrated by the sixth and the last two attempts.

Discussion

As a general rule for all optimization problems, solutions become feasible if two or more conflicting constraints have been resolved. This is signaled by an error message, and in order to restart the computation, modification of some of the constraints must be made.

In the present optimization procedure, two constraints, one for the upper boundary and the other for the lower boundary, can be simultaneously introduced to any desired reference point. This exercise was illustrated by a pair of constraints assigned to Point D from the beginning and two other pairs during the 8th and the 9th. Bounded constraints prove to be particularly helpful in limiting the range of dose variation to be delivered to certain critical organs.

The experience reveals that the activity of sources to be optimized is quite sensitive to the constraints introduced. A small variation in dose specification, especially to the bladder and rectum may, lead to considerably different loading configuration (as exemplified by the first two attempts) and even to non-feasibility of the solutions.

Of all the 9 successful attempts, the 4th and the last appeared to be satisfactory; both would provide adequate dose to appropriate tumor points while not exceeding overall normal tissue tolerance. Fig. 3 gives the isodose rate distribution according to the loading given by the last attempt with total activity normalized to 100 mg-Ra (i.e. 9.33×10^9 Bq) equivalence. It should be emphasized that the numbers in mg-Ra (Bq) equivalence as shown in Fig. 3 a represent an idealized situation. In actual implant, the approximate total activity needs to be specified, for this will in turn determine the loading sequence based upon available inventory. Very often some of the source strengths so determined may not be available in the inventory. In such cases, it is necessary to adjust the total activity or re-evaluate other optimized loading configurations. A ± 10 per cent deviation, for example, between the calculated source strengths with those in the inventory might serve as a guideline in determining the acceptance of such a treatment plan.

Nevertheless, the Program (available on request only) has been tested and found to be applicable even when ovoids are not considered. With little modification, it can also be applied to those situations when sources other than ^{137}Cs are used.

Conclusions. The present report addresses the problem of computerized intracavitary dose optimization by varying the activity of a given number of sources under the constraints of delivering an adequate dose to appropriate tumor volumes while not exceeding normal tissue tolerance to all other organs. The linear programming technique allows this to be accomplished.

Appendix

In order to make use of KRISHNASWAMY's published data, it is necessary to resolve the positional parameter into the transverse and away components with respect to each source, and then perform the table look-up routine.

Let $p(p_x, p_y, p_z)$ be assumed to be the positional parameter for the anatomic point of interest, and $s_1(s_{1x}, s_{1y}, s_{1z})$ and $s_2(s_{2x}, s_{2y}, s_{2z})$ to be the spatial parameters of the upper and lower ends of the active length of the source. It should be noted that small letters are used to represent those three-dimensional variables, while capital letters are reserved later for the two-dimensional parameters. Nevertheless, the distance between the anatomic point of interest and the source end can be computed according to the following:

$$r_1 = |r_1| = |p - s_1| = \sqrt{(p_x - s_{1x})^2 + (p_y - s_{1y})^2 + (p_z - s_{1z})^2}$$

and

$$r_2 = |r_2| = |p - s_2| = \sqrt{(p_x - s_{2x})^2 + (p_y - s_{2y})^2 + (p_z - s_{2z})^2}$$

The coordinate system is now redefined so that the source will lie on the y-axis in a two-dimensional system in accordance with the system of KRISHNASWAMY (Fig. 4). As generally assumed that the source activity is uniformly distributed everywhere along the line source,

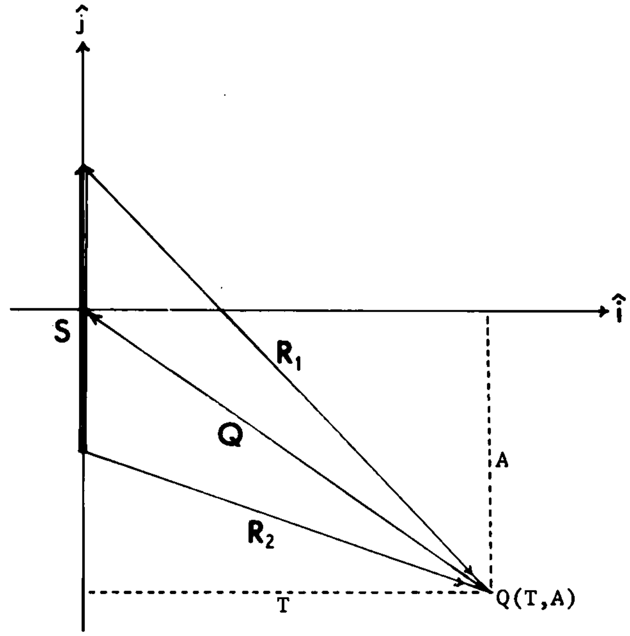

Fig. 4. Relationship of the position vector, Q, and the line source, S.

only two variables, transverse and away distances for example, are sufficient to describe the spatial coordinates of any given point with respect to the line source due to the inherent cylindric symmetry. Then

$$R_1 = r_1$$
$$R_2 = r_2$$
$$S = |S| = |s_2 - s_1|$$

and a simultaneous equation containing the two unknowns, T and A, for the transverse and away distances.

$$Q - \frac{S}{2} = R_1$$
$$Q + \frac{S}{2} = R_2$$

or expressed in terms of x and y components,

$$(T\hat{\imath} + A\hat{\jmath}) - \left(\frac{S}{2}\right)\hat{\jmath} = R_1$$
$$(T\hat{\imath} + A\hat{\jmath}) + \left(\frac{S}{2}\right)\hat{\jmath} = R_2$$

where i and j are the unit vectors along the x and y directions in the cartesian coordinate system. To solve for T and A, all x and y components are grouped together on the left side of each equation and then an absolute value is taken. The equations are now reduced to

$$T^2 + (A - S/2)^2 = R_1^2$$

$$T^2 + (A + S/2)^2 = R_2^2$$

which yields the solution of A

$$A = (R_2^2 - R_1^2)/(2S)$$

T can then be found by substituting the value of A into either of the equations mentioned.

The solutions of these two components may sometimes carry negative sign, only the positive quantities are sought because of symmetry.

SUMMARY

Linear programming can be used to optimize intracavitary brachytherapy for carcinoma of the cervix. A method has been developed which gives meaningful output and is described. A set of reference points were necessary in addition to the standard reference points. Point A as well as an array of points for adjacent radiation sensitive normal structures were used in order to obtain isodose curves conforming to those commonly used for therapy. In addition, arbitrary upper and lower limits of dose at selected points were needed and were set to conform to systems commonly used clinically for intracavitary therapy. It was immediately evident that a wide variety of loadings can be used that deliver appropriate or improved doses to reference points while minimizing normal tissue dose. The loadings.represent arrangements which are not commonly used in many clinics but offer potential for clinical use.

ZUSAMMENFASSUNG

Eine lineäre Programmierung kann verwendet werden um die intrakavitäre Brachytherapie wegen eines Cervixkarzinoms zu optimieren. Eine neuentwickelte Methode, die in der Praxis gute Resultate gibt, wird beschrieben. Einige Referenzpunkte waren notwendig zusätzlich zu den Standardreferenzpunkten. Punkt A sowie eine Reihe von Punkten für die angrenzenden strahlenempfindlichen Normalstrukturen wurden verwendet in der Absicht, Isodoskurven in Übereinstimmung mit den gewöhnlicherweise bei der Therapie verwendeten zu erhalten. Zusätzlich wurden willkürliche obere und untere Begrenzungen der Dosen in ausgesuchten Punkten verwendet, um mit Systemen, die gewöhnlicherweise klinisch bei der intrakavitären Therapie verwendet werden, zu vergleichen. Es wurde unmittelbar deutlich, dass eine grosse Verschiedenheit von Ladungen verwendet werden kann, um angemessene oder verbesserte Dosen zu den Referenzpunkten zu geben während die Normal-Gewebedosen ein Minimum erreichen. Die Ladungen repräsentieren Anordnungen, die gewöhnlicherweise in vielen Kliniken nicht verwendet werden, aber für klinischen Gebrauch verwendet werden könnten.

RÉSUMÉ

On peut utiliser une programmation linéaire pour optimiser la brachythérapie intracavitaire pour le carcinome du col de l'utérus. Les auteurs ont mis au point une méthode qui donne des résultats intéressants et qu'ils décrivent. Une série de points de référence est nécessaire en plus des points de référence standard. Le point A ainsi qu'une rangée de points concernant les structures normales voisines sensibles aux radiations ont été utilisées pour obtenir des courbes isodoses qui se conforment à celles qui sont habituellement utilisées pour le traitement. De plus, il a été nécessaire de fixer des limites de doses supérieures et

inférieures arbitraires à des points sélectionnés et ces limites ont été déterminées de façon à se conformer au système habituellement utilisé en clinique pour la thérapie intra-cavitaire. Il est devenu immédiatement évident qu'une grande variété de charges peuvent être utilisées pour délivrer des doses appropriées ou améliorées à des points de référence en même temps qu'on minimise la dose au tissu normal. Ces charges représentent des arrangements qui ne sont pas habituellement utilisés dans beaucoup de services mais qui peuvent offrir un intérêt potentiel pour l'utilisation clinique.

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