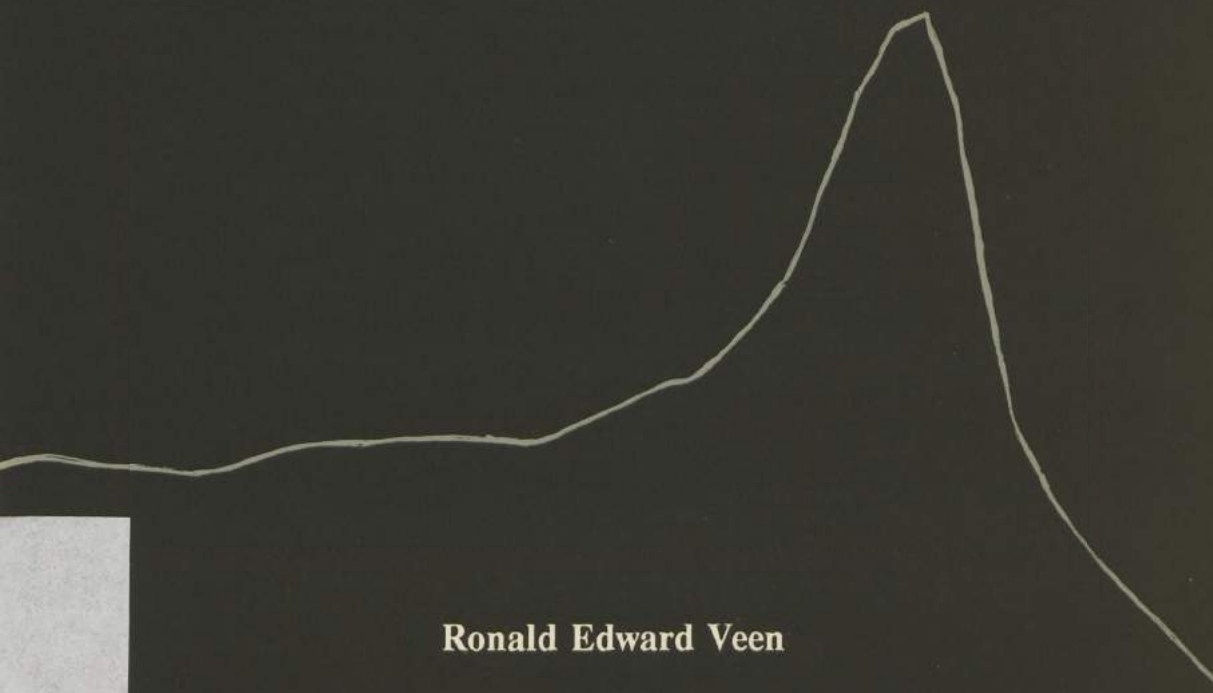
APPLICATORS IN INTERSTITIAL RADIOTHERAPY, "THE DEVENTER SYSTEM"



Ronald Edward Veen

APPLICATORS IN INTERSTITIAL RADIOTHERAPY, "THE DEVENTER SYSTEM"

APPLICATORS FOR INTERSTITIAL RADIOTHERAPY, "THE DEVENTER SYSTEM"

APPLICATOREN VOOR INSTERSTITIELE RADIOTHERAPIE, "HET DEVENTER SYSTEEM"

(met een samenvatting in het Nederlands)

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IMAGINATION IS THE KEY
FOR CREATIVE AND TECHNICAL ADVANCEMENTS

(W. Disney)

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CHAPTER 1

GENERAL INTRODUCTION AND AIM OF THE STUDY

1.1 Introduction

The history of brachytherapy begins in 1896 in Paris, with the observation of Becquerel of the darkening of a photographic plate in contact with uranium crystals. In 1898 Marie and Pierre Curie succeeded in the isolation of this new radioactive substance, which they called radium. In 1903 Pierre Curie suggested to Dr. Danlos the use of radium powder in glass tubes, to be inserted into a tumour. The first radium implant was reported by Abbe in 1905 in the treatment of cancer [19]. In 1909 the first textbook concerning radium therapy was published by Wickham and Degrais [28].

In the beginning radium was used for superficial and intracavitary lesions, but later on also for interstitial implantation. The medical use of radium increased all over the world, but it was in France where "curietherapy" would have its most important development. As in external radiotherapy, treatment techniques and times were established from emperical observations. Although in brachytherapy the dose distribution around and between the sources never can be homogeneous, it became apparent that the arrangement of the sources can be optimized, resulting in a homogene dose distribution at a certain distance from the sources.

Because of the poor beam characteristics of the orthovoltage machines used in the past, it was very hard to deliver a sufficient radiation dose to deep seated tumours without causing serious skin damage. Brachytherapy had the advantage of not traversing the skin and so the dose to a certain tumour area was not limited by skin tolerance and other intervening tissues. Thus the dose applied to a tumour area could be much higher than with external beams. All accessible sites, especially gynaecological and head and neck, have been treated with interstitial, intracavitary or mould applications. The early practice of brachytherapy showed the possibilities of success, as well as the complications. It became evident that tumours had to be accessible and of moderate size to be eligible for this approach. For larger tumours and tumours metastasizing in an early stage brachytherapy offered no benefits. Since the late 1950's, megavoltage equipment became available to treat deep seated tumours more effectively. However, it soon became apparent that external beam irradiation could not compete with brachytherapy for tumours of the oral cavity and of the uterine cervix.
A decline in the use of brachytherapy was caused by the growing appreciation of the necessity for radiation protection [16]. The radiation exposure of medical staff using radium, as well as the dangers in case of leakage from a radium capsule or needle, were more and more considered to be serious disadvantages of brachytherapy. Fortunately, the development of nuclear science in the sixties and seventies led to the introduction of artificial radioactive elements, which offered special advantages over radium, such as their gamma ray energy, source flexibility, source size, half life and decay products.

These advantages started a new era of brachytherapy and resulted in:

* a better protection of radiological workers by using afterloading techniques
* less shielding by using isotopes of lower energy
* less danger of contamination as no radioactive gas is produced in the decay of the isotopes

* adapatation to more complicated anatomical situations by using flexible sources
* no dose adjustment due to decay of the isotope because of a comparative long half-life compared with the treatment time.

In current brachytherapy practice the use of radium is almost completely replaced by the use of artificially produced radionuclides such as Caesium-137, Iridium-192 and Iodine-125.
Especially the French school has developed new tools to reduce radiation to staff, together with an appropiate system of source arrangement. Automatic devices with remote control to deliver controlled radiation exposure, both for low and high activity sources finally offer full radiation protection. Brachytherapy continues to be an important modality in the management of malignant diseases, either alone or in combination with external beam irradiation.

1.2 Physical considerations

1.2.1 Physical parameters of brachytherapy sources

In table 1.1 some of the relevant parameters are listed for those radionuclides which have been and currently are being used in brachytherapy. In general, a lower photon energy is an advantage. So, the energy of Ir-192 relative to that of Ra-226 allows a more effective shielding and at the same time a specific normal tissue protection, because of the reduced penetration of the gamma rays. At still lower energy, such as in I-125 (mean energy 27 KeV), radiation protection to staff is almost assured and a further reduced radiation dose is given to the patient's normal tissues.

Table 1.1 Physical characteristics of radionuclides in brachytherapy

Radionuclide	Half-life		Mean photon energy (MeV)	Half-value layer (mm lead)
Radium-226	1620	years	0.78	8
Caesium-137	30	years	0.66	6.5
Cobalt-60	5.3	years	1.25	11
Iridium-192	74	days	0.35	2.5
Iodine-125	60	days	0.027	0.025
Palladium-103	17	days	0.021	0.008
Radon-222	3.83	days	0.78	8
Gold-198	2.7	days	0.412	2.5

Radium

In the early days brachytherapy was carried out with radium or radon sources. Discrete sources were used containing radium sulfate powder encapsulated in two layers of a metal alloy, usually gold and platinum. The beta-rays of radium were shielded completely and the walls were made strong enough to withstand the increasing pressure of helium gas, resulting from the alpha-emission of radium. Radium desintegrates with a half-life of about 1600 years to form radon. Radium sources were manufactured as needles or tubes in a variety of lengths and activities. Common sizes for tubes were 1 to 2 cm long and 3 to 5 mm thick, containing 10 to 25 mg radium for intracavitary applications, and needles 2 to 6 cm long and 2 to 3 mm thick, to be used interstitially. Due to the long half-life of radium, the dose rate of these sources is considered constant.

Caesium

Caesium sources are available in many sizes and shapes, including tubes for gynaecological applications. They have dimensions and linear activities similar to those of traditional radium they should replace. With a half-life of about 30 years, these sources can be used clinically for at least 10 years without replacement, although the treatment times have to be adjusted about 2% per year to allow for radioactive decay. The gamma-rays from caesium have nearly the same penetrating range as radium gamma-rays in tissue, however, caesium emits monoenergetic gamma-rays while radium emits gamma-rays of a wide energy range.

Iridium

Iridium-192 sources are available as thin flexible wires sheathed in pure platinum, which absorbs the associated beta-rays. The wires are easily cut to any desired length. Nylon ribbons containing iridium seeds are also commonly used, especially in the U.S.A. Both wires and seed ribbons are suitable for afterloading techniques. Iridium has a complicated gamma-ray spectrum with an average energy of 0.38 MeV and so these sources require less shielding for personnel protection. The half-life of 74.2 days is long enough, compared to the average treatment time, to use the sources in temporary implants similar to radium and caesium. The activity varies by only a few percent during an average implant duration and has not to be corrected.

Cobalt

Cobalt-60 sources can be used to replace Ra-226 in intracavitary applications, especially in high dose rate remote afterloading devices such as the Cathetron or HDR-Selectron.

Gold

Seeds, also called grains, consisting of a radioactive isotope of gold (Au-198) are used in brachytherapy as well. Gold has a half-life of 2.7 days and emits a monoenergetic gamma-ray energy of 0.412 MeV. A gold seed is typically 2.5 mm long with an outer

diameter of 0.8 mm.

Iodine

Iodine-125 has gained a wider use for permanent implants in radiotherapy. Its half-life of 60.2 days is convenient for storage and its low photon energy (27.4 KeV) requires hardly any shielding. The I-125 seed consists of a titanium tube containing a silver rod with the iodine damped on it.

New radionuclides such as Palladium -103 may have advantage over I-125 since they have a shorter half life (17 days) than iodine and a similar low energy.

1.2.2 Implantation techniques

In brachytherapy sealed radioactive sources are used to deliver radiation at a short distance. These sources are applied in three ways:

a. external applicators or moulds
b. interstitial implantation
c. intracavitary (or intralumenal) applicators or moulds.

The choice of a technique is dictated primarily by the size and location of the tumour. For example, surface moulds are used to treat small superficial areas such as the ear; intracavitary therapy is used when applicators containing radioactive sources are introduced into body cavities (uterus) or a lumen (oesophagus); interstitial therapy is indicated when the tumour is well localized and accessible. In all these cases, because of the short treatment distance, the geometry of the source distribution is critical.

a. surface moulds

Moulds are prepared conform to the surface to be treated. With the help of a mould, small superficial tumours of the skin or tumours in body cavities can be treated. The sources are positioned such, that the distance between the plane of the sources to the tumour surface is 0.5 to 1.0 cm. The dosimetry and source distribution rules are similar for moulds and for interstitial sources.

b. interstitial therapy

In interstitial therapy the radioactive sources are placed into the tissue, either directly (preloaded implantation technique, eg. radium needles), or in a second phase after the initial insertion of unloaded carriers, stainless steel needles or plastic tubes (afterloading technique).
Direct implants have been performed since the beginning of this century, using radium and later on caesium needles. All tumour sites were implanted, ranging from head and neck, breast to bladder. A major disadvantage of this technique of course is the exposure of staff to radiation. With afterloading techniques this can be reduced to a great extent.

So, single pin and hairpin techniques were developed, to be implanted before the active sources are introduced. The sources are not loaded until the radiotherapist is satisfied with the geometry of the implant, as checked with fluoroscopy or radiographs. These techniques are specially used in the treatment of head and neck tumours and tumours in the perineal area (vulva, vagina, anus).

To ensure a perfect geometry of the sources, templates can be used with fixed positions for the needles. For this purpose either stainless steel needles can be placed as source carriers, or the needles can be replaced by plastic tubes. The source positioning is checked by introducing dummy sources and making localisation radiographs or by using direct fluoroscopy. At deep seated tumour sites (eg. bladder, base of tongue) plastic tubes are introduced in loops to adapt to the curved anatomy.

c. intracavitary therapy

Intracavitary therapy is widely used for cancers of the uterine cervix, uterine body, and vagina, either alone or in combination with external irradiation. The obvious advantage of intracavitary irradiation is the higher dose delivered to the tumour than to the adjacent tissues, thus improving the therapeutic ratio.
Intralumenal therapy (oesophagus, bronchus, bile duct) regained the interest of radiation oncologists with the introduction of high dose rate afterloading machines such as the HDR-microSelectron. Because of its simplicity, this technique is specially suitable in palliative situations. Furthermore, with a HDR stepping source the dose distribution can be optimized by varying the treatment time per dwell position.

d. permanent implantation technique

In contrast to temporary implantation techniques as described above, permanent implants also can be utilised, eg. in the management of prostate cancer, tumours of the lung and some lesions of the oral cavity. Advantages of permanent implants over temporary or removable implants include:

* it is a simple procedure
* more comfortable to the patient
* well tolerated even by the elderly patient
* the mobility of the implanted site is not impaired
* it reduces complications such as haemorrhage
* it can be performed in poorly accessible tumour sites such as prostate, lung and brain.

New techniques ensure a better distribution of the seeds to obtain a more homogeneous dose distribution, including pre-operative planning.

1.2.3 Dose calculation systems

With brachytherapy a high radiation dose can be delivered locally to the tumour with

rapid fall off in dose to the surrounding normal tissues [2]. An increase in dose of radiation will increase the chance to control a malignant tumour.

On the other hand, when the dose over the target volume is not homogeneous, tumour areas will receive a higher or lower dose than intended, with consequently a greater chance of either severe damage to normal tissues or of tumour recurrence. Because of this, systems of source arrangements have been developed that guarantee a certain pattern of dose distribution. Such a system avoids large differences in dose within the volume to be treated.
The problem of reference dose was solved by specifying a give dose to one or more points in a known relation to the radioactive sources, arranged according to a known pattern. Brachytherapy treatments were mostly given at a continuous dose rate within one till ten days. An important development is the use of computer methods for the calculation of the dose distribution between and around the sources.
Numerous systems of dosimetric planning have been devised over the past 50 years [7,15,18,23]. The objectives of treatment planning are [5]:

* rules that ensure adequate coverage of the target volume
* a method to determine the actual distribution of the sources
* a calculation method to evaluate the dose at one or more reference points; in some systems this may amount to the determination of a complete isodose distribution.

Many of these systems were designed before computers became available for routine treatment planning. Extensive tables and elaborate rules of source distribution were devised to facilitate the process of manual treatment planning (the Patterson-Parker system and the Quimby system were the most widely used). The use of computers gave the radiotherapist the possibility to deviate from the established systems, although the basic rules for implantation remained the same.

The *Patterson-Parker system* [18] or Manchester system was developed to deliver a uniform dose to a plane or volume. The system specified rules for the geometrical arrangement of sources, and for the linear activity required in order to cover a planned target volume with a sufficiently homogeneous dose and provided dosage tables for interstitial or mould irradiation treatments. When the rules were applied correctly, the dose rate at a certain distance from the radioactive plane of the implant could be predicted. The system is still used for single- and double-plane implants in many centres. As nowadays calculation of dose distributions is computerized, the rules will not be discussed in detail here.

The *Quimby system* [23] was characterized by a uniform distribution of sources of equal linear activity. Consequently, this arrangement of sources resulted in a non-uniform dose distribution, higher in the central region of treatment. This system was particularly used in American centres.

The Paris system

In 1966 Pierquin and Dutreix defined a system of manual dosimetry, the so called Paris system, in which target volume, irradiation volume and volume of overdosage were defined [8,9,14,15,20]. In 1969 Wambersie and Chassange adjusted the system [21]. In this Paris system iridium sources are used of equal linear activity, parallel placed at equal distances and arranged in such a way, that their centres are in the same plane, perpendicular to the direction of the lines. This plane, called the central plane, is the midplane of the application. If the volume to be treated is larger, it will be necessary to implant the sources in more than one plane. Again, equidistance of the radioactive lines is required. This means, that their intersections with the central plane are arranged according to the apices of equilateral triangles or squares. As a result the spacing between the lines is equal to 0.87 times the spacing E between the lines in case of patterns in triangles, and equal to the latter in case of patterns in squares. This regular distribution of the wires leads to a slight overdose at the centre of the target volume.

Endocurietherapy leads to a heterogeneous distribution of dose. The dose is very high close to the radioactive sources and passes through minima between them. Nevertheless, judicious arrangement of the radioactive sources, such as recommended in the Paris system, enables a relatively constant dose to be obtained in the zones of the minima which can serve as a reference for evaluating the dose delivered to the tumour [8,9,14,15]. The dose-rate at a point in the middle of a group of sources is called the basal dose-rate (= BD). This basal dose-rate is always calculated from the position of the sources in the central plane and is the minimum dose-rate between a pair or group of sources. These points, at which the dose-rate is minimal, are geometrically defined, being at equal distances from the nearest source intersections in the central plane. The values of the isodose curves are expressed as a percentage of the basal dose-rate. The reference dose-rate is derived from the basal dose-rate, too. This reference dose-rate is 85% of the basal dose-rate and the dose-rate used for calculating the total treatment time of the implant (fig. 1.1). The reference dose has been obtained by both clinical experience and theoretical calculations.
Within the limits of source geometry used, this system leads to an acceptable compromise between a too steep dose gradient in passing from the margin of the treatment envelope towards its interior and a too great ripple of the contour of the treatment envelope.

The lengths of the sources and the distance between them will be chosen according to some rules in which the dimensions of the target volume are the decisive factor. Just around the sources the dose will be highest. When considered in three dimensions, it is an amalgamation of several adjacent cigar-shaped isodose envelopes ("manchons"). The minimum dimensions of this envelope should correspond as accurately as possible with those of the target volume, which it must enclose.

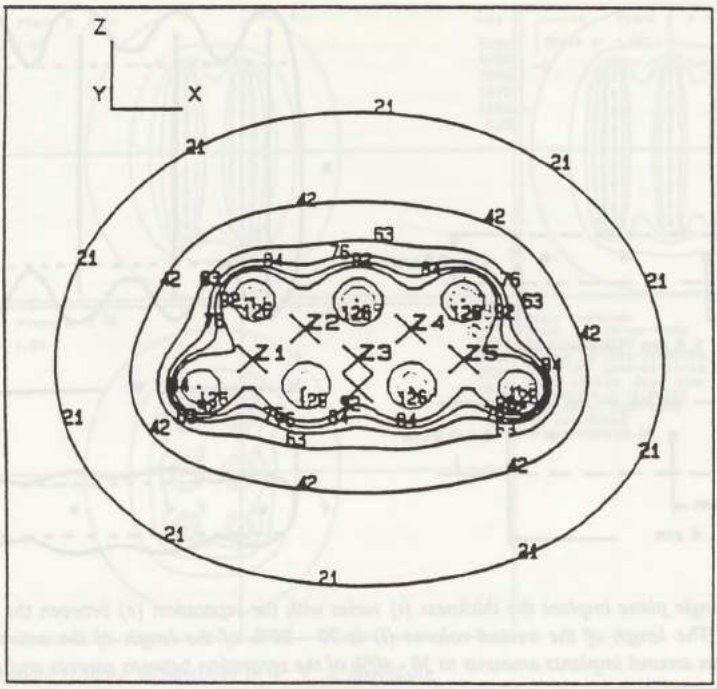

Fig 1.1 Seven iridium sources in a triangular configuration. The reference dose rate is 85% of the basal dose-rate, indicated as the 92 cGy/h isodose.

The relation between source distribution and target volume depends on the active length of the sources and the separation between the sources (fig. 1.2). The length of the treatment volume is defined as the smallest distance between the invaginations of the treatment isodose at either end of this volume, between the active lines and parallel to them. This is measured in the same plane as the lines, if there is only one plane or midway between the planes for more than one plane. Since the ends are not crossed, the active sources should be 20 to 30% longer than the target volume at both ends. The width of the treatment volume is simple the distance between the treatment isodose line perpendicular to the direction of the sources. The thickness of the treatment volume is defined as the smallest distance between two parallel planes which are tangents to those isodose invaginations, which give the target volume its least thickness. In a single plane implant, the thickness of the treatment volume depends on the separation between the sources. As the separation between the sources increases, there is an increasing dose gradient between the minimum dose-rate between the sources (BD) and that achieved adjacent to them. If the high dose volume surrounding each source is too great, there is a risk of necrosis. As a rule, the distance between two sources should not exceed 2 cm.

Dosimetry according to the Paris system has many advantages. The use of equal linear activity, equal distance between the sources and the fact that no crossing needles are

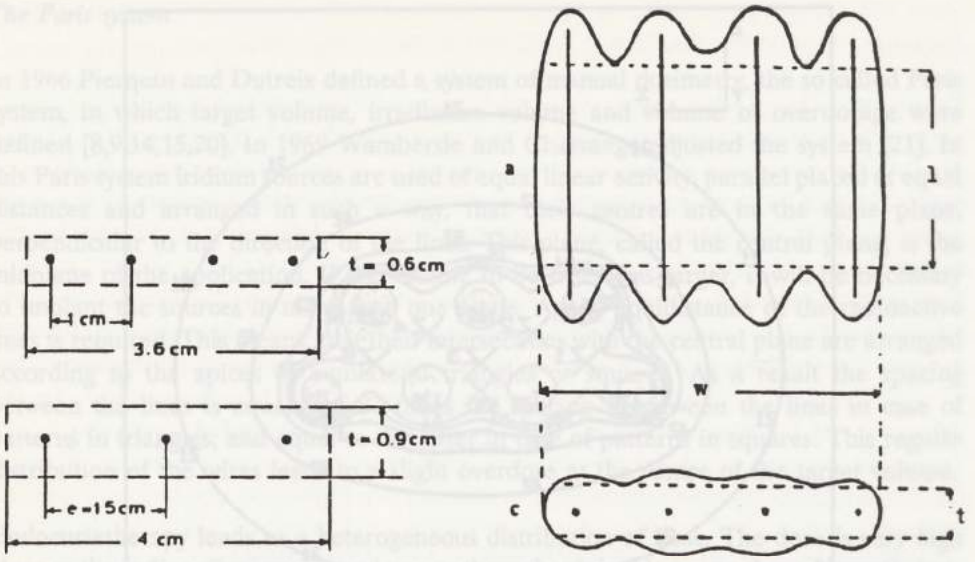

Fig 1.2 In a single plane implant the thickness (t) varies with the separation (e) between the sources, and t= 0.6 e. The length of the treated volume (l) is 70 - 80% of the length of the active sources. The treatment margin around implants amounts to 30 - 40% of the separation between sources and determines the width of the implant (w).

used, make the application itself relatively easy. The relationship between the geometry of the implant and the dimensions of the target volume can easily be determined. The dose can be quickly controlled with a planning computer, even in complicated implantations.

1.2.4 The natural volume-dose histogram

The agreement between planned and realised source configuration is difficult to assess objectively by looking at localisation films, nor can it be assessed completely by comparing the two dimensional dose calculations from the pre-planned and realised implantation, see fig. 1.3 and 1.4. A better method to assess the quality of an implant is by a three dimensional volume-dose histogram. However, in a standard volume-dose histogram, the much higher volume associated with low doses tends to obscure any interesting variations occuring at higher doses. In figures 1.5 and 1.6 the standard volume-dose histograms of figures 1.3 and 1.4 are shown. Although there are major differences between the planned and realised implantation, the volume-dose histograms are quite similar.

A volume-dose histogram which suppresses the influence of the inverse square law effects was published by Anderson [1] in 1986 and is called the "Natural Volume-Dose Histogram" (NVDH).

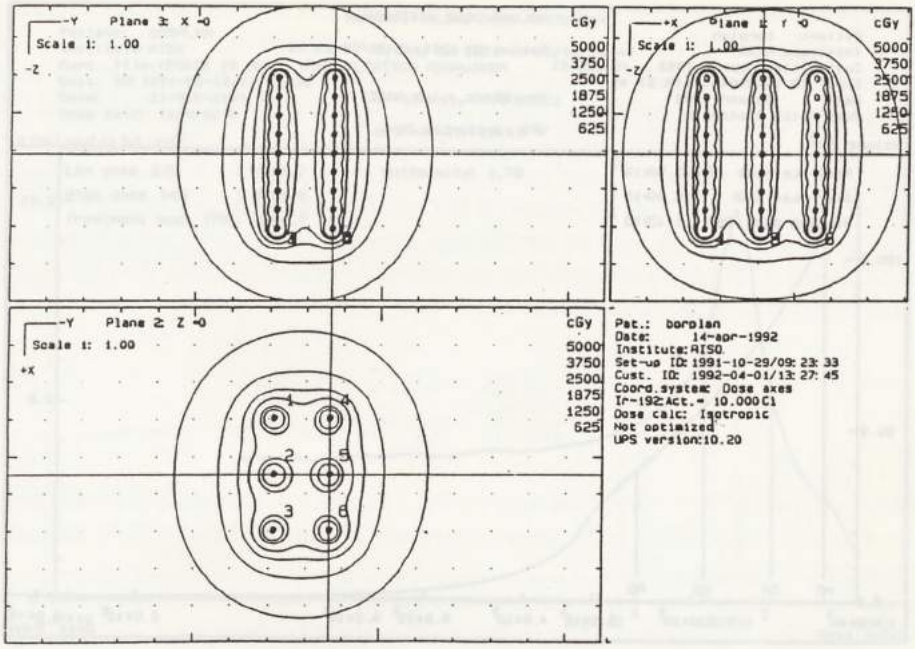

Fig 1.3 Preplanned isodose distribution in X, Y, Z directions.

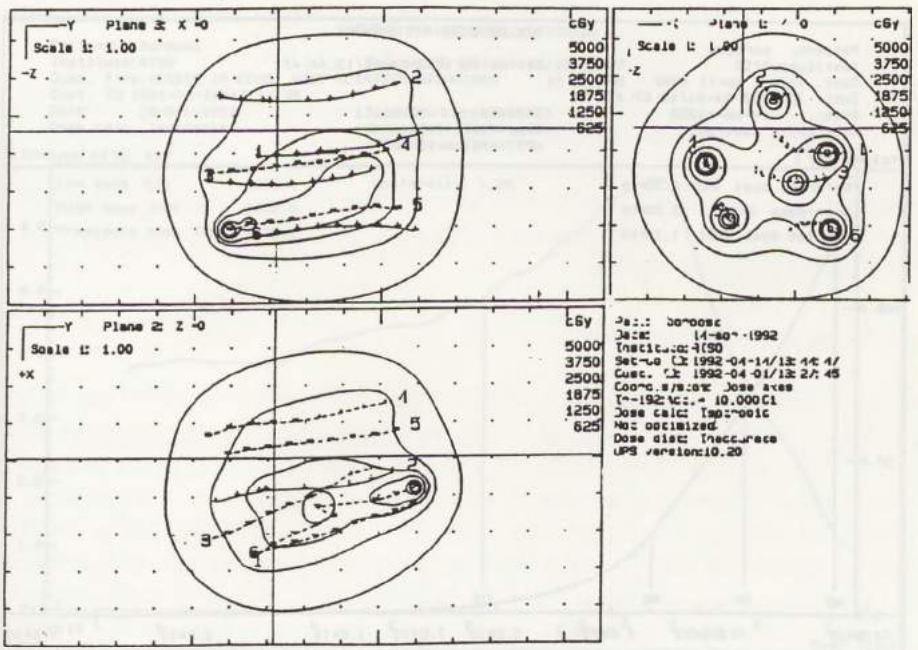

Fig 1.4 Realized implant with a loop technique shows an inhomogeneous dose distribution compared with preplanned distribution in fig 1.3.

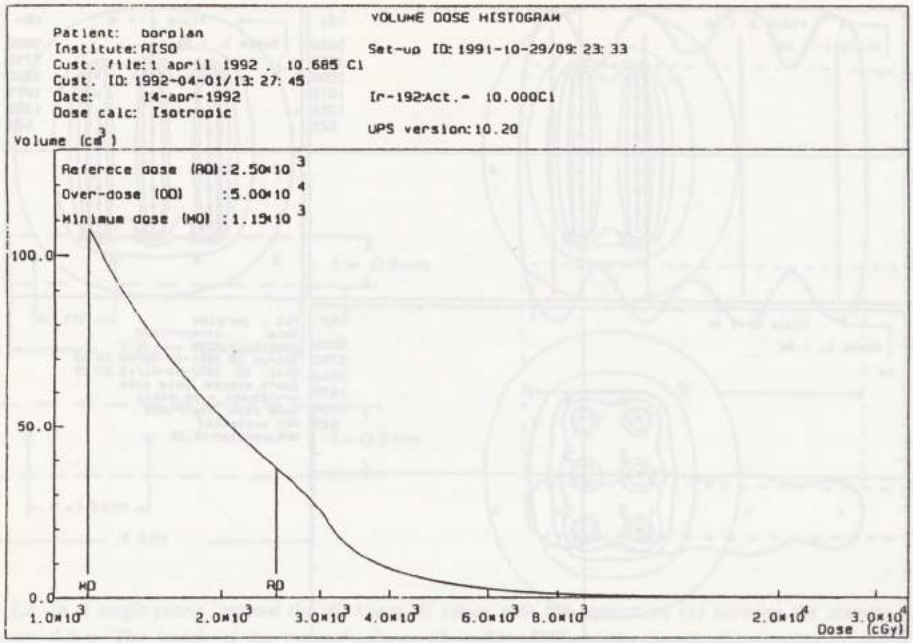

Fig 1.5 Standard volume-dose histogram of preplanned implant in fig 1.3.

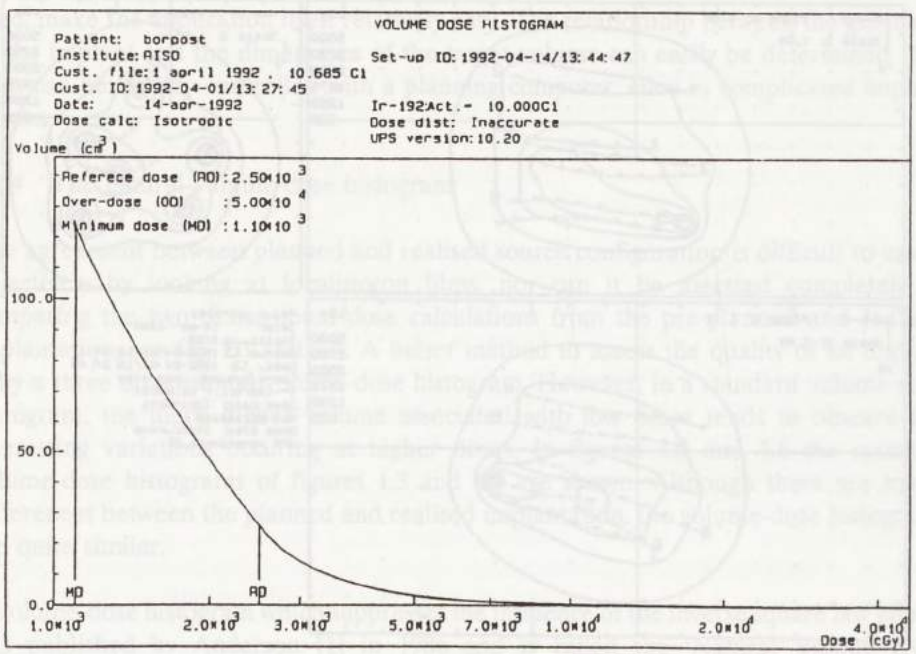

Fig 1.6 Standard volume-dose histogram of realized implant in fig 1.4.

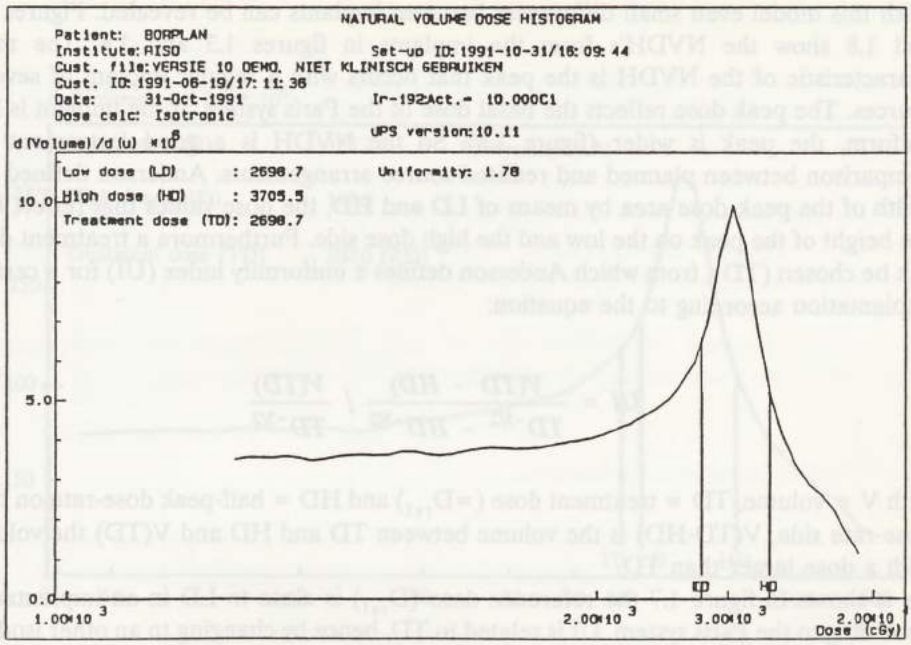

Fig 1.7 Natural volume-dose histogram of preplanned implant in fig 1.3.

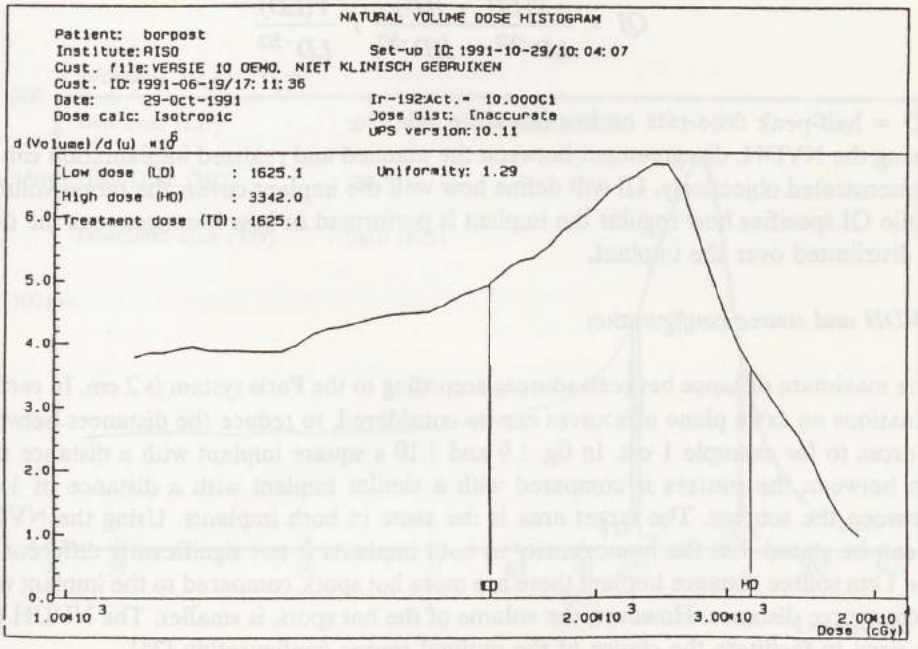

Fig 1.8 Natural volume-dose histogram of realized implant in fig 1.4.

With this model even small differences between implants can be revealed. Figures 1.7 and 1.8 show the NVDH's from the implants in figures 1.3 and 1.4. The main characteristic of the NVDH is the peak that occurs with a regular implant of several sources. The peak dose reflects the basal dose of the Paris system. If the implant is less uniform, the peak is wider (figure 1.8). So the NVDH is a good instrument for comparison between planned and realised source arrangements. Anderson defined the width of the peak dose area by means of LD and HD, the dose values that reflect half the height of the peak on the low and the high dose side. Furthermore a treatment dose can be chosen (TD), from which Anderson defines a uniformity index (UI) for a certain implantation according to the equation:

$$UI = \frac{V(TD - HD)}{TD^{-3/2} - HD^{-3/2}} \Big/ \frac{V(TD)}{TD^{-3/2}}$$

with V = volume, TD = treatment dose (=D_{ref}) and HD = half-peak dose-rate on high dose-rate side, V(TD-HD) is the volume between TD and HD and V(TD) the volume with a dose larger than TD.
As is shown in figure 1.7 the reference dose (D_{ref}) is close to LD in an implantation according to the Paris system. UI is related to TD, hence by changing to an other isodose line for dose calculation, also UI changes. Since this is unfavourable in a comparison of implantations, a quality index QI is defined:

$$QI = \frac{V(LD - HD)}{LD^{-3/2} - HD^{-3/2}} \Big/ \frac{V(LD)}{LD^{-3/2}}$$

LD = half-peak dose-rate on low dose-rate side.
Using the NVDH, disagreement between the planned and realized implantation can be demonstrated objectively. UI will define how well the implant covers the target volume, while QI specifies how regular the implant is performed or how homogeneous the dose is distributed over the implant.

NVDH and source configuration

The maximum distance between sources according to the Paris system is 2 cm. In certain situations an extra plane of sources can be considered, to reduce the distances between sources to for example 1 cm. In fig. 1.9 and 1.10 a square implant with a distance of 2 cm between the sources is compared with a similar implant with a distance of 1 cm between the sources. The target area is the same in both implants. Using the NVDH it can be stated that the homogeneity in both implants is not significantly different. In the 1 cm source distance implant there are more hot spots, compared to the implant with 2 cm source distance. However, the volume of the hot spots, is smaller. The NVDH can be used to facilitate the choice of the optimal source configuration [24].

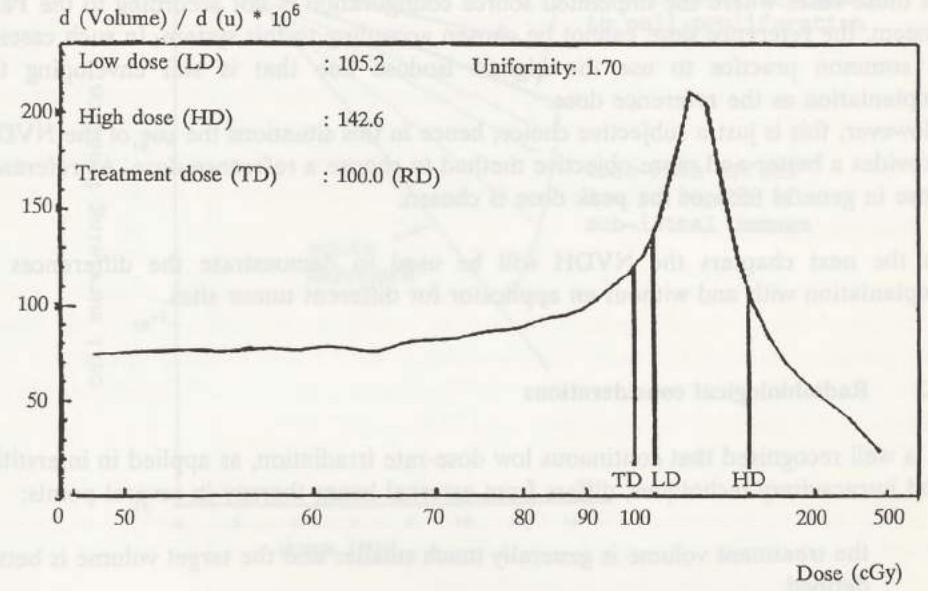

Fig 1.9 Natural volume-dose histogram of an implant, 6 sources of 7 cm with a square configuration and a mutual source distance of 2 cm.

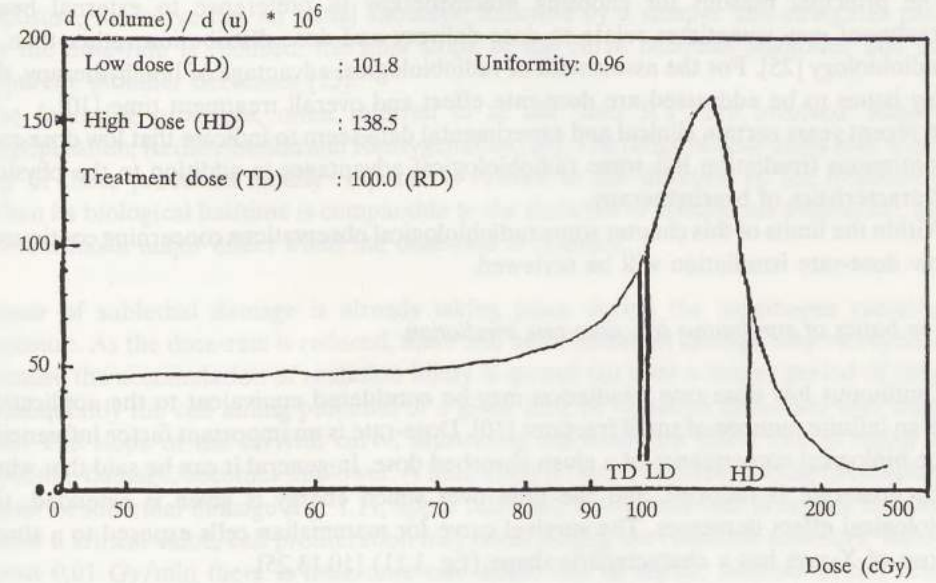

Fig 1.10 Natural volume-dose histogram of an implant, 15 sources of 7 cm with a square configuration an a mutual source distance of 1 cm.

NVDH and the choice of the reference dose

In those cases where the implanted source configuration is not according to the Paris system, the reference dose cannot be chosen according to this system. In such cases it is common practice to use the highest isodose line that is still enveloping the implantation as the reference dose.
However, this is just a subjective choice, hence in this situations the use of the NVDH provides a better and more objective method to choose a reference dose. As reference dose in general 85% of the peak dose is chosen.

In the next chapters the NVDH will be used to demonstrate the differences in implantation with and without an applicator for different tumor sites.

1.3 Radiobiological considerations

It is well recognised that continuous low dose-rate irradiation, as applied in interstitial and intracavitary techniques, differs from external beam therapy in several points:

* the treatment volume is generally much smaller and the target volume is better defined
* in view of the rapid dose fall off outside the implanted volume, higher doses can be tolerated
* the tumour dose is administered in a shorter time period.

The principal reasons for choosing brachytherapy in preference to external beam treatment may sometimes relate to dose delivery and dose distribution rather than to radiobiology [25]. For the assessment of radiobiological advantage of brachytherapy, the key issues to be addressed are dose-rate effect and overall treatment time [10].
In recent years certain clinical and experimental data seem to indicate that low dose-rate continuous irradiation has some radiobiological advantages in addition to the physical characteristics of brachytherapy.
Within the limits of this chapter some radiobiological observations concerning continuous low dose-rate irradiation will be reviewed.

The basics of continuous low dose-rate irradiation

Continuous low dose-rate irradiation may be considered equivalent to the application of an infinite number of small fractions [10]. Dose-rate is an important factor influencing the biological consequence of a given absorbed dose. In general it can be said that when the dose-rate is reduced, and the time over which energy is given is extended, the biological effect decreases. The survival curve for mammalian cells exposed to a single dose of X-rays has a characteristic shape (fig. 1.11) [10,13,25].

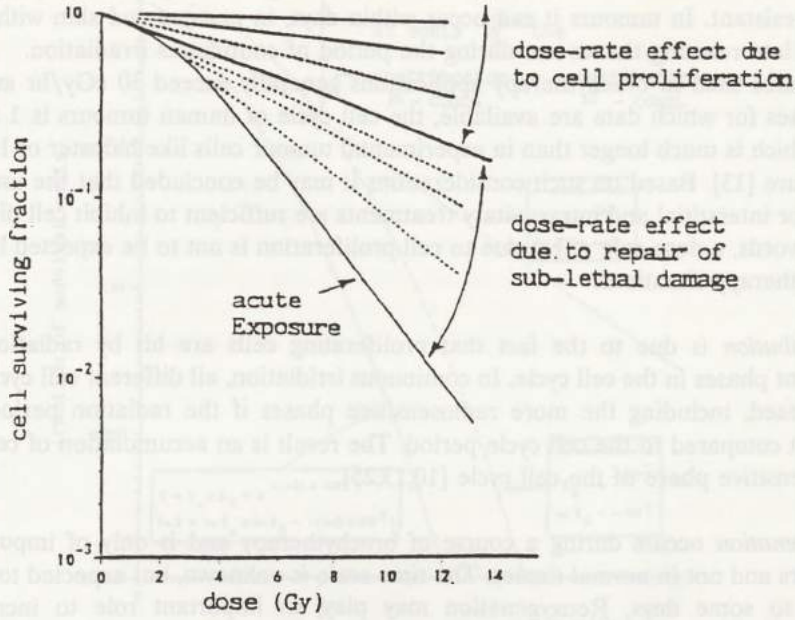

Fig 1.11 Relationship between dose-rate and cell surviving fraction (from Hall, ref. 13).

When surviving fraction is plotted against dose on a semilogarithmic scale after acute exposure, the curve has an initial shoulder, followed by a steeper and straighter part. As the dose-rate is reduced, the final slope of the curve becomes shallower and the apparent shoulder decreases [13].
The following processes, often referred to as the "four R's", are involved: Repair, Repopulation, Redistribution and Reoxygenation [29]. The range of dose-rates over which any of these processes modify response is related to the duration of the irradiation. When its biological halftime is comparable to the duration of continuous irradiation, any process has a major effect when the dose-rate is changed.

Repair of sublethal damage is already taking place during the continuous radiation exposure. As the dose-rate is reduced, more and more sublethal damage may be repaired because the accumulation of radiation injury is spread out over a longer period of time; consequently the cell killing potential of a given dose of radiation decreases with dose-rate. The slope of the survival curve, illustrating the dose-rate effect due to repair of sublethal damage, becomes shallower. A final slope is reached corresponding to complete repair of sublethal damage (fig. 1.11, upper full line). If the dose-rate is further reduced below a critical value, cell proliferation may occur during the radiation exposure. Below about 0,01 Gy/min there is little dose-rate effect due to repair, because at this level essentially all sublethal damage is repaired during the exposure and the residual cell killing effect is due to non-repairable injury.

Repopulation occurs as a result of cell division, making the cell population progressively more resistant. In tumours it can occur within days, in mucosa and skin within weeks and in late reacting tissues not during the period of continuous irradiation.
Dose-rates used in brachytherapy applications generally exceed 30 cGy/hr and in the few cases for which data are available, the cell cycle of human tumours is 1 to 5 days [25], which is much longer than in experimental tumour cells like hamster or Hela cells in culture [13]. Based on such considerations it may be concluded that the usual dose-rates for interstitial and intracavitary treatments are sufficient to inhibit cell division. In other words, a dose-rate effect due to cell proliferation is not to be expected in clinical brachytherapy situations.

Redistribution is due to the fact that proliferating cells are hit by radiation during different phases in the cell cycle. In continuous irridiation, all different cell cycle phases are passed, including the more radiosensitive phases if the radiation period is long enough compared to the cell cycle period. The result is an accumulation of cells in the radiosensitive phase of the cell cycle [10,13,25].

Reoxygenation occurs during a course of brachytherapy and is only of importance in tumours and not in normal tissues. The time scale is unknown, but expected to be a few hours to some days. Reoxygenation may play an important role to increase the therapeutic ratio in low dose-rate irradiation.

In clinical practice of brachytherapy the question arises how to adjust the total dose according to dose-rate or overall treatment time. Pierquin [22] dit not find any effect on local control or necrosis rate with a dose of 70 Gy delivered with a dose-rate of 0.5 cGy to 1.67 cGy per minute in interstitial implants. He concluded that dose adjustment according to overall treatment time was unnecessary and might result in underdosage of the tumour. This conclusion is supported by Awwad et al. [3] and by Fu et al. [12]. However, Mazeron et al. [17] recently observed an increased necrosis rate according to dose-rate in T 1 en T 2 tumours of the mobile tongue. It is obvious that for a given dose-rate the volume and total dose in relation to tumour control and normal tissue tolerance should be considered.

α/β model

The introduction of remote afterloading machines has allowed sources of increased strength to be utilized. Dose-rates can be increased and treatment times reduced. The concept of low, medium and high dose-rate brachytherapy has appeared. The ICRU Report no. 38 (1985) defines high dose-rate (HDR) as exceeding 0.2 Gy per minute, medium dose-rate (MDR) between 2 and 12 Gy per hour and low dose-rate (LDR) between 0.4 and 2 Gy per hour.
Since the results in the treatment of cervix cancer with HDR have proven to match those for low dose-rate treatments, the application of high dose-rate brachytherapy is increasing [27]. The application of HDR brachytherapy for palliative situations is also gaining acceptance and is likely to increase, especially the intraluminal treatments of cancer of

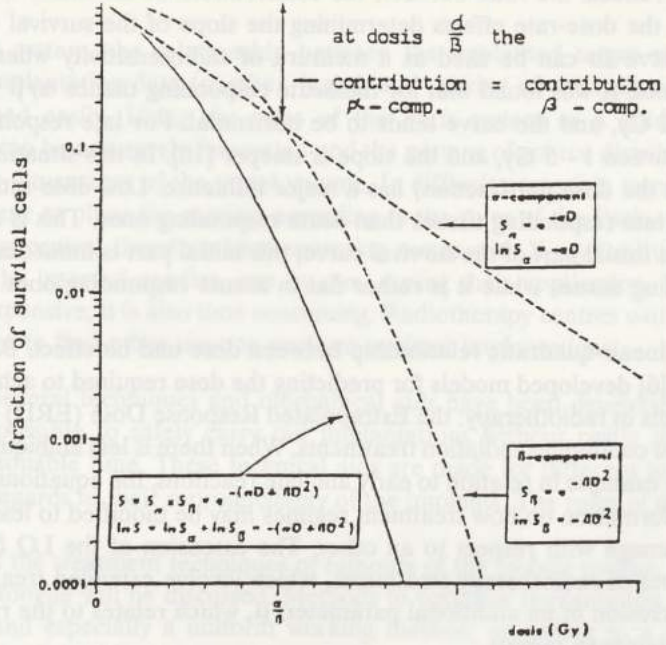

Fig 1.12 Linear quadratic model. The biological effect (E) is the sum of two components: $E = \alpha D + \beta D^2$. After a dose D the function of surviving cells is $S = N/N_0 = e^{-(\alpha D + \beta D2)}$ and $LnS = -(\alpha D + \beta D^2)$. At dose $D = \alpha/\beta$, there is a similar contribution of the α and β components (from Reinhold HC (ed), Tumorbiologie en radiobiologie voor klinici, Integraal Kanker Centrum Rotterdam, 133-135, 1984).

the oesophagus and bronchus. Although high dose-rate techniques have been used for over two decades and have logistic and safety advantages, the therapeutical effect has still to be proven and prospective studies are needed in this field.

Some biological parameters that underly dose-rate and fractionation effects are [26]:

* the acute single-dose response curve
* the half-time for repair of sublethal damage
* the fading time for repairable damage, which is the total time required for complete repair of sublethal damage.

The fading time of repairable damage, introduced by Fowler [11], describes the effective repair time of a tissue and depends on the absolute number of lesions to be repaired. The shape of the acute single-dose response curve for the target cells of a tissue can be fairly described by the linear quadratic (LQ model) for the clinical dose range [25]. The survival curve as described by the LQ model (fig. 1.12) is a combination of two factors, the α and the β component. The α component represents lethal cell damage due to a single hit by ionizing radiation, while the ß component represents lethal cell damage caused by multiple hits. At lower doses the α component is predominant and at higher doses the β component.

The ratio α/β reflects the ratio between the contributions of the linear and quadratic components of the dose-rate effects determining the slope of the survival curve. The slope of the curve so can be used as a measure of radiosensitivity when comparing different cell lines. It was found that for the acute responding tissues α/β is high, with values of 6 - 12 Gy, and the curve tends to be horizontal. For late responding tissues, α/β is low, between 1 - 5 Gy, and the slope is steeper [10]. In this situation, the dose-rate (as well as the dose per fraction) has a major influence. Low dose-rate irradiation better protects late responding tissues than acute responding ones. This is explained by the shape of the initial part of the survival curve; this initial part is immediately bending in late responding tissues while it is rather flat in accute responding ones.

Based on this lineair-quadratic relationship between dose and bioeffect, Barendsen [4] and later Dale [6] developed models for predicting the dose required to achieve specific clinical endpoints in radiotherapy: the Extrapolated Response Dose (ERD) equation for fractionated and continuous radiation treatments. When there is less ambiquity regarding α/β values, for example in relation to early and late reactions, the equations are capable of providing information on how treatment regimes may be modified to lessen one type of radiation damage with respect to an other. The extension of the LQ formulism to cover those types of radiotherapy treatments, which involve extended treatment times, requires the inclusion of an additional parameter, μ, which relates to the rate of repair of sublethally damaged targets.

The ERD-equations for fractionated (equation 1) and continuous radiation treatments (equation 2) are respectively [4,6,25]:

$$ERD = Nd\left[1+\frac{d}{\alpha/\beta}\right] \qquad (1)$$

in which N = Number of fractions
d = dose per fraction (Gy)
α/β = the tissue specific parameter (Gy)

$$ERD = RT\left[1+\frac{2R[1-1/(\mu T)]}{\mu(\alpha/\beta)}\right] \qquad (2)$$

in which R = dose-rate (Gy/hr)
T = implant time (h) : T> 10 hr
μ = tissue specific parameter (hr^{-1}) related to the rate of repair of sublethal radiation damage.

Within certain limits this model may be used as a guideline for predicting the reactions of different tissues on radiation treatments (see Chapter 2.6).

1.4. Aim of the study

In the Paris system, the relationship between the implanted target volume and the geometric implantation data (number, length and spacing of the radioactive lines) can be determined easily. Using the rules of the Paris system as a guideline the dose distribution can be accurately forecasted and the pattern of source distribution adjusted, based on the dimensions of the target volume. In difficult accessible tumour sites it may be troublesome to place the carriers according to the rules of the Paris system. Modern brachytherapy centres therefore have operating rooms with X-ray facilities to check the position of the inserted needles, one by one, during their application. This procedure is not only expensive, it is also time consuming. Radiotherapy centres without such X-ray facilities have to find other ways to perform optimal implantations.

Since 1984 several techniques and mechanical aids have been developed in Deventer, to make it possible to safely carry out implantations without costly investments and within a reasonable time. These technical aids are made for different tumour sites and tested with regards to their reproducibility of the implants. The rules of the Paris system are applied.
In Chapter 2 the treatment techniques of tumours of the mobile tongue, floor of mouth and base of tongue will be discussed. Methods to optimize implantation techniques are introduced and especially a uniform working method, according to a predicted dose distribution plan, is shown.
The same scheme is followed in the next chapters, where the implantation techniques are discussed to aim at a uniformity of implantation techniques in breast conserving therapy (Chapter 3), bladder carcinoma (Chapter 4) and tumours in the distal part of the vagina and the vulva (Chapter 5). All procedures are designed in such a way that the burden of the treatment for the patient is restricted to a minimum.

In this thesis the different implantation techniques and the technical aids are described. Results of retrospective studies from our own institute are discussed and compared with results from the literature and current implantation techniques with applicators. The NVDH is used to demonstrate differences in homogeneity with and without an applicator. Especially complications have our interest. We do realize that the follow-up time of most patients is too short to give final conclusions. However, the emphasis of this study is on implantation techniques more than on clinical results.

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CHAPTER 2

ORAL CAVITY TUMOURS

2.1 Introduction and review of the literature

The majority of mucosal carcinomas of the head and neck originate in the oral cavity and oropharynx. The incidence in Europe and the USA is 1.5 - 3% of all malignant tumours [1]. Carcinoma of the oral tongue is one of the most frequent tumours of the oral cavity, second only to cancer of the lip and followed by carcinoma of the floor of the mouth. Oral cavity tumours occur most frequently in men aged 60 years and older, and are often associated with poor oral hygiene and abuse of alcohol and tobacco. In most cases a squamous cell carcinoma is diagnosed and the lesion may vary in degree of differentiation, ranging from in situ to verrucous and poorly differentiated carcinoma. The tumours have a high frequency of neck node metastases (up to 70%), depending on the initial stage of the disease [2].

Tumours of the mobile part of the tongue, floor of the mouth and base of the tongue

Both surgery and radiotherapy have shown to be equally effective in local control and long term disease-free survival in patients with carcinoma of the mobile tongue. Radiation therapy has the obvious advantage of preserving anatomy and function. A three-years disease free survival with surgery alone is reported in 60 - 70% of cases [17,20,31]. This is comparable with the results reported for megavoltage beam irradiation alone [4,6,12,21]. Ildstad et al. [16] reviewed the records of 122 patients with carcinoma of the mobile tongue with a minimum follow-up of 5 years after therapy. Patients were treated with surgery or radiation therapy. Radiation therapy was given as a combination of fractionated external therapy and an interstitial radium implant. No significant difference in survival rates was noted between the two groups.
In a retrospective study Owen et al. [23] described the results of radium implantation in 82 patients with cancer of the mobile part of the tongue and floor of the mouth. The local control rates varied from 94% for T_1 tumours to 55% for T_3 tumours. Similar results were described by various other authors [3,9,11,14,18,19,24,25]. For tumours of the base of the tongue a combination of external radiotherapy and interstitial radiotherapy is used in many centres [5,13,15,26,30] and discussed by others [8,10].

In terms of complications it is generally mentioned that acute mucosal reactions are observed in almost all implanted patients and occur within 7 - 14 days after removal of the sources. Mucositis responded to conservative management within 3 - 4 weeks. Patients who developed necrosis initially had ulcerating lesions [23]. The incidence of such complications as soft tissue necrosis and mandibular osteoradionecrosis can be reduced to a minimum by ensuring meticulous oral hygiene. Surgical manipulation should be avoided not only prior to, but also after radiation therapy. In literature the data for necrosis varies from 3.4% [22] up to 19% [27]. Delclos [7] noted that 5% of the patients with soft tissue necrosis and 35% of those with bone necrosis require surgery. Similar data are given for necrosis after treatment of tumours of the base of tongue [15,26,30].

2.2 Treatment results of tumours of the mobile tongue, a retrospective study

Between January 1977 and August 1984 14 patients with histologically confirmed squamous cell carcinoma of the mobile part of the tongue were treated at the Radiotherapy Department in Deventer. The breakdown in tumour stage is shown in table 2.1. Combined external irradiation and radium implantation was given in 10 patients. All patients had elective irradiation to the neck nodes using a Cobalt-60 source, at a dose of 40 - 50 Gy in 4 - 5 weeks, with a mean dose of 44 Gy and a mean overall time of 33 days. Radium implant to boost the primary site was given to a minimum tumour dose of 25 Gy, the average dose-rate ranged from 50 to 96 cGy per hour. The combination of external irradiation and brachytherapy resulted in a total average dose of 90 Gy. Four patients were treated by brachytherapy only (patients nr. 1, 4, 9 and 11) with a minimum tumour dose of 60 Gy. For dose calculation of brachytherapy the Paterson and Parker rules were followed.

Results

By the end of 1989 4 out of 14 (28%) patients were alive without evidence of disease (see also table 2.1). One of these patients was re-treated by an iridium implant to a minimum tumour dose of 50 Gy in 100 hours, because of a nodal recurrence in the neck, 8 months after completion of the treatment. Four patients died of intercurrent disease, three of them were re-treated because of a local recurrence. Six patients died with active tumour. Two of these patients with nodal recurrences were successfully re-treated by neck dissection and external irradiation. They died with lung metastases. One patient died with bone metastases but without evidence of local disease. Three patients died with a local recurrence. The interval between completion of the primary treatment and local recurrences ranged from 3 to 46 months (average 14 months). However, most patients experienced a recurrence within 12 months following primary treatment. Most patients who developed a nodal recurrence subsequently died of their disease.
Acute mucosal reactions were less severe in all cases because of the limited dose of external irradiation. The mucosal reactions from interstitial radium implant were confined to a limited area and healed spontaneously within 1 to 5 months (average 3 months). Treatment related late complications such as soft tissue necrosis or osteoradionecrosis were not seen.

Conclusion

The main finding of this clinical study was that more recurrences and less normal tissue damage was seen than in literature mentioned before.

Table 2.1 **A survey of tumour stages and treatment results of 14 patients with squamous cell carcinoma of the mobile tongue and floor of mouth treated between January 1977 and August 1984**

Pat. no.	Tumour stage	Recurrence*) Local	Recurrence*) Nodal	Treatment of recurrence	Death*) with cancer	Death*) Intercurrent
1	T_3N_1	3		excision		126
2	T_1N_0		7	neck diss.+X-RT	10	
3	T_2N_0	8		none	10	
4	T_2N_0					88
5	T_2N_0	46		excision		96
6	T_4N_0					
7	T_2N_0	5	5	none	10	
8	T_3N_0		8	Ir.-implant		
9	T_1N_0		11	X-RT	19	
10	T_2N_0					
11	T_2N_0		7	neck diss.+X-RT	12	
12	T_2N_0					
13	T_2N_0	32		excision		56
14	T_3N_0				9	

*) months after treatment

2.3 Treatment techniques of oral cavity tumours with iridium

Because of its smaller diameter and its variable length, but above all because of its flexibility, Iridium-192 has a greater application field than radium or caesium needles. In addition, when iridium is used in rigid needles or nylon tubes, it offers the possibility of (remote) afterloading. In an attempt to obtain optimal and reproducible implantation our institute has made use of accessory aids since 1984. For a given tumour localization the applicator has to meet certain requirements, it has to be simple and reproducible. With the aid of the applicator the penetrating needles are brought into position in the target area parallel and equidistant to each other. The applicator has to be sufficiently versatile to result in such a source configuration that a given tumour can be covered adequately.
The target volume is determined as early as possible and definitely before the start of external radiotherapy. In this way the brachytherapist is not distracted by radiation evoked tissue reactions or possible regression of the tumour and geographical misses thus can be avoided. At this time, a pre-treatment planning is made.

In this chapter the implantation techniques and the applicators used in our institute in the treatment of tumours of the oral cavity are described.

Preparation for implantation

Before the onset of external irradiation all patients are submitted to a careful dental examination. Carious teeth are extracted. Patients with bone destruction due to the tumour or with a severe haemorrhagic diathesis are excluded from brachytherapy. A plaster of Paris impression of the mandible and floor of mouth, together with a dental acrylic shield and one shield with 2 mm of lead, are made for every individual patient prior to therapy (fig. 2.1). The target volume is determined by physical examination, the tumour contour is projected on the plaster of Paris impression. Thus an accurate assessment of the relationship of the tumour boundaries to the mandible is achieved (fig. 2.2). The target contours are transmitted on graphic paper and a source configuration with an appropriate dose pattern is determined (fig. 2.3). Estimating the length of the iridium sources to be used, the dose distribution of the volume at various levels can be calculated (fig. 2.4). When the target volume is adequately covered by the irradiated volume, the desired source configuration can be transported to an applicator. In case of tumours of the mobile tongue or floor of mouth, with a maximum diameter of 3 cm in cross-section, implantation can be performed with the aid of the oral cavity applicator. This applicator consists of two parallel metal plates measuring 4x5 cm which can be moved in relation to each other just like vernier callipers (fig. 2.5). Small openings in the plates are made at 4 mm distances for the placement of interchangeable needle guides and receivers. The desired source configuration is now transferred to the applicator by arranging the needle guide tunnels and receivers according to the desired source configuration.

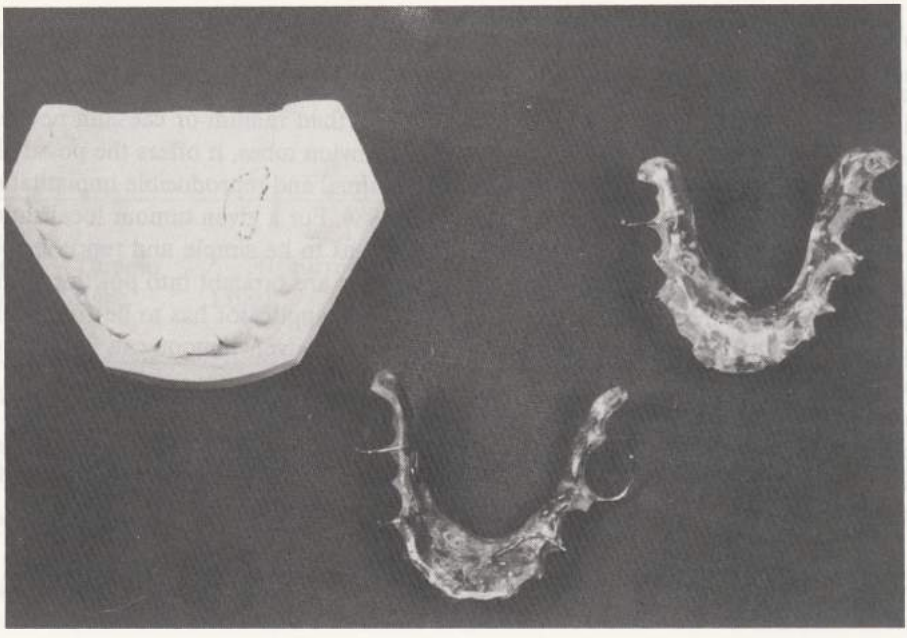


Fig 2.1 A plaster of Paris impression of the floor of mouth, together with a dental acrylic shield and a shield with 2 mm of lead.

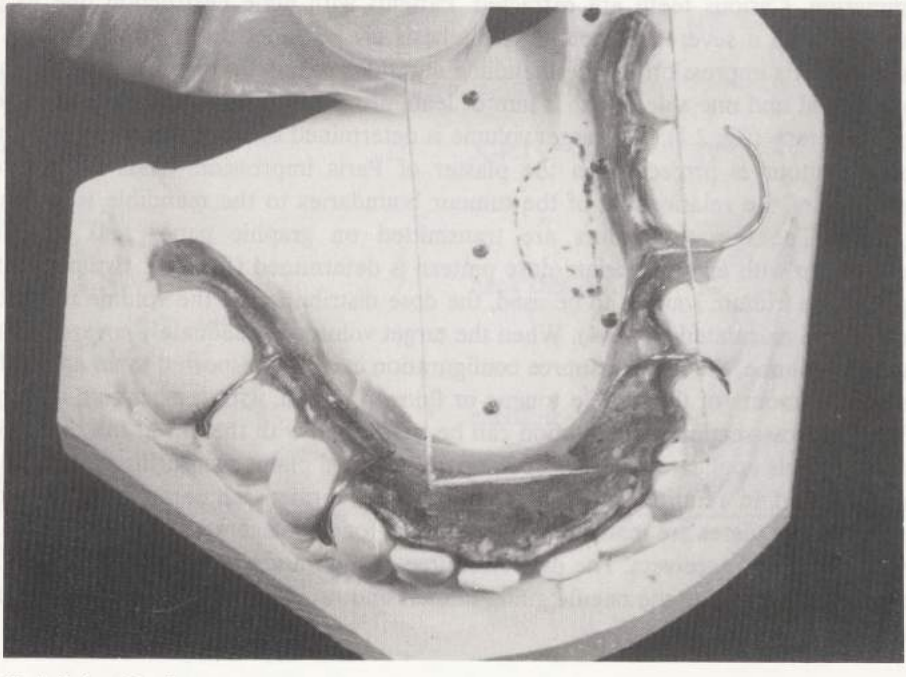


Fig 2.2 Relationship of tumour boundaries to the mandible.

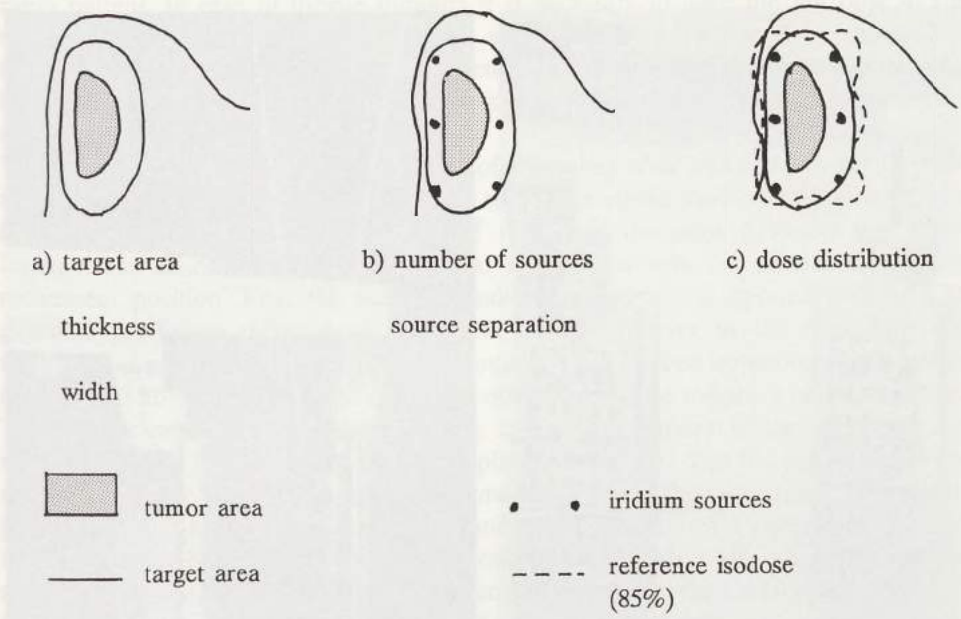


Fig 2.3 Source configuration and appropriate isodose pattern are determined.

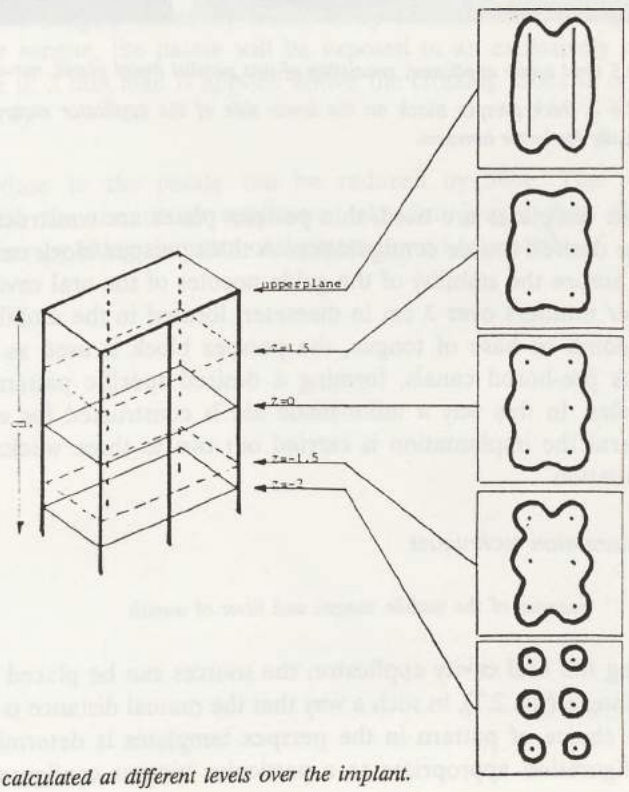
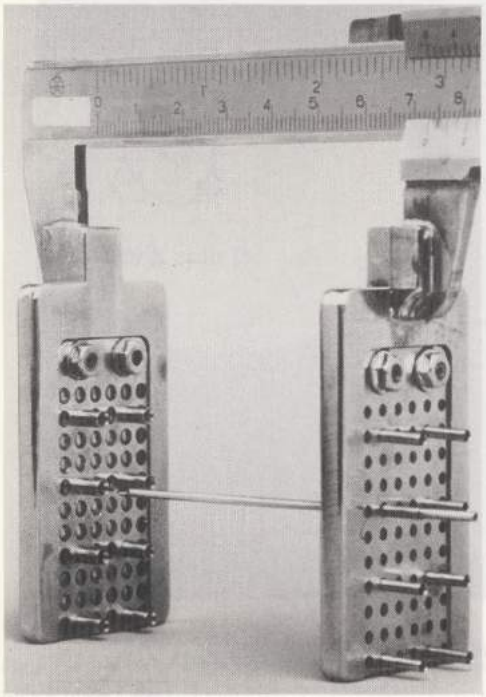


Fig 2.4 Dose distribution can be calculated at different levels over the implant.



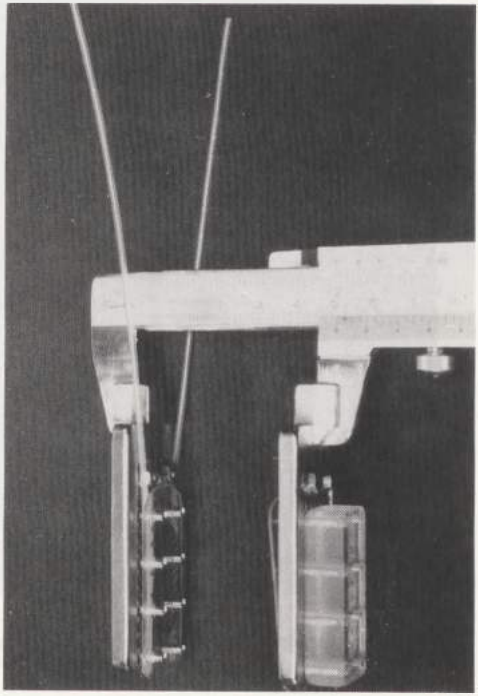


Fig 2.5 Oral cavity applicator, consisting of two parallel metal plates, movable like Vernier callipers.

Fig 2.6 A thick perspex block on the lower side of the applicator ensures stability of the guide needles, especially for larger tumours.

When templates are used, thin perspex plates are constructed in accordance with the same desired source configuration. A thick perspex block on the lower side of the plate can ensure the stability of the guide needles of the oral cavity applicator (fig. 2.6). For larger tumours over 3 cm in diameter, located in the mobile part of the tongue, floor of mouth or base of tongue, the perspex block is used as applicator. In the perspex block pre-bored canals, forming a desired specific pattern, serve as guides for the needles. In this way a tailor-made aid is constructed for every individual patient. In general the implantation is carried out two to three weeks after the end of external irradiation.

Implantation techniques

a. tumours of the mobile tongue and floor of mouth

Using the oral cavity applicator, the sources can be placed in the form of a square or a triangle (fig. 2.7), in such a way that the mutual distance is always a multiple of 4 mm. The choice of pattern in the perspex templates is determined by the desired source configuration appropriate to a particular tumour configuration and custom-made for

every patient. In case of tongue tumours it is necessary to have the full dose at the surface. For this purpose nylon outer tubes are placed intra-orally on the perspex plate (fig. 2.8), these outer tubes ensure transsection of the interstitially situated tubes. The length of the intra-orally situated sources is determined by the distance between the most peripherally lying nylon outer tubes.
With this technique twisting and kinking of the tubes after replacement of the rigid needles is avoided, in contrast to a loop technique where twisting and kinking is a frequent problem, especially in view of the short distances between the tubes. Implantation is carried out under general anaesthesia with the patient in a semi-recumbent position. First the acrylic mandibular protector is applied (fig. 2.9), to guarantee sufficient distance of the lateral needles relative to the mandible. The applicator is placed in position, with the target volume clasped between the two plates (fig. 2.10). The conductors ensure, that the otherwise mobile tongue is held in position. The needles can be placed one by one (fig. 2.11). After removal of the applicator, the needles are kept in position by plastic templates, in the next step the rigid needles are replaced by nylon outer tubes (external diameter 1.2 mm). The outer tubes are fixed by plastic buttons on the oral side and by metal buttons on the chin side (fig. 2.12). The length of the active sources is determined radiologically, either with a C-arm or with a simulator, using dummy sources of a fixed length (inner tube, external diameter 0.5 mm) (fig. 2.13). The length of the final sources of course depends on the expected infiltration depth of the tumour. For the actual treatment the dummy sources are replaced by iridium sources of the same length, either by hand or by remote afterloading. In definitive treatments of the tongue, the palate will be exposed to an excessively high dose. In these cases a plate of 2 mm lead is applied above the crossing tubes in order to reduce this dose (fig. 2.14).

With this technique the dose to the palate can be reduced by 50%. The total implantation procedure with the use of an applicator takes no longer than three quarters of an hour. The therapy using the intra-oral plates is well tolerated.

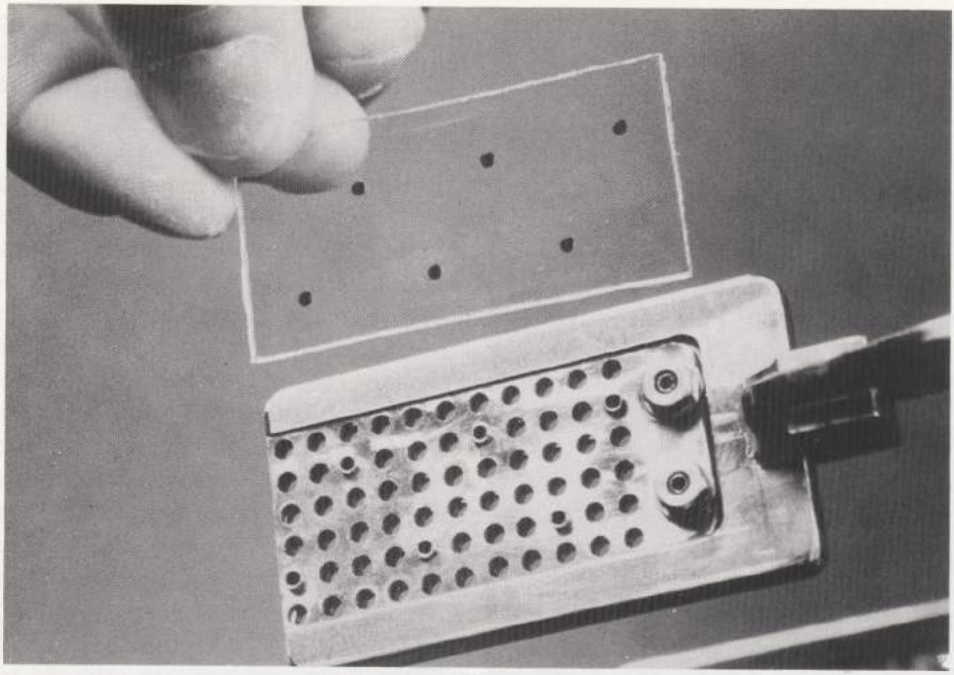


Fig 2.7 Needles can be placed in the form of a triangle or a square, in such a way that the mutual distance is always a multiple of 4 mm. The choice of pattern in the template is determined by the desired source configuration and custom-made for every patient.

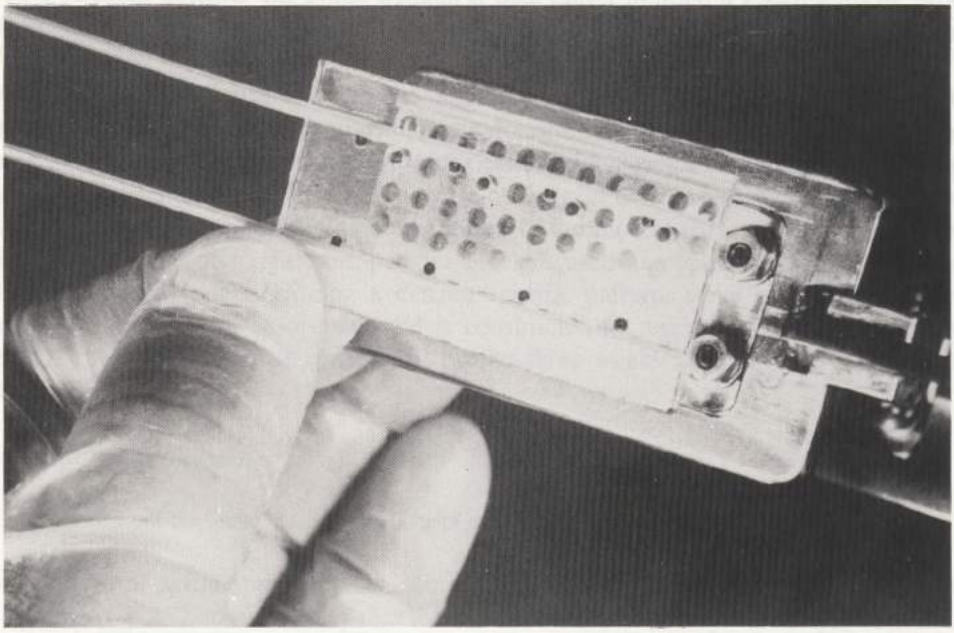


Fig 2.8 Outer tubes are placed intra-orally on the perspex plate to achieve full dose at the surface in case of tongue tumours.

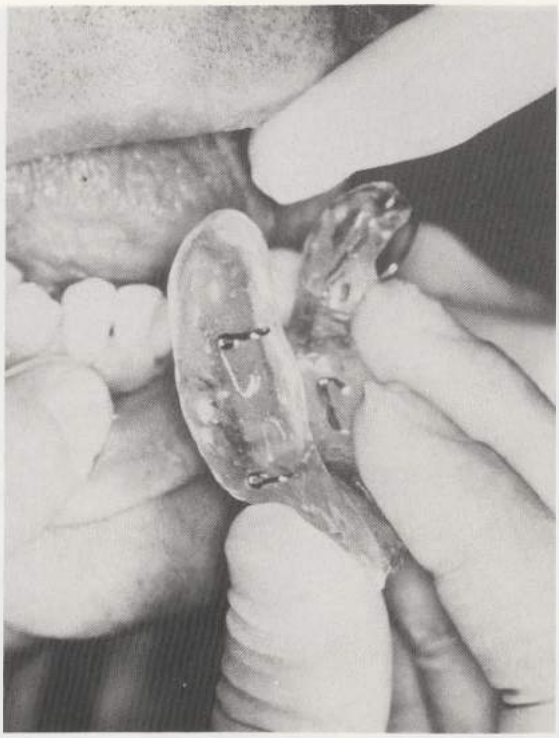


Fig 2.9 The acrylic protector is applied to guarantee sufficient distance of the lateral needles relative to the mandible.

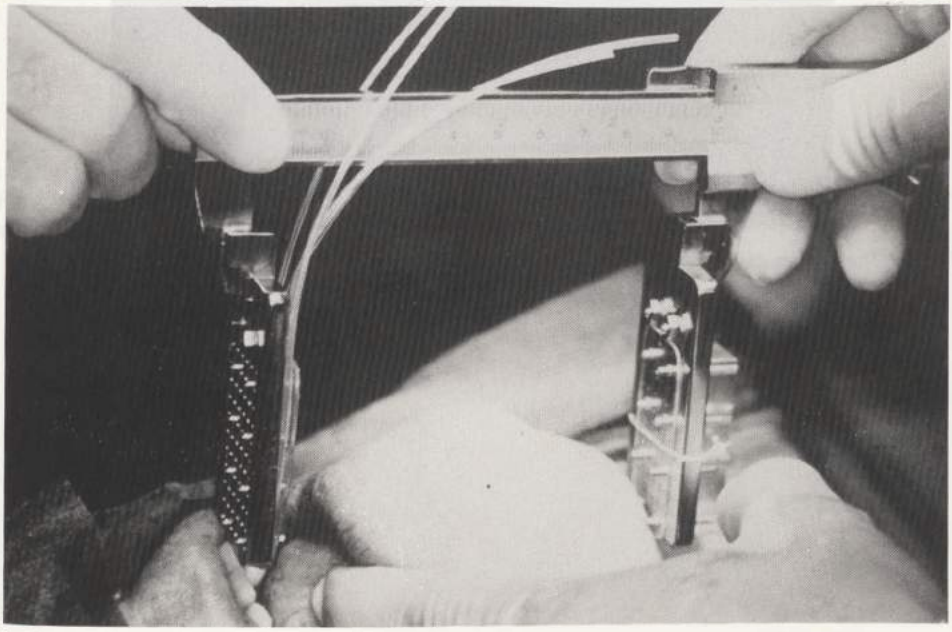


Fig 2.10 The applicator is placed in position.

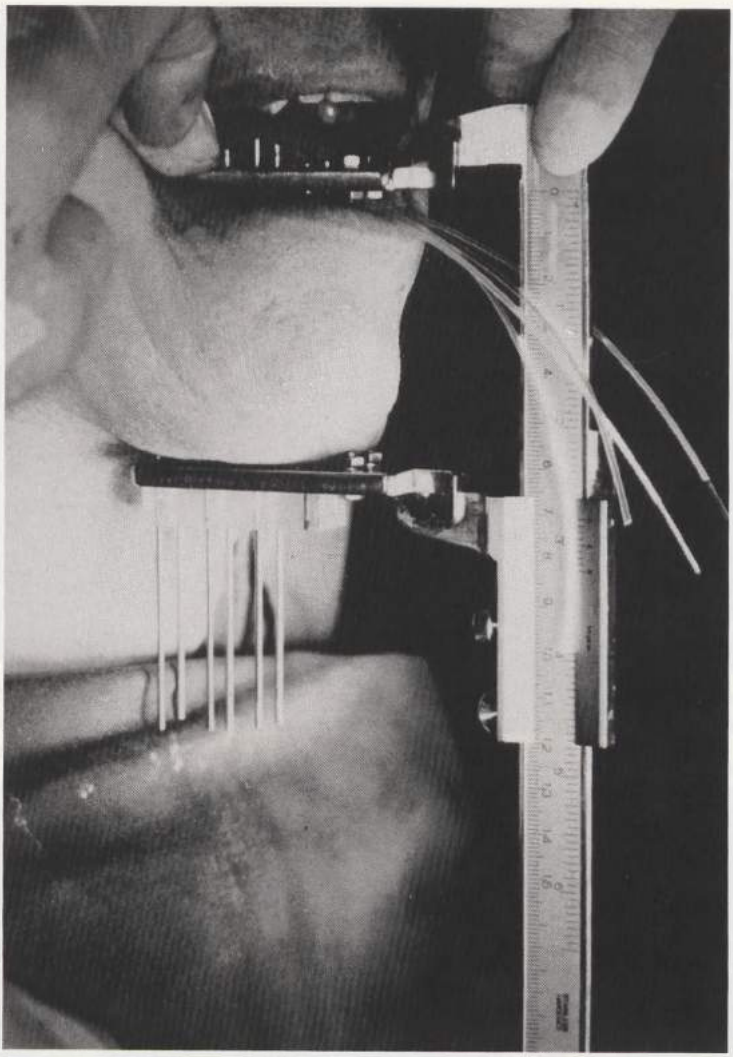


Fig 2.11 The needles are placed one by one.

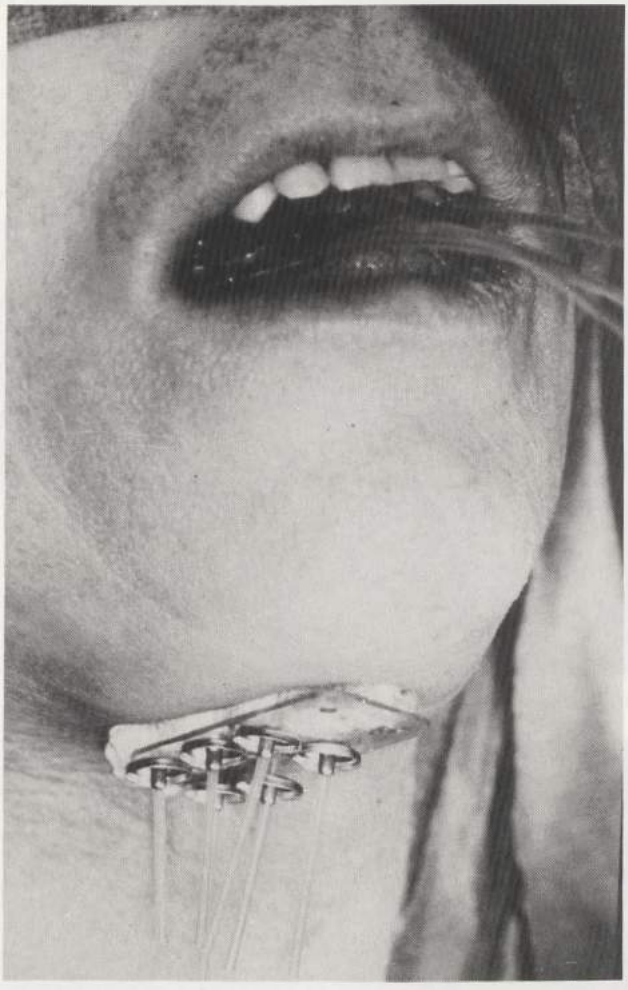


Fig 2.12 After removal of the applicator, the needles are kept in position by the templates. In the next step the needles are replaced by nylon outer tubes. The tubes are fixed by metal buttons.

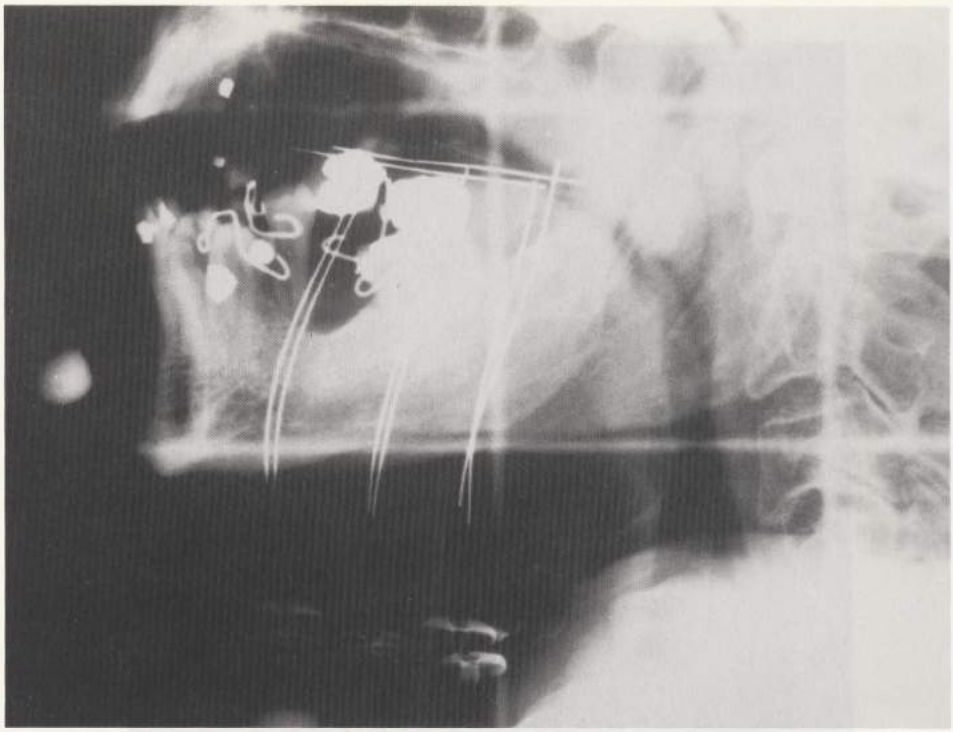


Fig 2.13 The length of the sources is determined radiologically, using dummy sources.

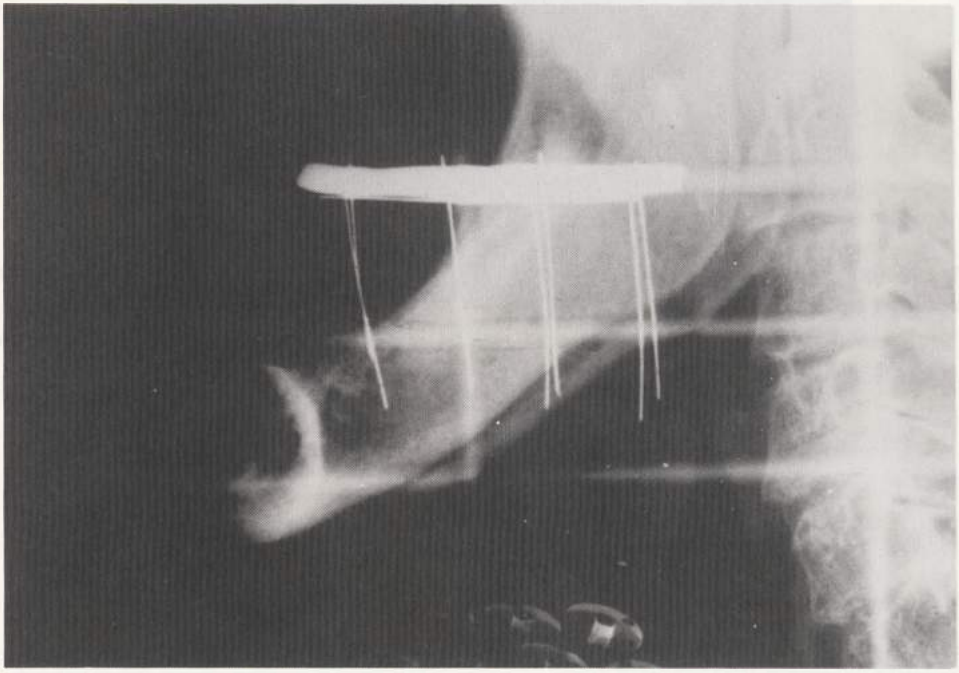


Fig 2.14 To reduce the dose to the palate, in case of tongue implantation, a plate of 2 mm lead is applied above the crossing tubes.

b. Tumours of the anterior part of the tongue and floor of mouth

The described applicator is not suitable for all sites of the oral cavity. Especially in case of tumours in the anterior part of the floor of mouth the shape of the applicator should be modified according to the shape of the floor of the mouth (fig. 2.15). Again pre-bored channels are made in a thick perspex block, at a constant distance relative to each other to serve as conductors for the hollow needles. The distance between the needles is chosen 12 or 15 mm, depending on the dimensions of the target volume. The further steps are identical to the ones described above.

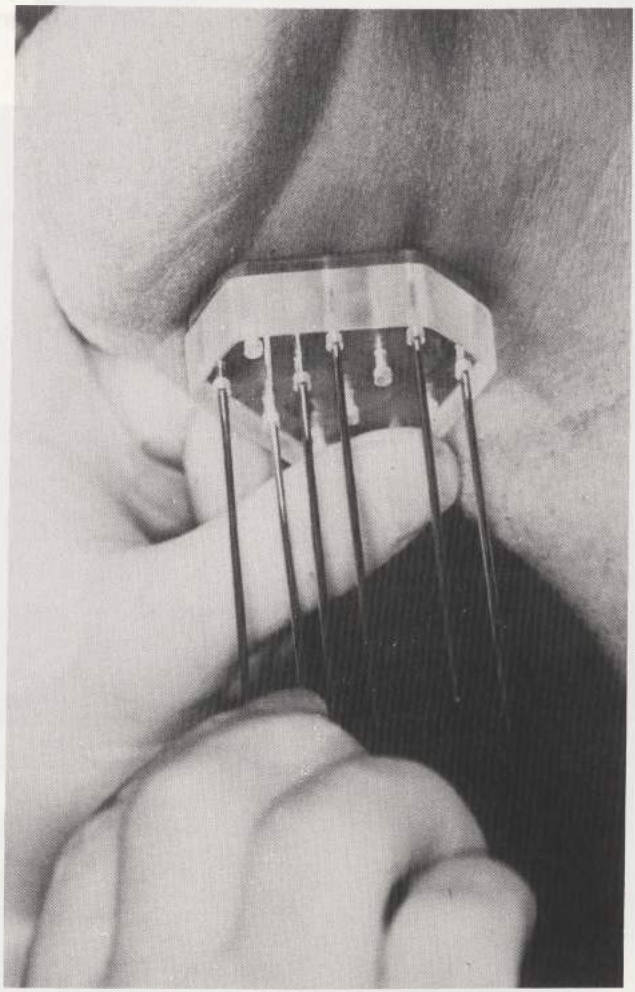


Fig 2.15 For implantation of the anterior part of the floor of mouth the shape of the applicator is modified according to the shape of the floor of mouth.

c. Tumours of the base of tongue

In cancers of the base of tongue a thick perspex block (fig. 2.16) is used to introduce the hollow needles at a distance of 15 or 20 mm. The needles enter through the skin in the submental area, covering the whole surface of the base of tongue even in lateraly situated tumours. The rigid needles are replaced by nylon tubes, leading the thin ends of the double leader outer tubes through the intra-oral ends of the needles to form a loop. The outer tubes are fixed at the submental area using metal buttons. After the introduction of dummy sources into the loops, antero-posterior and lateral orthogonal X-rays of the implanted area are made for localization and dosimetry (fig. 2.17 a,b). These and the following steps are identical to the ones described before.

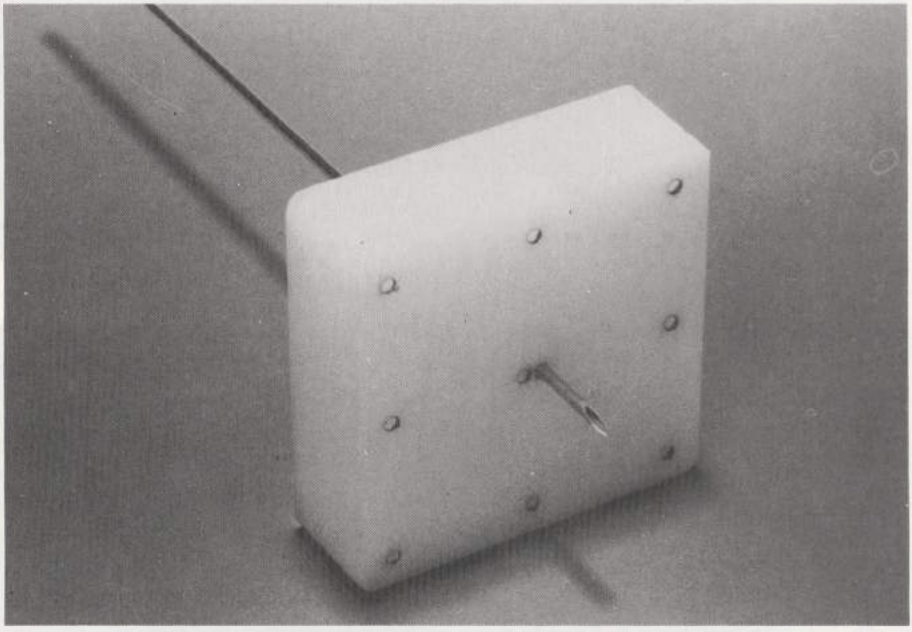


Fig 2.16 For implantation of the base of tongue a thick perspex block is used to guide the needles.

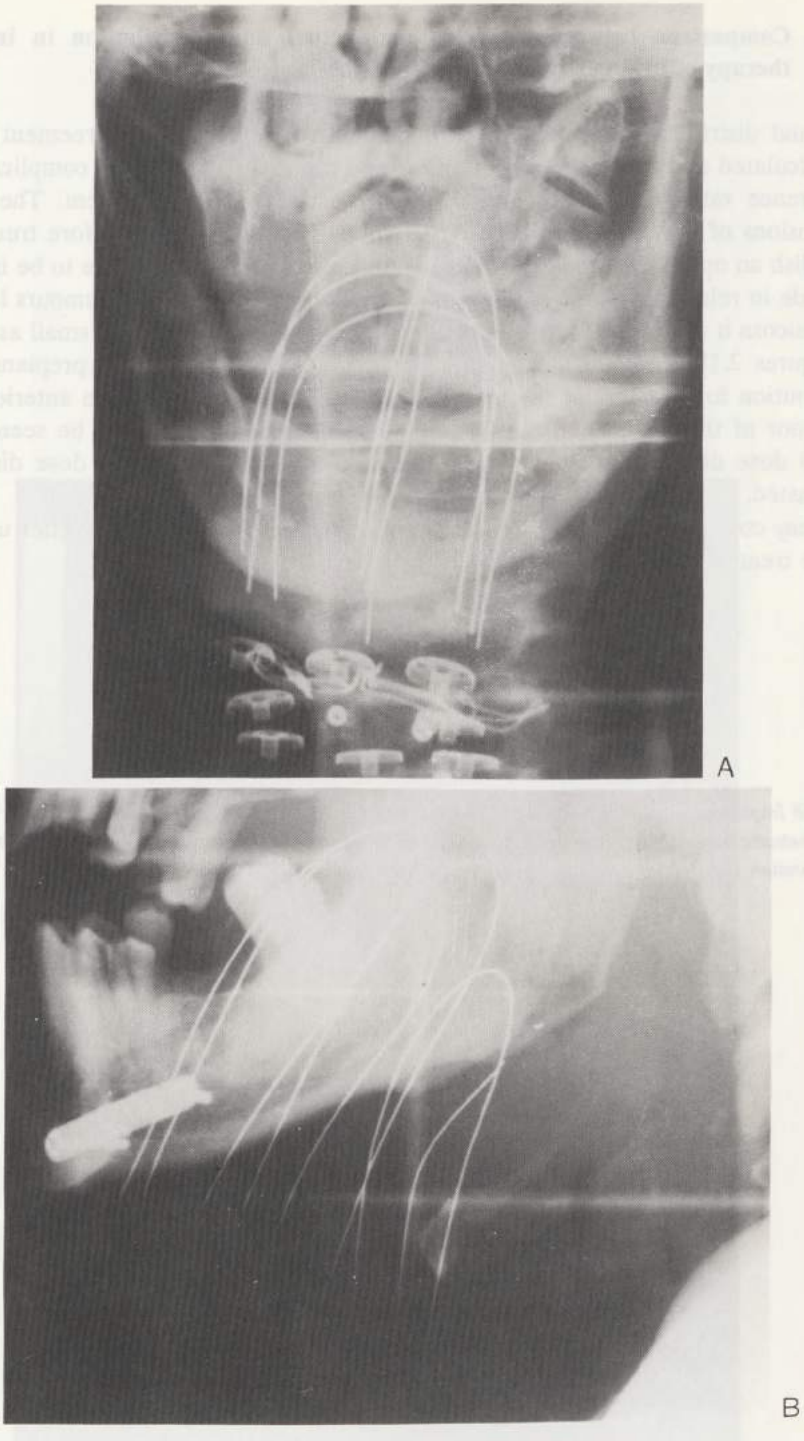


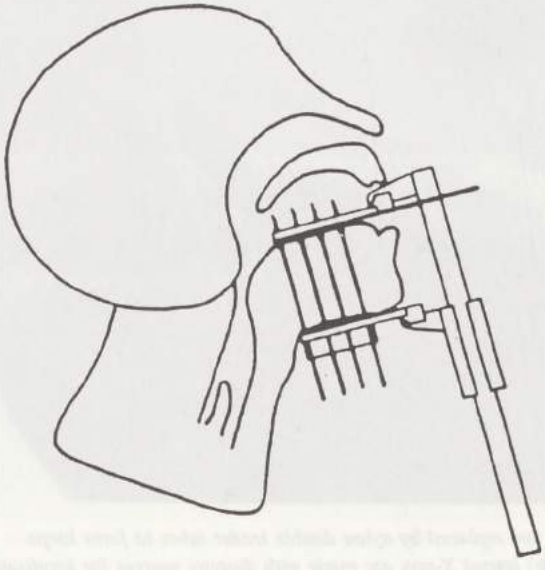
Fig 2.17 The rigid needles are replaced by nylon double leader tubes to form loops. (a) antero-posterior and (b) lateral X-rays are made with dummy sources for localization.

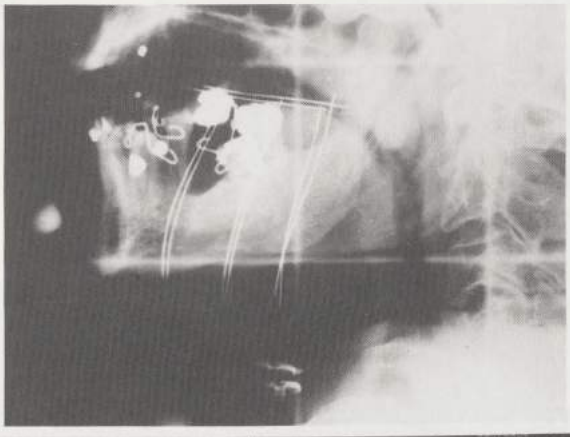
2.4 Comparison between predicted and actual dose distribution in intersitital therapy of oral cavity tumours using an applicator

Unequal distribution of the sources in implants results in a disagreement between precalculated and actual dose distribution, and thus may increase the complication and recurrence rates. The use of an applicator can avoid this problem. The physical dimensions of the tumour and the target volume are determined before treatment to establish an optimal source arrangement. An estimation of the volume to be implanted is made in relation to the volume of high dose areas. Especially in tumours located in the mucosa it is attempted to keep the volumes of high dose areas as small as possible. In figures 2.18, 2.19 and 2.20 typical examples are given for the preplanned dose distribution for tumours of the lateral part of the mobile tongue, the anterior part of the floor of the mouth and the base of tongue, respectively. It can be seen that the actual dose distribution is in almost complete agreement with the dose distribution forecasted.

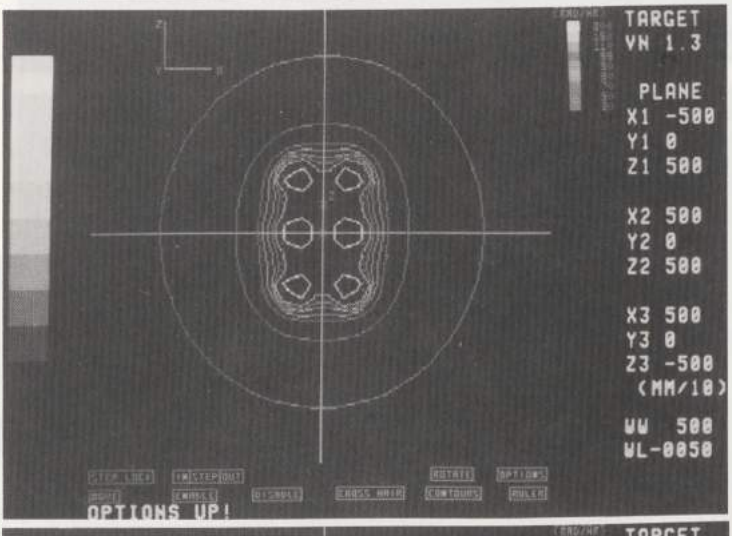
We may conclude from this, that the use of an applicator results in a better uniformity in the treatment of lesions in the head and neck areas described.

Fig 2.18 Implantation of a tumour of the mobile tongue, using an applicator
(a) schematical view (b) localization film (lat. view) of a realized implantation (c) preplanned isodose configuration (d) isodose configuration of the realized implant.





B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PLANE
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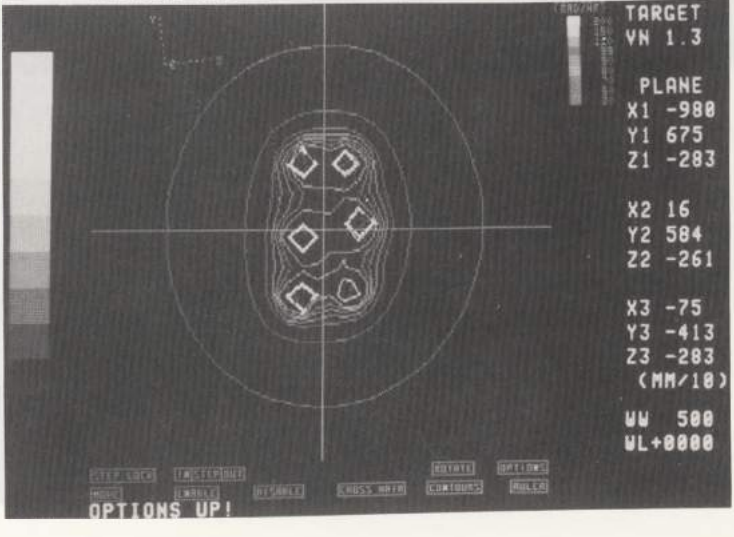
Y1 0
Z1 500
X2 500
Y2 0
Z2 500
X3 500
Y3 0
Z3 -500
(MM/10)
WW 500
WL-0050
OPTIONS UP!

C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PLANE
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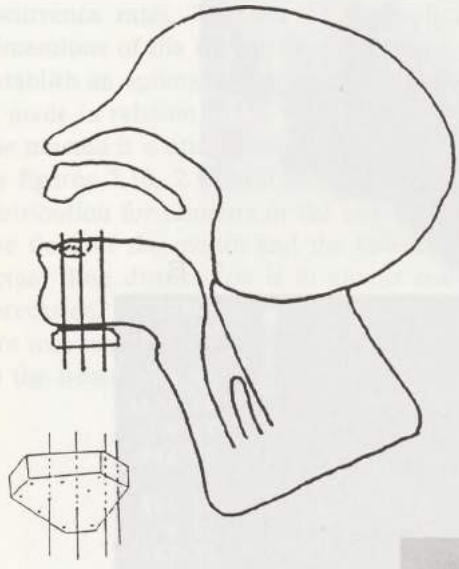
Y1 675
Z1 -283
X2 16
Y2 584
Z2 -261
X3 -75
Y3 -413
Z3 -283
(MM/10)
WW 500
WL+0000
OPTIONS UP!

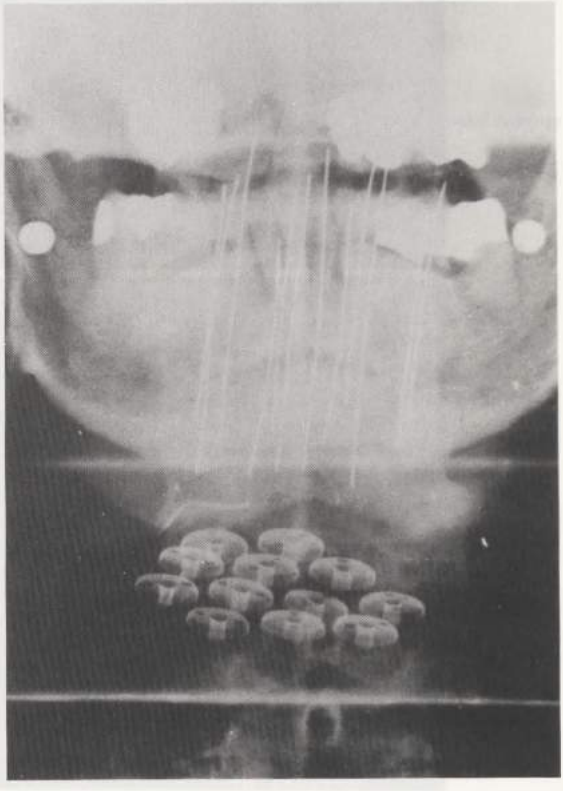
D

Fig 2.19 Implantation of a tumour of the anterior part of the floor of mouth, using a custom-made perspex block

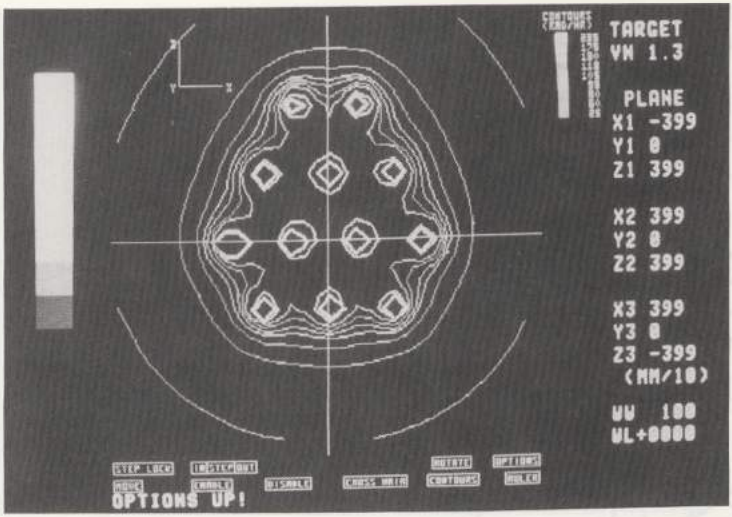
(a) schematical view (b) localization film (AP view of a realized implantation) (c) preplanned isodose configuration (d) isodose configuration of the realized implant.



A



B


CONTOURS (ENG/MM)
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PLANE
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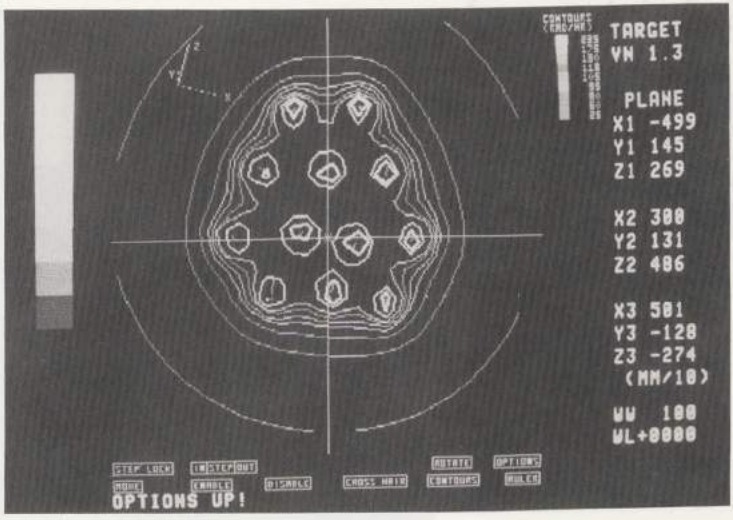
Y1 0
Z1 399
X2 399
Y2 0
Z2 399
X3 399
Y3 0
Z3 -399
(MM/10)
WW 100
WL+0000
STEP LOCK
IN/STEP/OUT
MOVE
ENABLE
DISABLE
CROSS HAIR
ROTATE
CONTOURS
OPTIONS
RULER
OPTIONS UP!

C


CONTOURS (ENG/MM)
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PLANE
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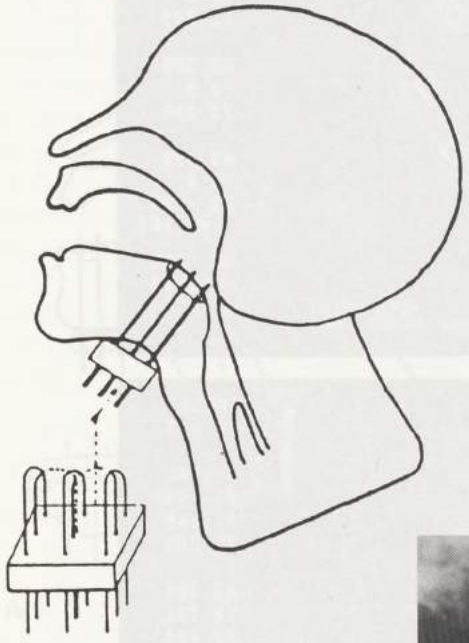
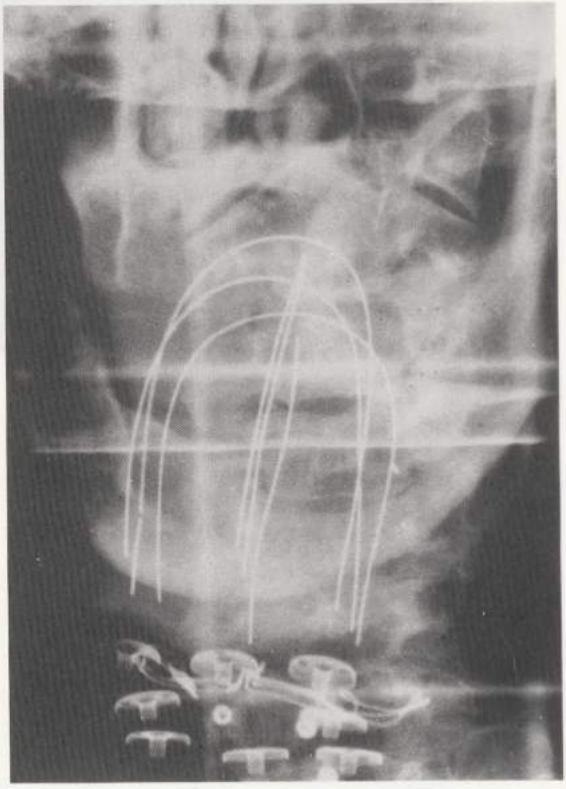
Y1 145
Z1 269
X2 300
Y2 131
Z2 486
X3 501
Y3 -128
Z3 -274
(MM/10)
WW 100
WL+0000
STEP LOCK
IN/STEP/OUT
MOVE
ENABLE
DISABLE
CROSS HAIR
ROTATE
CONTOURS
OPTIONS
RULER
OPTIONS UP!

D

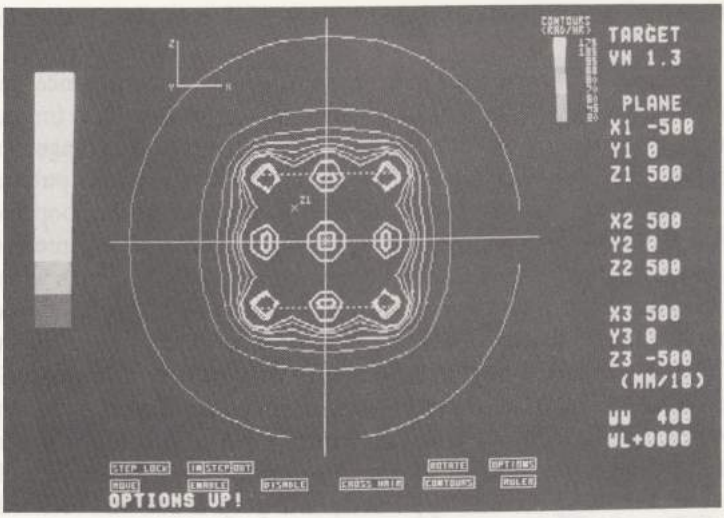
Fig 2.20 Implantation of the base of tongue, using a thick perspex block to guide the needles (a) schematic view (b) localization film (AP view) for a realized implantation (c) preplanned isodose configuration (d) isodose configuration of the realized implant.



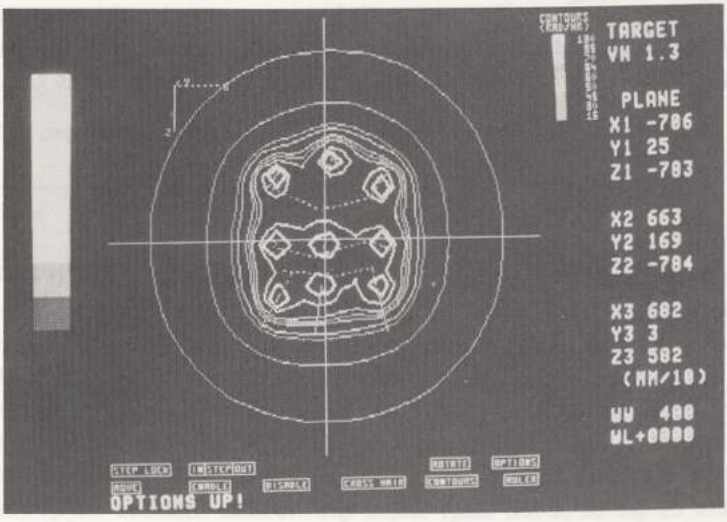
A



B


CONTOURS (RAD/MM)
TARGET
VM 1.3
PLANE
X1 -500
Y1 0
Z1 500
X2 500
Y2 0
Z2 500
X3 500
Y3 0
Z3 -500
(MM/10)
WW 400
WL+0000
STEP LOCK
INSTEP/OUT
MOVE
ENABLE
DISABLE
CROSS HAIR
ROTATE
CONTOURS
OPTIONS
RULER
OPTIONS UP!

C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VM 1.3
PLANE
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Y1 25
Z1 -703
X2 663
Y2 169
Z2 -704
X3 682
Y3 3
Z3 502
(MM/10)
WW 400
WL+0000
STEP LOCK
INSTEP/OUT
MOVE
ENABLE
DISABLE
CROSS HAIR
ROTATE
CONTOURS
OPTIONS
RULER
OPTIONS UP!

D

2.5 The Anderson natural volume-dose histogram of oral cavity implants

The natural volume-dose histogram can be used to evaluate the diffence between the predicted source arrangements in oral cavity implants and the realised implants. When a loop technique was used, in almost all cases, the planned source arrangement was not in agreement with the realised implant as we described in a previous publication [28]. The natural volume-dose histogram of a realised implant using the loop technique is compared with the same histogram of the preplanned source arrangement (fig. 2.21). The peak in the histogram of the realised implant was found to be much wider than the predicted one, indicating less uniformity. Also the position of the peak differed from the peak position of the predicted implant and in some cases this even resulted in the necessity to choose a different treatment reference dose-rate than planned. Since these implants were done without the help of a C-arm it can be concluded that the placement of guide needles parallel and at a constant distance from each other is very difficult when done by free hand. The natural volume-dose histogram of an implant of a tumour of the floor of mouth using the oral applicator, both preplanned and realised, is shown in fig. 2.22. A good agreement between both histograms can be observed, indicating a good uniformity. These histograms show, that the use of an oral cavity applicator results in a close agreement between planned and actual source arrangements [29].

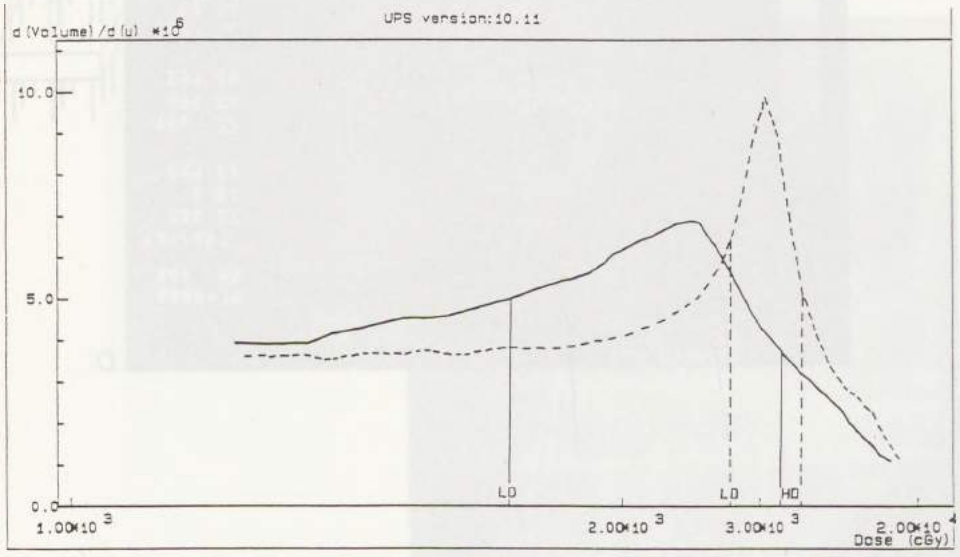

Fig 2.21 NVDH preplanned and realized for a looping technique.

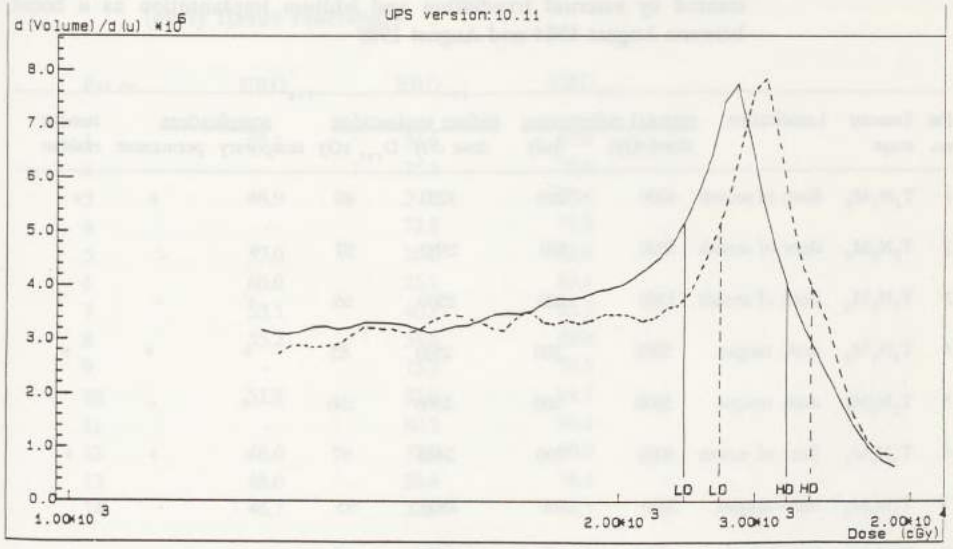

Fig 2.22 NVDH preplanned and realized for an implantation in the floor of mouth, using the oral applicator.

2.6 Results

Since 1984 15 patients with tumours of the mobile tongue, floor of mouth or base of tongue have been treated with this technique. The average minimum tumour dose was 25 Gy with the Paris system as a guide. All patients received external irradiation at a dose of 50 Gy in 5 weeks before implantation (table 2.2). In all patients a radiation mucositis developed about 2 weeks after removal of the implant. After conservative treatment spontaneous healing occurred in 6 patients (pat. no. 5, 7, 8 , 9 , 10 and 15), in 5 patients superficial necrosis was found, treated by local curettage or excision. In these 5 patients no residual tumour was found (pat. no. 2, 3, 12, 13 and 14). In 3 patients (pat. no. 1, 4 and 6) no healing occurred after conservative treatment and a necrotic area persisted. Three months after implantation biopsies showed persistent tumour in all these patients. Salvage surgery was unsuccesfull in these patients, in spite of chemotherapy they all died with residual tumour. In one additional patient (pat. no. 11) an necrotic area was removed six weeks after implantation. In this patient again residual tumour was found, the excision was complete and the patient is doing well. The last patient (pat. no. 8) kept complaints of pain in the region of the hypopharynx without visible abnormalities. However, six months after the onset of the complaints a local recurrence was discovered.

Patients with lymphadenopathy were submitted to radical neck dissection six weeks after the end of external irradiation. In all 4 patients no vital tumour was found in the operation specimen.

Table 2.2 **A survey of 15 patients with squamous cell carcinoma of the oral cavity treated by external irradiation and iridium implantation as a boost between August 1984 and August 1989**

Pat. no.	Tumour stage	Localization	external radiotherapy dose(cGy)	daily	iridium implantation dose cGy	D_{ref} cGy	complications temporary	permanent	tumour residue
1	$T_4N_1M_0$	floor of mouth	4000	200	3200	80	+	+	+
2	$T_2N_0M_0$	floor of mouth	5000	200	2500	50	+	-	
3	$T_2N_0M_0$	floor of mouth	5000	200	2500	66	+	-	
4	$T_3N_1M_0$	mob. tongue	5000	200	2500	85	+	+	+
5	$T_2N_0M_0$	mob. tongue	5000	200	2500	100	+	-	
6	$T_3N_0M_0$	floor of mouth	5000	200	2400	97	+	+	+
7	$T_2N_0M_0$	mob. tongue	5000	200	2500	95	+	-	
8	$T_3N_1M_0$	base tongue	5000	200	2500	60	+	+	+
9	rec.*)	base tongue	3000	200	4000	80	+	-	
10	$T_1N_0M_0$	mob. tongue	-	-	6500	90	+	-	
11	$T_2N_0M_0$	mob. tongue	5000	200	3000	180	+	+**)	
12	$T_2N_0M_0$	mob. tongue	5000	200	3000	80	+	-	
13	$T_1N_0M_0$	floor of mouth	5000	200	2500	100	+	-	
14	$T_4N_2M_0$	mob. tongue	5000	200	2500	73	+	-	
15	$T_3N_0M_0$	mob. tongue	5000	200	3000	124	+	-	

*) pat. no. 9: recurrence after external radiotherapy (5000 cGy)

**) pat. no. 11: excision of necrosis

2.7 Discussion

The described applicator allows a better control of the placement of sources and thus a better agreement between the preplanned and actual dose distribution. The non-loop technique has the advantage over the loop technique that it is possible to work with shorter distances between the sources to keep the high dose volume around the sources smaller. The risk of kinking the nylon tubes is avoided and furthermore it offers the possibility of reducing the dose to the palate in appropriate cases by placing a lead-plate on the intra-oral template. The assessment of the treatment volume prior to external

Table 2.3 a Extrapolated response dose (ERD) in 14 patients treated with radium (early tissue reactions)

Pat.nr.	ERD_{ext}	ERD_{int}	ERD_{tot}
1	53.1	34.5	87.6
2	-	75.3	75.3
3	48.9	39.5	88.4
4	-	72.8	72.8
5	57.0	26.6	83.6
6	60.0	25.1	85.1
7	53.1	40.2	93.3
8	55.2	34.6	89.8
9	-	75.3	75.3
10	51.8	32.9	84.7
11	-	80.3	80.3
12	48.0	32.0	80.0
13	48.0	30.4	78.4
14	46.7	32.0	78.7

The values used for the calculation are: α/β = 10 Gy (for early tissue reactions)
and: μ = 0.46 h^{-1}

The average total radiation dose was: ERD_{tot} average: 82.4 (stand. dev. 6.1)

Table 2.3 b Extrapolated response dose (ERD) in 14 patients treated with radium (late tissue reactions)

Pat.nr.	ERD_{ext}	ERD_{int}	ERD_{tot}
1	77.4	57.0	134.4
2	-	121.0	121.0
3	68.0	68.0	136.0
4	-	111.0	111.0
5	83.1	46.3	129.4
6	90.0	40.3	130.3
7	77.4	70.8	148.2
8	82.8	63.3	146.1
9	-	121.0	121.0
10	72.0	53.4	128.7
11	-	141.0	141.0
12	72.0	53.4	125.4
13	72.0	46.6	118.6
14	68.1	53.4	121.5

The values used for the calculation are: α/β = 2.5 Gy (for late tissue reactions)
and: μ = 0.46 h^{-1}

The average total radiation dose was: ERD_{tot} average: 129.5 (stand. dev. 10.8)

Table 2.4 a Extrapolated response dose (ERD) in 15 patients treated with iridium (early tissue reactions)

Pat.nr.	ERD_{ext}	ERD_{int}	ERD_{tot}
1	48.0	42.5	90.5
2	60.0	30.2	90.2
3	60.0	31.8	91.8
4	60.0	33.6	93.6
5	60.0	34.9	94.9
6	60.0	33.2	93.2
7	60.0	34.5	94.5
8	60.0	31.2	91.2
9	36.0	53.3	89.3
10	-	89.7	89.7
11	56.6	45.4	102.0
12	60.0	31.7	91.7
13	60.0	34.9	94.9
14	60.0	32.4	92.4
15	60.0	44.7	104.7

The values used for the calculation are: α/β = 10 Gy (for early tissue reactions) and: μ = 0.46 h^{-1}

The average total radiation dose was: ERD_{tot} average: 93.6 (stand. dev. 4.4)

Table 2.4 b Extrapolated response dose (ERD) in 15 patients treated with iridium (late tissue reactions)

Pat.nr.	ERD_{ext}	ERD_{int}	ERD_{tot}
1	72.0	74.0	146.0
2	90.0	46.0	136.0
3	90.0	52.0	142.0
4	90.0	59.0	149.0
5	90.0	65.0	155.0
6	90.0	59.0	149.0
7	90.0	62.9	152.9
8	90.0	49.7	139.7
9	54.0	93.2	147.2
10	-	163.7	163.7
11	88.3	91.7	180.0
12	90.0	54.7	145.0
13	90.0	64.7	154.7
14	90.0	54.7	144.7
15	90.0	88.8	178.8

The values used for the calculation are: α/β = 2.5 Gy (for late tissue reactions) and: μ = 0.46 h^{-1}

The average total radiation dose was: ERD_{tot} average: 152.2 (stand. dev. 12.9)

irradiation and the consequent determination of the dosimetry avoids the risk of geographical misses during implantation. Since flexible tubes are used for afterloading the removal of the tubes is easy and without the need for medication.
The whole procedure may seem inefficient, in fact the time involved in the initial preparation is regained in the shorter duration of the final implantation.

Although the follow-up is short and the number of patients small some conclusions can be drawn from the above described data regarding the treatment policy. Necrosis after treatment is especially seen in patients with ulcerating tumours (pat. no. 1, 4, 6, 11 and 14). In case of local recurrence, salvage surgery still can be succesfull. Persisting necrosis is suspect for recurrence and should be removed with a curette, taking biopsies at the margins of it. For that reason patients have to be followed frequently until the lesion has healed.
In the retrospective study the low complication rate after external irradiation and radium implantation in patients with a tumour of the mobile part of the tongue already suggested that the given dose was relatively low. Using the Extrapolated Response Dose (ERD), we tried to compare the dose given in the retrospective series with radium and the current series with iridium. The calculations are done according to the formula of Dale (see also Chapter 1.3). The results of the calculations are given in tables 2.3 and 2.4 and show a higher dose given with iridium. Since the current series of patients received a higher total dose, a better tumour control can be expected, as well as more early and late damage compared with the patients treated with radium.

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CHAPTER 3

BREAST CONSERVING THERAPY

3.1 Introduction and review of the literature

Breast cancer is the most frequently observed malignant disease in women in Europe and the U.S.A. [9,2]. In the Netherlands the mortality rate is about 27 per 100.000 women [30]. Most of the increase in incidence over the last two decades has occurred among women aged 45 tot 74 [22]. The risk factors for breast cancer in women are well documented, age over 50, personal or family history of breast cancer, never had children or first child after age of 30 [22]. Environmental factors, including diet may influence the incidence among the various countries [22,38]. The most common site of origin of breast cancer is the upper outer quadrant (40%), followed by the central area (30%) [14,18]. Fisher et al. described the pathological features and clinical implications of carcinoma of the breast [15]. Since the histological characteristics of carcinoma of the breast affect prognosis, they have an important therapeutical implication. Both intrinsic and extrinsic factors are of importance. For instance the presence of estrogen or progresterone hormonal receptors has indicated that patients without these receptors have a significantly lower survival rate, not only because these patients have a small probability of responding to hormonal therapy. The growth rate of a tumour in the breast is thought to be constant from the date of origin [16]. Using the established estimates of doubling times it would take an average of approximately 5 years for a tumour to reach palpable size and those lesions with a longer doubling time would have an even longer latent period. So, with the increased use of screening mammography more patients will be seen with clinically silent carcinomas [7].

Numerous data appeared in literature to establish the good results obtained with breast conserving therapy. Both unrandomized and randomized trials suggest that the overall survival, disease specific survival, time to relapse, etc., are not significantly different from mastectomy [1,8,10,11,14,29,33]. Breast conserving therapy may include lumpectomy or not [12,26], may include external irradiation to the whole breast or not [35], may include a local boost or not (current EORTC study), may include booster dose by implantation or not [6]. Already in the twenties pioneers advocated conservation, using radium needles, in the management of operable breast cancer [23]. Pierquin [32] reported the results of patients treated since 1961 by radical radiation therapy, including brachytherapy, of early operable breast cancer (T_1, T_2 and small T_3). The paper reports an uncorrected 5-year loco-regional control rate of 95.5% for T_1 lesions and 92.5% for T_2 lesions. The treatment protocol included tumorectomy for T_1 and small T_2 tumours (less than 3 cm in diameter), while larger tumours were left in situ. From the Netherlands Cancer Institute, Bartelink et al. [3] published a local recurrence rate of 2% in 585 conservatively treated patients at 6 years, similar for stage 1 and stage 2 localized breast cancers. Their series included patients with incomplete resection of the primary tumour and patients with an extensive in situ component. The high radiation dose of 25 Gy given by interstitial iridum implant after 50 Gy of external irridiation to the whole breast and the size of the implanted volume (two plane implant in the majority of the patients) are probably the reasons for this high local control rate.
Next to local control cosmesis is an issue of prime importance.

All authors report minor complications in the range of 10 to 20% [13,31,39], including asymptomatic postradiation teleangiectasies, fibrosis of the breast and parasternal region, and mild arm lymphoedema. The combination of optimal oncological treatment and an acceptable cosmetic result is a matter of concern both for the surgeon and the radiation oncologist. Furthermore, a good cosmetic result renders the organ at risk more accessible for assessment during follow-up. For cosmetic result, the treated breast is in general compared with the contralateral, untreated organ with reference to symmetry, cutanous and subcutanous reactions and size. During the first two years after treatment, considerable changes may take place in the treated breast and scoring should be delayed till this time. Pierquin et al. [32] reviewed their cosmetic results, and found that 82% of the patients with T_1 lesions had results classified as excellent (no sequelae visible at first glance) or good (minimal sequelae on close inspection). With T_2 lesions these results were achieved in 70%. None of the patients with T_1 lesions had a poor result, and only two patients with a T_2 lesion were classified as poor. Recently Van Limbergen et al. [26,27] described a cosmetic evaluation of breast conserving therapy. Different patients and treatment-related factors responsible for cosmetic damage were investigated. The results showed that increased radiation doses, the occurence of matchline fibrosis between the tangential and the axillary fields, the extent of tumour excision, the use of "en bloc" axillary dissection, and the site of the primary tumour in the breast were significantly correlated with a poor cosmetic outcome. In general, the cosmetic outcome is hard to qualify and several authors [4,10,27] used a subjective point scale to categorize the cosmetic results into excellent, good, poor, or bad. One can raise the question whether the value of quantitative measurements such as proposed by several authors [27,34] contributed to a better judgement of the cosmetic outcome.

3.2 The Deventer results of treatment for stage 1 and 2 carcinoma of the breast with primary radiation therapy

The effectiveness of local treatment of the breast should be judged by two criteria: local control and cosmesis. The cosmetic result following radical mastectomy is limited due to the extent of tissue resected. For most women there is the psychological importance for breast preservation. Radiation therapy offers the possibility of both local control and breast preservation. In this retrospective study the results of a series of 111 patients treated between 1981 and 1986 are reported. Two patients had bilateral breast carcinoma, so the number of tumours treated was 113. The size of the tumours was measured at the time of surgery and only patients with tumours of a macroscopic diameter up to 3 cm were eligible for conservative treatment. Surgery consisted of tumorectomy and axillary node dissection. External radiotherapy was given with telecobalt equipment and 50 Gy was applied to the entire breast via two tangential fields at a rate of 2 Gy per day over 5 weeks. The ipsilateral internal mammary node chain was irradiated via a separate field at a depth of 3 cm when indicated. Tissue equivalent bolus to the skin has not been applied, due to our telecobalt irradiation.

Finally, the dose to the primary tumour site was boosted by endocurietherapy, using iridium. A tumour dose calculated at the reference isodose of the implant of 25 Gy was

given in the first years of the series (n=79) and of 20 Gy later on (n=34). The whole treatment was given over a period of 8 to 10 weeks.

In figure 3.1 the uncorrected actuarial disease-free survival is found to be 89% after 5 years. Only one of the 113 treated small breast tumours recurred locally. This recurrence occurred 17 months following therapy. Six patients died with distant metastases, 14 to 57 months, with an average of 37 months, following implantation. Five other patients developed distant metastases, 17 tot 44 months after therapy, with an average of 26 months. They are still alive without evidence of local recurrence. The cosmetic results were graded by both the radiation oncologist and the surgeon. At each follow-up visit the result was graded as good, fair, or poor. The cosmetic outcome of 79 patients who had a boost of 25 Gy was scored as good in 45 cases (57%), fair in 26 cases (33%) and poor in 8 cases (10%). The cosmetic result of 34 patients with a boost of 20 Gy was good in 18 patients (53%), fair in 14 patients (41%) and poor in 2 patients (6%).

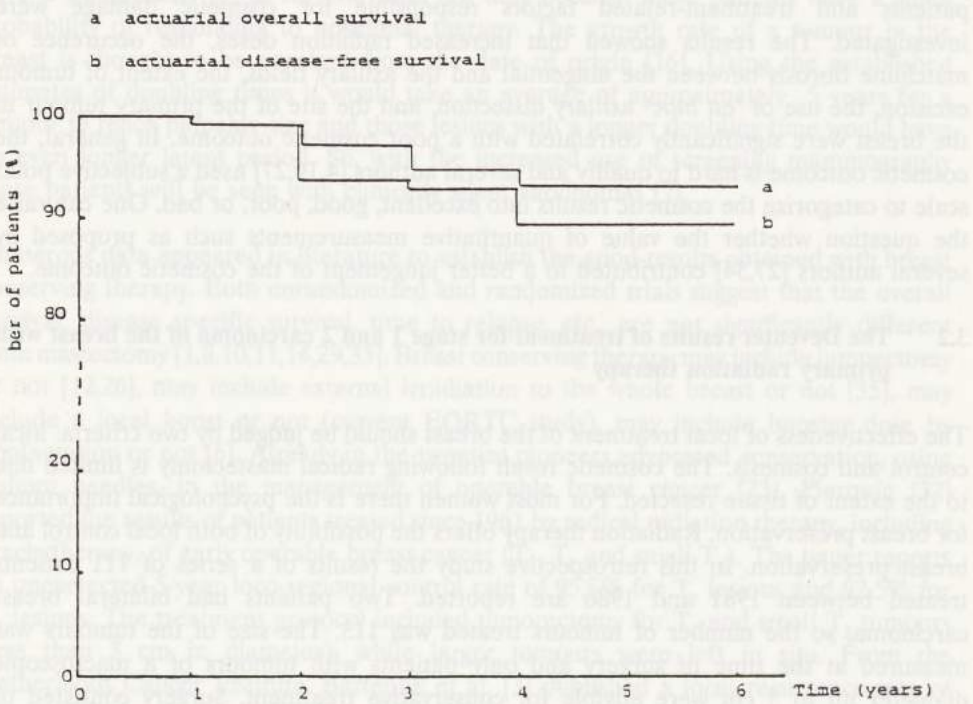

Fig 3.1 Actuarial overall and disease-free survival in a group of 113 breast tumours after conservation therapy; the Deventer experience 1981-1986.

The local-regional recurrence rate in our series was low in T_1 and limited T_2 tumours. With a minimum follow-up period of four years only one of 113 treated tumours recurred locally. Of course it is impossible to draw definitive conclusions before a longer

follow-up period has elapsed. However, in literature [10,15,17,37] good results with follow-up times of ten years are described. The cosmetic outcome of our series seems to be inferior to that described in literature [4,13,19,20,24,26,36,39], reporting a good or excellent result in 70 to 80% of stage 1 and 2 breast cancer. Differences may be the result of a different way of grading. With respect to cosmetic outcome a number of variables can be considered. In our series 20 to 25 Gy interstitial dose was added to the external beam dose of 50 Gy and that may be in agreement with the high local control rate and relatively poor cosmetic outcome [15,32,36]. In literature conflicting results are given for the influence of dose-rate on cosmesis and complication [28,36]. We found no relationship between dose-rate and cosmetic result. We should consider to reduce the total dose to the target area, for instance by reducing the dose of brachytherapy.

3.3 Comparison of dose volumes in a number of breast implantations

As stated before, one of the factors influencing cosmesis is the radiotherapy. Since Cobalt-60 beam irradiation was used for this series of patients, the dose distribution is less homogeneous than with megavoltage X-rays. Especially in larger breasts it might be an advantage to use a lineair accelerator with a photon energy of 6 to 10 MV. Harris et al.[20] noted a trend of more fibrosis and retraction in women with larger breasts. Apart from the inhomogeneity caused by the use of cobalt irradiation, differences in cosmetic outcome can also be explained by the surgical techniques and by the way of boosting. Even small differences in implantation technique will lead to large differences in dose volumes, influencing the cosmetic result of the treatment.

Implantation models

Tables 3.1 and 3.2 show for a number of source configurations the dose volumes for the reference dose and the dose volumes of the high dose areas defined as twice the reference dose (170% of the basal dose). A target volume with dimensions of 5.5 cm (l) x 4.5 cm (w) x 2 cm (t) can be treated with 7 sources of 7 cm length if the implantation is carried out in the direction of the excision scar and the implantation takes place according to a triangular configuration with a mutual source distance of 15 mm. The 4 lower needles are placed in the undermost part of the tumourbed; the 3 upper needles are located in the scar and at 15 mm from the scar on both sides. In case of a radial incision the implantation will be perpendicular to the scar. When the target volume is the same as mentioned before, 9 needles will be used in a triangular configuration with a mutual source distance of 15 mm and a source length of 5 cm. In a plane parallel to the sources and at equal distances between the source planes, both source configurations give the same area for the reference dose (fig. 3.2 a and 3.2 b). Moreover, the volume 2 x Dref is the same for both implantations. Dosimetrically there is no difference between an implantation of 7 sources of 7 cm length and 9 sources of 5 cm length when the mutual source distance is 15 mm. In practice however, when the implantation is carried out perpendicular to the scar, not a source length of 5 cm, but more likely a source length of 6 or 7 cm will be used. The increase of dose volumes of Dref and 2 x Dref is shown in the table 3.1 and in fig. 3.2. c and 3.2 d. Table 3.2 demonstrates the effect of introducing the source distance as a variable. A target volume

Table 3.1 Influence of source length

Double plane implantation, triangular configuration, mutual source distance 15 mm

	$volume\ D_{ref}$	$volume\ 2x\ D_{ref}$	$volume \frac{2x\ D_{ref}}{D_{ref}} \times 100\%$
7 x 7 cm	54.27 cm^3	5.09 cm^3	9.4 %
9 x 5 cm	50.30 cm^3	4.89 cm^3	9.4 %
9 x 6 cm	60.20 cm^3	5.48 cm^3	9.1 %
9 x 7 cm	70.89 cm^3	8.11 cm^3	8.6 %

Table 3.2 Influence of distance between sources

Double plane implantation, triangular configuration,mutual source distance 15 mm and 20 mm

	$distance$	$vol\ D_{ref}$	$vol\ 2xD_{ref}$	$vol\ \frac{2xD_{ref}}{D_{ref}} \times 100\%$	D_{ref}
7 x 7 cm	20 mm	93.13 cm^3	10.08 cm^3	10.8 %	57.30 cGy/h
9 x 7 cm	15 mm	70.89 cm^3	6.11 cm^3	8.6 %	88.02 cGy/h

of 6 cm (l) x 5.5 cm (w) can be implanted with 9 sources of 7 cm lengths at a mutual source distance of 15 mm or with 7 sources of 7 cm length at a mutual source distance of 20 mm. In a plane parallel to the sources and at equal distances between the source planes a similar dose distribution is obtained (fig. 3.3). The thickness of the implantation will be bigger in case of a mutual source distance of 20 mm than for a distance of 15 mm (26 mm and 20 mm respectively), but this difference can partially be compensated for by compression of the implantation. Nevertheless, table 3.2 shows that the volumes of Dref and 2x Dref are substantially larger for a mutual source distance of 20 mm than for a distance of 15 mm.

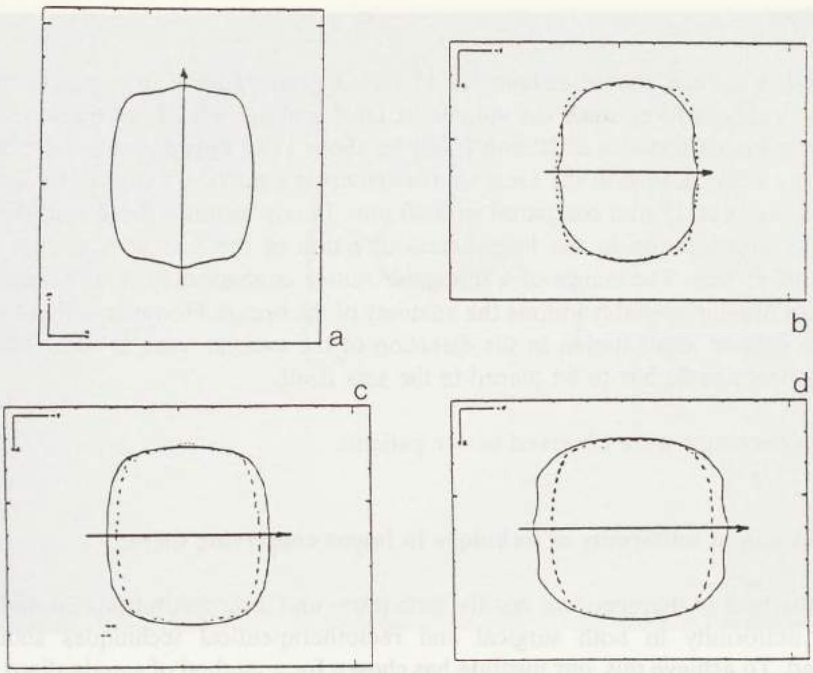

Fig 3.2 Reference isodose in a plane parallel to the sources and at equal distances between the source planes, using sources of different lengths
a. implantation of 7 sources of 7 cm in the direction of the scar,
b, c and d. implantation perpendicular to the scar,
b. 9 sources of 5 cm
c. 9 sources of 6 cm
d. 9 sources of 7 cm
The difference in treated volume is caused by difference in length or width (see table 3.1).

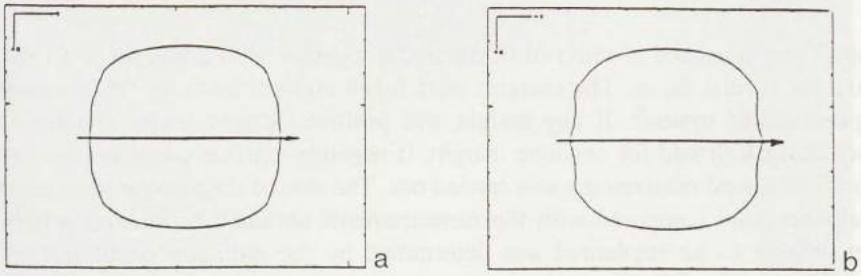

Fig 3.3 Reference isodose in a plane parallel to the sources and at equal distances between the source planes, using different mutual source distances
a. 7 sources of 7 cm, mutual source distance of 20 mm
b. 9 sources of 7 cm, mutual source distance of 15 mm
The same area is treated with 7, resp. 9 sources; the thickness of the treated volume is different (see table 3.2).

Conclusion

In general, a mutual source distance of 15 mm is preferred for an implantation in a triangular configuration, since the volume 2x Dref is about 9% of the treated volume, while for a source distance of 20 mm it will be about 11%. Furthermore the treatment time for a similar dose with the same source activity is a factor 1.5 shorter for a mutual source distance of 15 mm compared with 20 mm. In our institute these considerations led to the implantation in the longitudinal direction of the scar at a mutual source distance of 15 mm. The choice of a triangular source configuration in an implantation of a breast tumour probably follows the anatomy of the breast. However, a disadvantage is that in case of implantation in the direction of the excision scar, in some cases the upper central needle has to be placed in the scar itself.

So far no problems were observed in our patients.

3.4 An aim at uniformity of technique in breast conserving therapy

For comparison of therapeutical results, both intra- and inter-institutional, a method to achieve uniformity in both surgical and radiotherapeutical techniques should be developed. To achieve this, our institute has chosen for a method of standardised breast conserving therapy [21].

Methods and materials

Between January 1987 and December 1988 49 patients were treated by lumpectomy, per-operative interstitial irradiation and subsequent external beam therapy. In all patients a complete dissection of the axillary nodes was performed. The tumours were staged, using the UICC staging system of 1978. Included were patients with T_1 or T_2 lesions, N_0 or N_1, and M_0.

Lumpectomy

Lumpectomy consisted of removal of the tumor together with a margin of 1 to 2 cm of apparently normal tissue. The margins were inked and examined by frozen section for the presence of tumour. If any margin was positive, further tissue at that site was excised and confirmed for negative margin. If negative margins could not be obtained, a modified radical mastectomy was carried out. The size of the tumour was determined by palpation and compared with the measurements obtained on mammography. The target volume to be implanted was determined by the radiation oncologist with the tumour in situ (fig. 3.4). The radiation oncologist indicates the direction of the incision by performing the excision in the line of the volume to be implanted (fig. 3.5). Implantation can take place longitudinally in the tumour bed, so the number of sources can be reduced to a minimum, in general not exceeding 7. The tumour bed determines the booster volume.

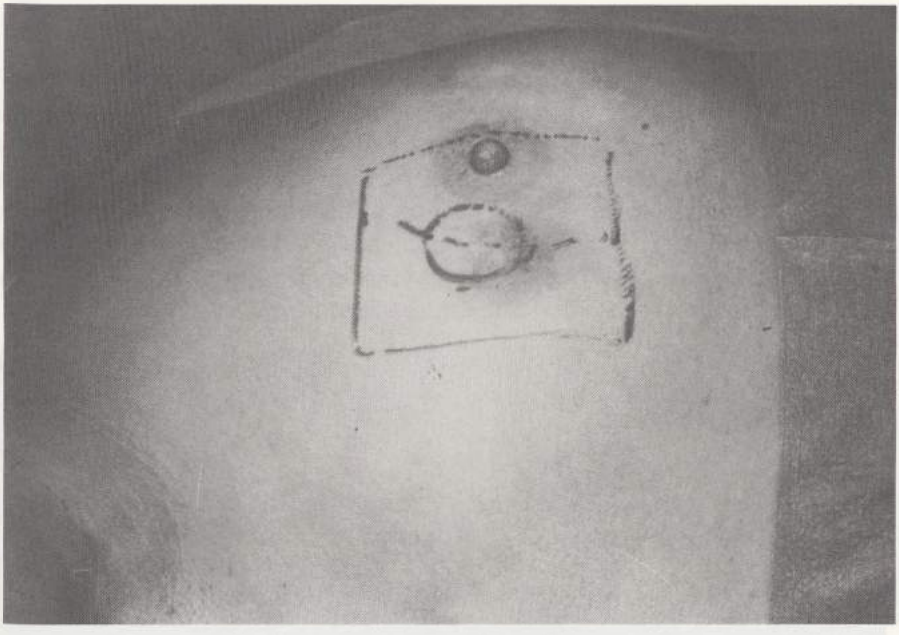

Fig 3.4 The target volume and the direction of the incision are determined while the tumour is still in situ.

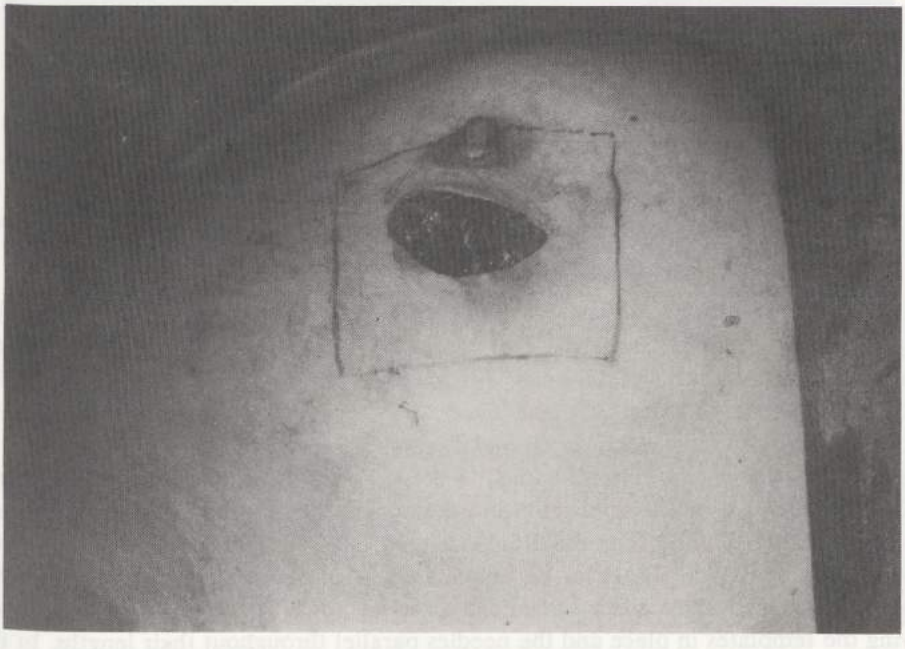

Fig 3.5 Lumpectomy with the line of incision according to the line of implantation.

Interstitial implant

Implantation is performed, using an applicator. The applicator (fig. 3.6) exists of two parallel perspex blocks, used both as needle guide and holder. Their position relative to each other can be altered by movement along two metal rods bearing a centimetre scale. The scale indicates the desired source length, taking into consideration skin conservation at the sites of entrance and exit of the needles. The needles are placed in triangles at a distance of 15 mm from each other. The length of the needles depends on the desired source length. The thick perspex blocks ensure the needles being placed at equal distances from each other in the target volume.

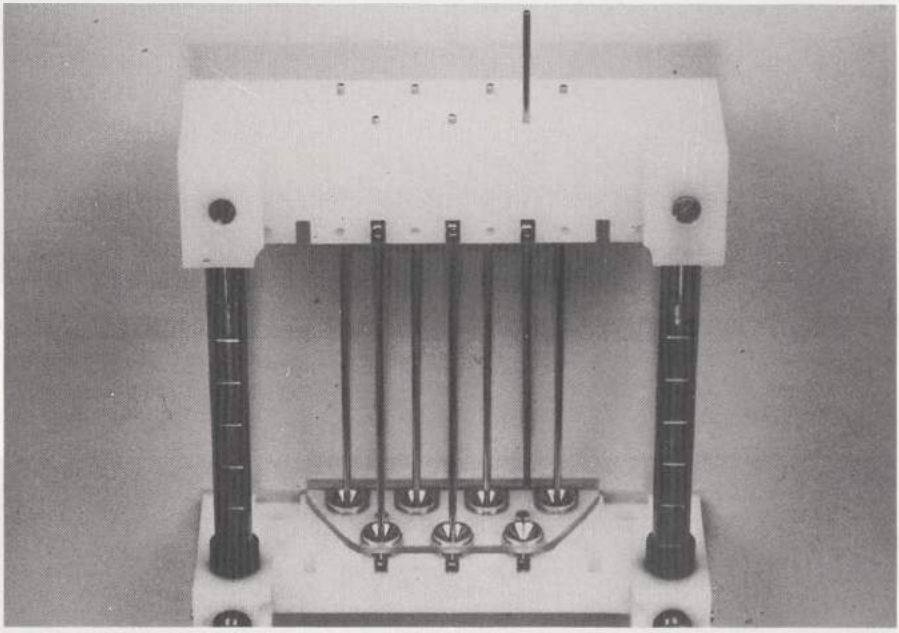

Fig 3.6 The breast applicator, two parallel gliding perspex blocks over metal rods bearing a centimetre scale.

The funnel shaped metal receivers at the opposite side accept the penetrating needles, which can be fixed with a screw. The applicator is brought into position after the lumpectomy with the wound still open. The lower four needles are placed by palpation under the tumour bed (fig. 3.7) and fixed with adjusting screws. The applicator is adjusted to the desired source length and fixed (fig. 3.8).
The wound is then closed with or without a drain. Using the perspex plate the tissue is elevated to the level of the applicator and the upper three needles are introduced and fixed in position (fig. 3.9). The middle needle comes to rest in the area of the wound. The lateral needles take care of an ample margin of 15 mm on either side of the tumour bed. Once all needles have been fixed in place the applicator is removed, leaving the templates in place and the needles parallel throughout their lengths. In this way the implantation can be carried out meticulously according to a previously designed

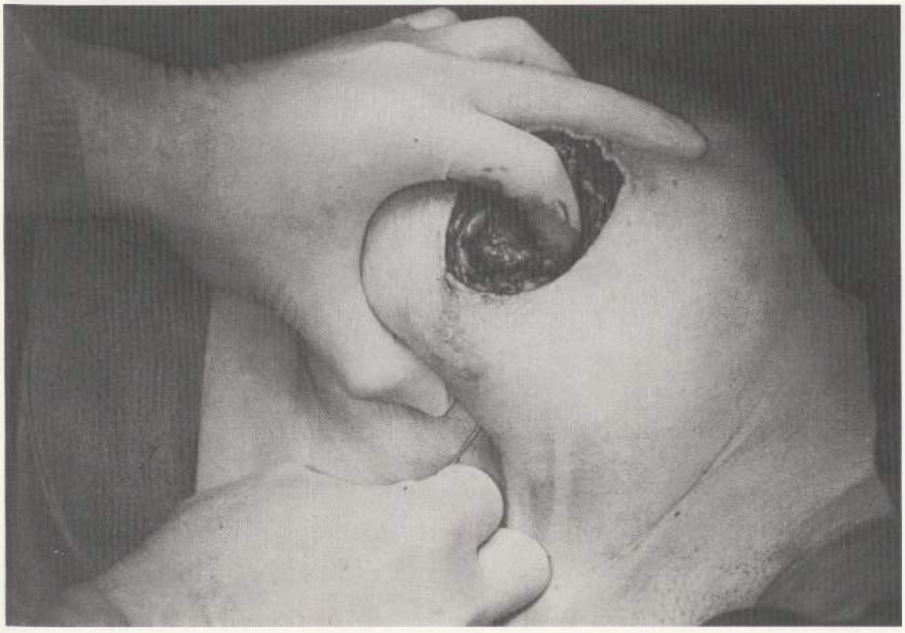

Fig 3.7 The lower row of needles is placed under the tumour bed with the wound still open.

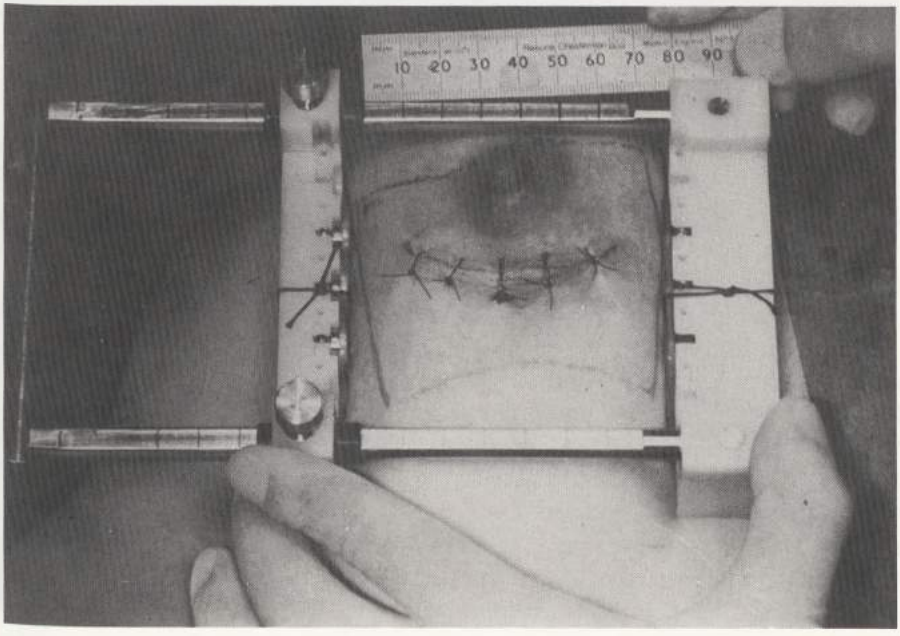

Fig 3.8 The applicator is adjusted to the desired length by compressing the tissue to be treated.

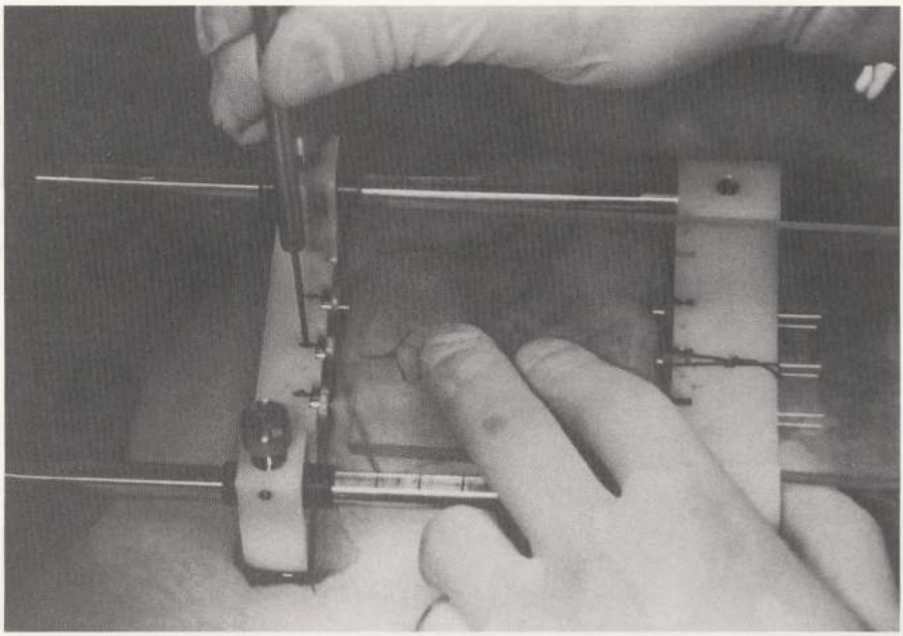

Fig 3.9 The upper row of needles is placed 0.5 - 1 cm below the skin to avoid overdosing the skin.

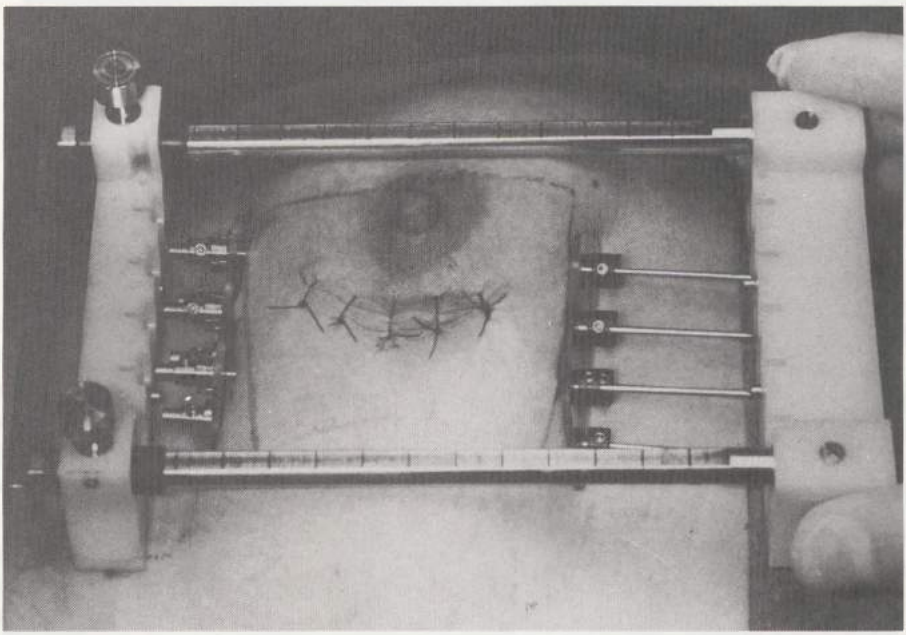

Fig 3.10 The applicator is removed.

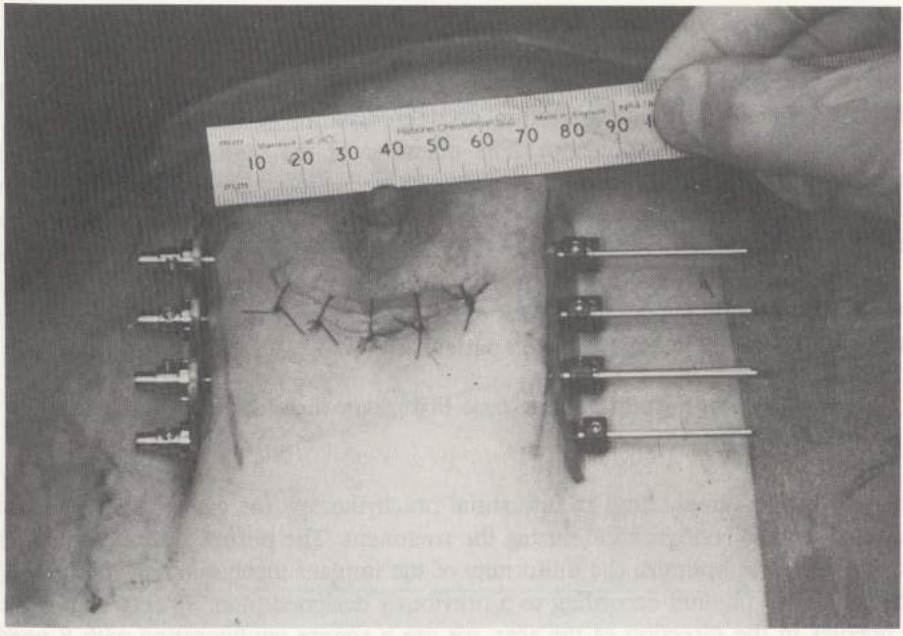

Fig 3.11 The templates are left in place to ensure parallelism and fixation of the needles. The final source lengths are determined.

plan.

Introduction of the iridium sources occurs by remote afterloading. A dose of 20 Gy is administered at the edge of the tumour bed, dosed on the 85% isodose. Lumpectomy and interstitial implantation are followed by dissection of the axillary nodes. Per-operative iridium implantation did not result in delayed wound healing in any of the patients. In one patient a blocked drain was responsible for a haematoma a couple of hours following lumpectomy and implantation. It was possible to start with external radiotherapy in all patients within three weeks after operation. No complications attributable to the combined therapy were observed.

External beam irradiation

External beam irradiation was commenced two to three weeks following operation in order to permit healing of the axillary wound and to improve mobility of the arm. The breast was treated with two tangential cobalt fields to 50 Gy at 2 Gy fractions during a period of 5 weeks. Wedges were used to ensure homogeneous dose distribution throughout the entire breast. The dose was specified according to the UICC recommendations. The ipsilateral internal mammary lymph chain was irridiated with an AP-field in appropiate cases. In these cases there was an overlap of 0.5 cm between the medial tangential and the parasternal internal fields.

The so-called Paris system of dose distribution (Chapter 1) is employed. The rules of the Paris system regarding parallelism and equidistance of the radioactive lines are guaranteed by using an applicator. The diameter of the high dose areas (2x Dref) immediately surrounding the sources is determined almost exclusively by the mutual distance of the sources. In case of a double level implant this diameter measures about 6 mm for a mutual source distance of 20 mm and 4 mm for a mutual source distance of 15 mm. The tissue to be treated is compressed in the applicator. This makes it possible to work with a fixed source distance of 15 mm, so no marked differences in size of the high dosage area exist between patients.

3.5 The Anderson natural volume-dose histogram in interstitial brachytherapy for breast carcinoma

Templates are routinely used in interstitial brachytherapy for cancer of the breast to guarantee a fixed configuration during the treatment. The purpose of an applicator in this situation is to optimize the uniformity of the implant technique and the possibility to carry out the implant according to a previously designed plan. Since we are placing the needles in the direction of the scar, we use a square configuration with 8 needles instead of the usual triangular configuration.
The natural volume-dose histogram of an implant with 7 needles at a source distance of 15 mm in a triangular configuration (fig. 3.12) is compared with an implant of 8 needles with a source distance of 15 mm in a square configuration (fig. 3.13). The histogram shows that the value of the quality index (QI) of the implant in a square configuration is increased compared to the triangular configuration. No significant differences in dose homogeneity can be observed between the two implants.

In fig. 3.14 and fig. 3.15 the natural volume-dose histogram of an implant of 9 needles of 7 cm and a source distance of 15 mm in triangular configuration is compared with an implant of 7 needles of 7 cm with a source distance of 20 mm. As shown in fig. 3.16 the surface of the reference dose is the same in both implants, as is the quality index. Table 3.2 shows an average volume of 2x Dref of 6.11 cm^3 in case of 9 needles and 15 mm source distance and an average volume of 10.08 cm^3 in case of 7 needles with a source distance of 20 mm.
The Anderson natural volume-dose histogram can be a useful parameter to express the degree of dose homogeneity within a treatment volume by using templates and rigid needles in interstitial brachytherapy. In case of breast implants the histograms demonstrate in all cases almost complete agreement with a planned situation [40].

3.6 Discussion

In general, high doses for larger tumour volumes will lead to higher complication rates in normal tissues [5,20,24]. The main advantage of interstitial therapy is the rapid fall off of the dose outside the treatment volume. In boost treatments given at the end of the external beam treatment, the implant volume is determined by the position of the

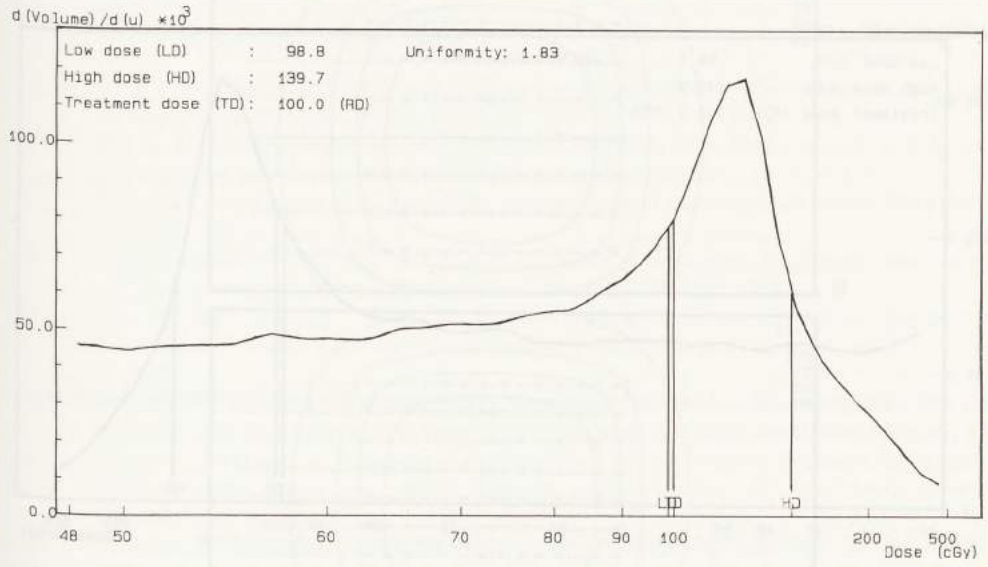

Fig 3.12 Natural volume-dose histogram for a triangular configuration of 7 needles of 7 cm length and a mutual source distance of 15 mm.

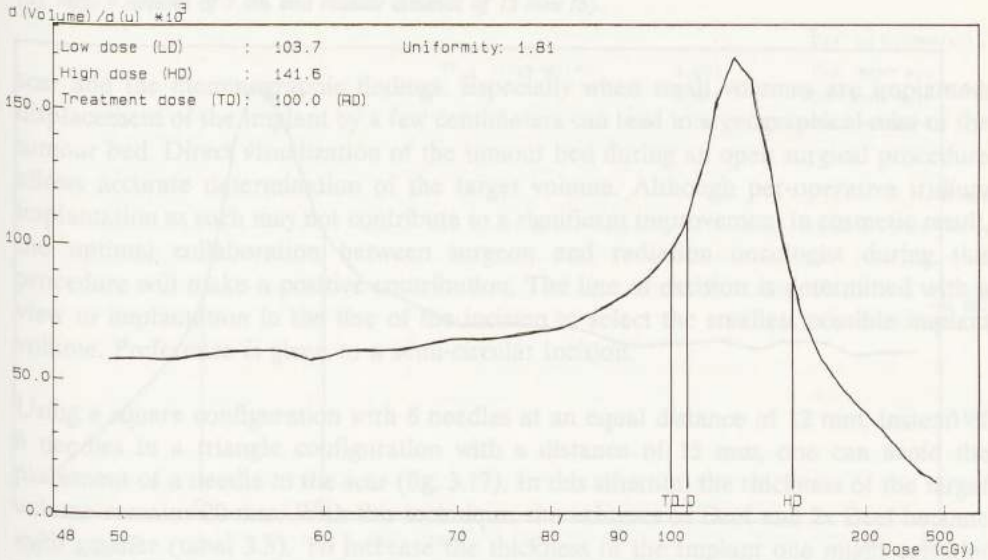

Fig 3.13 Natural volume-dose histogram for a square configuration of 8 needles of 7 cm length and a mutual source distance of 15 mm.

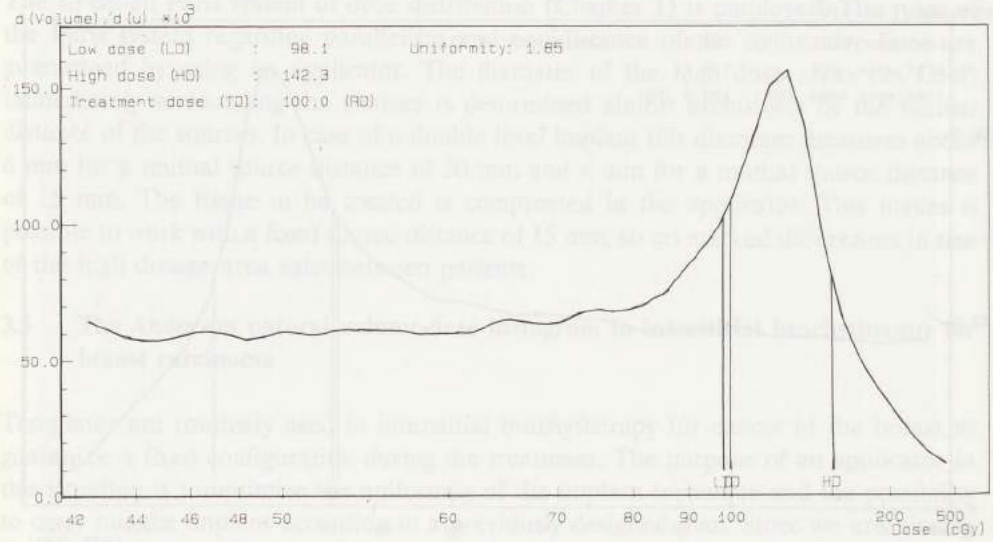

Fig 3.14 Natural volume-dose histogram for a triangular configuration of 9 needles of 7 cm length and a mutual source distance of 15 mm.

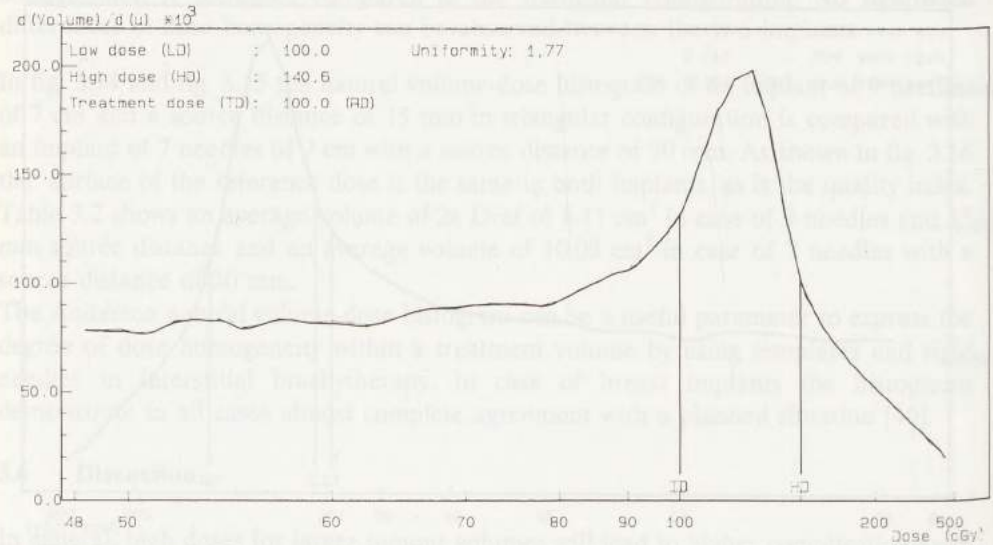

Fig 3.15 Natural volume-dose histogram for a triangular configuration of 7 needles of 7 cm length and a mutual source distance of 20 mm.

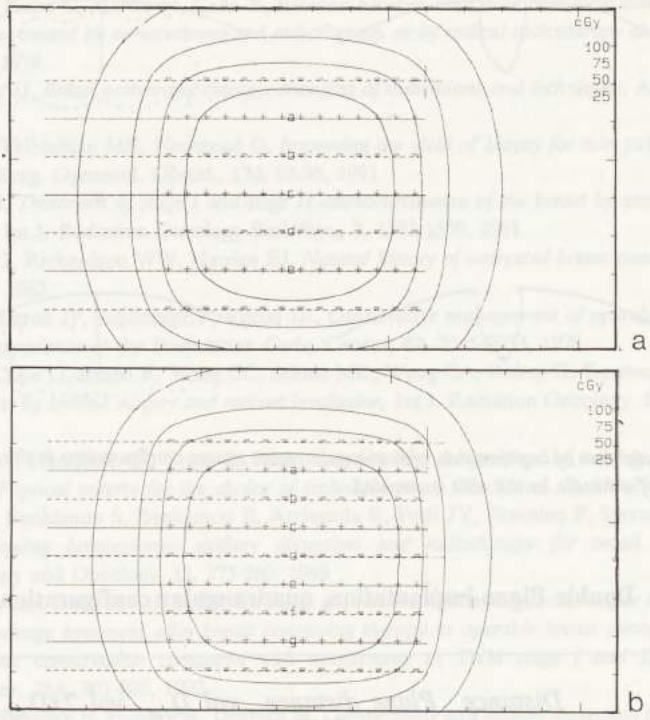

Fig 3.16 Isodose distribution of triangular configuration with 7 needles of 7 cm and mutual distance of 20 mm (a), resp. 9 needles of 7 cm and mutual distance of 15 mm (b).

scar and the mammographic findings. Especially when small volumes are implanted, displacement of the implant by a few centimeters can lead to a geographical miss of the tumour bed. Direct visualization of the tumour bed during an open surgical procedure allows accurate determination of the target volume. Although per-operative iridium implantation as such may not contribute to a significant improvement in cosmetic result, the optimal collaboration between surgeon and radiation oncologist during this procedure will make a positive contribution. The line of excision is determined with a view to implantation in the line of the incision to select the smallest possible implant volume. Preference is given to a semi-circular incision.

Using a square configuration with 8 needles at an equal distance of 12 mm, instead of 6 needles in a triangle configuration with a distance of 15 mm, one can avoid the placement of a needle in the scar (fig. 3.17). In this situation the thickness of the target volume remains 20 mm. With this technique, the volumes of Dref and 2x Dref become even smaller (tabel 3.3). To increase the thickness of the implant one might consider to increase the distance between the lower and upper source plane from 12 tot 15 mm. Although this technique is not in accordance with the Paris system, an increase in target volume thickness from 20 to 25 mm can be obtained with very acceptable volumes of

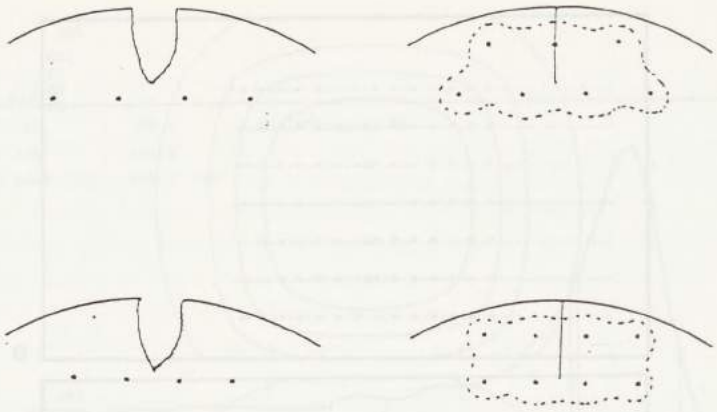

Fig 3.17 Schematic view of implantation with triangular, resp. square configuration; in the square configuration the placement of a needle in the scar is avoided.

Table 3.3 Double Plane implantation, quadrangular configuration

	Distance	*Plane distance*	*vol D_{ref}*	*vol $2xD_{ref}$*
8 x 7 cm	12 mm	12 mm	47.84 cm^3	4.06 cm^3
8 x 7 cm	12 mm	15 mm	59.16 cm^3	4.81 cm^3

Dref and 2x Dref.

In summary, per-operative interstitial implantation avoids geographical misses and will spare normal tissues. In other words, this technique will improve local control and cosmetic outcome [25].

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CHAPTER 4

SOLITARY BLADDER TUMOURS

4.1 Introduction and review of the literature

Bladder cancer is a disease of the sixth to eighth decade of life. It is the fifth leading cause of cancer death among men over age 75, responsible for 5% of cancer deaths in this age group in the United States [15]. In the Netherlands the incidence was 1597 males and 439 females with invasive bladder cancer, while 1127, respectively 275 patients had a non-invasive tumour. Of these groups, 782 males and 297 females died of their cancer [10]. Investigations over the years have shown a relationschip between bladder cancer and aniline dye, paint, rubber and cable industries, smoking, nitrates in smoked meat and some analgesics [6]. Transitional cell carcinoma is the most common histological type in the western world (75 to 85 %), squamous cell carcinoma has an incidence of 5 to 10% originating in areas of squamous metaplasia, schistosomiasis and perhaps carries a poorer prognosis. Adenocarcinomas compose only 1 to 4% of all bladder tumours [6]. Prognostic factors include stage, grade and tumour size [1,9,19].

For low grade and low stage carcinomas of the bladder the methods of treatment are transurethral resection (TURT), laser destruction and photodynamic therapy, intravesical therapy with cytotoxic drugs (Mitomycin-C and Doxorubicin) and with non-specific immunotherapy (BCG), segmental resection or interstitial implantation. For high staged tumours total cystectomy and external beam irradiation are used.
For interstitial implantation the tumour should be solitary, well localized, with a total area not more than 5 cm in diameter and accessible for implantation. The treatment method was introduced in the Netherlands by Breur in 1951 [5]. Nowadays interstitial therapy is an accepted method of treatment in the management of localized bladder cancer. Using radium needles Van der Werf-Messing showed good long term survival, not only for patients with superficial tumours T_1 and T_2, but also for those with T_{3a} tumours, if the size of the tumour was limited to 5 cm and if external irradiation produced a stage reduction [17,18]. In the Netherlands interstitial implantation is highly recommended by Van der Werf-Messing and Battermann [2,3] for treatment of suitable stage T_1 and T_2 carcinomas. They showed that bladder implantation produced excellent tumour control (over 80%) with acceptable morbidity. Encouraged by these results other Dutch radiotherapy centres started using this technique.

4.2 Treatment of bladder cancer with radium needles, a retrospective study

In the early seventies interstitial implantation in the treatment of solitary bladder cancer was introduced in Deventer. The objectives of the study were to evaluate treatment toxicity and tolerance, as well as the local tumour control rate and the incidence of distant metastases. Criteria for patient selection included solitary leasion, diameter not more than 5cm and primary tumour, staged T_1 or T_2 [16]. No evidence of carcinoma in situ should be present by random biopsies.

From 1974 through 1984 in Deventer 46 patients with a solitary bladder tumour were treated by interstitial radium implantation, after a short course of external irradiation. There were 15 patients with a T_1 tumour and 31 patients with a T_2 tumour (however,

in the T-category T_2 both T_2 and T_{3a} tumours are included because the clinical difference between these stages is hard to make and the histological findings are often not conclusive). The age varied from 37 to 84 years with an average of 65 years. Tumour diameter varied from 0.5 to 6.0 cm with an average of 2.8 cm. All tumours were histologically proven transitional cell carcinomas. Following three fractions of 3.5 Gy external irradiation, given via two opposed fields, a suprapubic cystotomy was performed. Radium needles with different lengths were used with a total activity of 8 to 34 mCi and an average of 20 mCi. A single plane implantation technique was used (fig. 4.1). Following implantation, the bladder was closed around a suprapubic catheter and a drain through which the threads of the needles passed the anterior abdominal wall. A reconstruction was made using orthogonal radiographs. A typical dose of 60 Gy was applied at the reference isodose on the basis of the computer calculated isodose lines covering the target area with a safety margin of about 5 mm. Typical application times for a tumour dose of 60 Gy varied from 48 to 167 hours with a median of 86 hours. After completion of the treatment time the needles were removed by pulling the threads. The results were evaluated in 1989, so the minimum follow-up period was 5 years.

Persisting local control for patients with T_1 tumours was 87% and for patients with T_2 tumours 74% (table 4.1). 11 patients died with distant metastases. The number of patients with distant metastases increased with increasing tumour stage. The hospitalization time from the day of operation varied from 15 tot 69 days, with an average of 29 days. In 5 patients a delayed wound healing occurred after removal of the drain, 4 patients suffered from a prolonged urinary leakage and 2 patients developed a bladder fistula requiring surgery. These 11 patients were responsible for the longest hospitalization times, 26 to 69 days with an average of 41 days. In one patient a

Table 4.1 Results of bladder implantation using radium needles in 46 patients in the period 1974-1984

Stage	T_1	T_2
Total number	15	31
alive and well	8	8
deceased of:		
intercurrent disease	4	5
metastases	1	10
local tumour	2	8
persisting local control	87%	74%

cystectomy was performed 5 years after implantation because of stone formation and bladder shrinkage. All other patients retained a normal bladder function.

The results of this retrospective study are in accordance with the results of others for T_1 and T_2 tumours [3,7,14,17,18]. The local control rate was high for T_1 and T_2 tumours. In our group of patients the incidence of acute side effects, mainly caused by disturbed wound healing and urinary leakage, is relatively high (24%), resulting in a longer time of hospitalization. Radium implantation for solitary bladder tumours preceded by 10.5 Gy external irrdiation to the pelvis, offers a good chance of local tumour control. The radiation dose delivered to the target volume seems to be sufficient.

4.3 A comparison between the Paterson and Parker rules of implantation and the Paris system

The principle of bladder implantation is in all cases a "single plane" implant. Both radium and caesium needle or iridium wire implants are possible and effective. Because the treated volume will vary with different source lengths and separations it is important to know the relationship between source distribution and volume.
In the Paterson and Parker system (Chapter 1) the rules of implantation for radium needles ensure a uniform dose with no more than 10% variation at a distance from the sources, which is usually specified as 0.5 cm. A single plane arrangement is usually rectangular in form (fig. 4.1), composed of parallel needles and two cross needles. The needles in the periphery should be of greater linear activity than those of the interior. A disadvantage of the Manchester system is the use of different linear activities within one implant, which easily leads to errors. Therefore, in many centres needles with equal activity were used, although this resulted in a higher central activity of the implant to avoid hot spots in the centre.

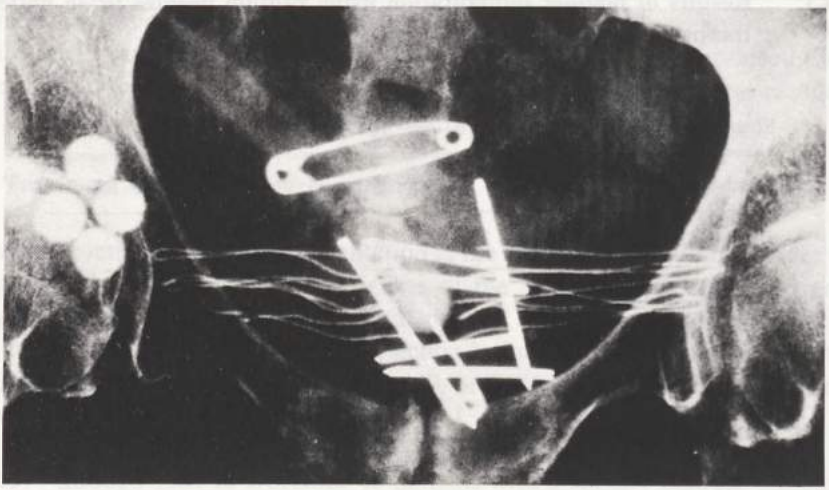


Fig 4.1 Localization films of bladder implantation using radium needles in a single plane configuration.

In the Paris system [11,12] the dosimetry is determined by the dose distribution in a plane in the centre of the implant, rather than based on a plan outside the sources, which defines the treated volume. The distribution rules also differ and, unlike the Paterson and Parker rules, the separation recommended for iridium wires may vary with the length and number of sources implanted and in general cross wires are not used at the ends. In the Paris system it is sonsidered that the length of the treated volume is about 70% of the length of the active lines. This corresponds to a 15% decrease of the treated length and therefore of the treated volume at each end. The thickness of the treated volume varies with the spacing between the sources. The mean thickness is equal to 60% of the spacing. The width of the treated volume is equal to the distance between the most lateral sources plus 37% (lateral margins) of the separation between the sources added on to each side. These rules are used to determine the target volume.

For a similar source arrangement, the planned target volume is thinner with the Paris system than with the Manchester system, and accordingly the Paris reference dose-rate is higher. Hence this might result in differences in source arrangements for the same target volume. Using a tumor model with a target volume of 5.5 cm length x 3 cm width

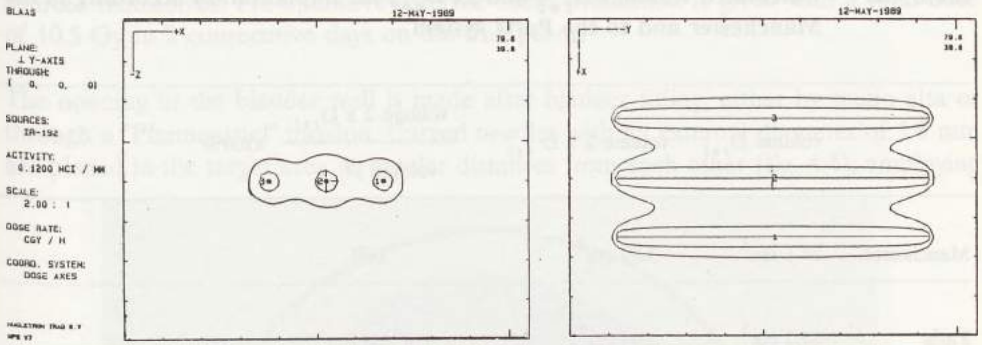


Fig 4.2 Isodose distribution according to Paris system for a tumour model, using 3 sources.

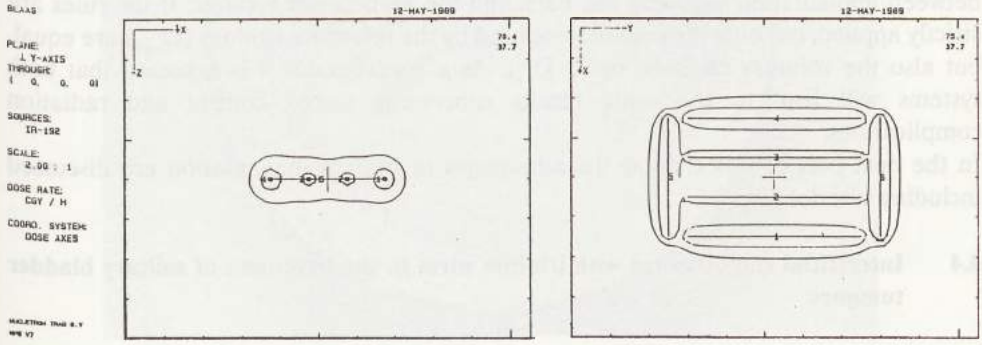


Fig 4.3 Isodose distribution according to Manchester system for same tumour model, using 6 sources.

x 1 cm thickness, according to the Paris system it will be implanted with three sources of equal lineair activity, placed parallel with a mutual distance between the sources of 15 mm and a source length of 8 cm (fig. 4.2). Following the Manchester system this volume will be implanted with 4 parallel sources at a mutual distance of 10 mm and with an active length of 4.5 cm, combined with two cross needles with an active length of 3 cm. The linear activity of the sources in the centre of the implantation amounts 2/3 of the activity of the peripheral sources (fig. 4.3).

Table 4.2 presents the calculated volumes enclosed by the reference isodoses and the calculated volumes of the high dose areas (2x D_{ref}). However, in the Manchester system the peripheral sources should be implanted on the outer surface of the target volume, while in the Paris system the size of a safety margin which is the minimum distance between the peripheral source and the reference isodose, is given as a fraction of the spacing between sources. It corresponds to 2 -4 mm and it is recommended in clinical practice to implant the peripheral sources on the outer surface of the target volume, as in the Manchester system.

Table 4.2. Calculated volumes D_{ref} and 2x D_{ref} for implantation according to the Manchester and to the Paris system

	volume D_{ref}	volume 2 x D_{ref}	$\frac{\text{volume 2 x } D_{ref}}{\text{volume } D_{ref}}$ x100%
Manchester	24.1 cm^3	3.89 cm^3	16%
Paris	27.2 cm^3	4.66 cm^3	17%

The ratios between the volumes, expressed in percentages, show hardly any difference between implantation following the Paris and the Manchester systems. If the rules are strictly applied, not only the volumes enclosed by the reference isodose (D_{ref}) are equal, but also the volumes enclosed by 2x D_{ref}. As a consequence it is expected that both systems will lead to the same results concerning tumor control and radiation complications.
In the next part of this chapter the advantages of iridium implantation are discussed including afterloading.

4.4 Interstitial radiotherapy with iridium wires in the treatment of solitary bladder tumours

Mazeron, et al. [8] described the Créteil technique in which afterloading with iridium-192 replaced radium or caesium needles. This technique uses hollow nylon outer tubes

whose ends are collected together and brought through the bladder and abdominal wall to be fixed to the skin. Later, iridium sources, each closed in an inner tube, can be introduced through these outer tubes. A possible disadvantage of this technique is that for a bundle of 4 outer tubes, an opening in the bladder wall of about 0.5 cm in diameter is still required. Therefore, removal of the tubes may be followed by slow healing and prolonged hospitalization. A modification of the Créteil technique was introduced in Deventer in 1984. By conducting the implant tubes separately through the bladder and abdominal wall, the risk of development of a vesico-cutaneous fistula was diminished. With the use of conical spacers specially designed for this purpose, equidistance and parallelism between the tubes implanted was ensured.

Implantation technique

Implantation is preceded by an implantation plan, using clinical information regarding the dimensions of the target volume obtained by cystoscopy. The number of sources, their distance and length are determined according to the Paris rules of a single plane implant. In general 2 or 3 sources, 10 mm apart and 4 to 6 cm long are sufficient. The matching dose distribution is calculated in the central plane and in the plane of the sources themselves. Pre-operative external beam irradiation is given with a total dose of 10.5 Gy in 3 consecutive days on the true pelvis.

The opening in the bladder wall is made after bladder filling, either by sectio alta or through a "Pfannenstiel" incision. Curved needles with an external diameter of 1.6 mm are placed in the target area at regular distances from each other (fig. 4.4), employing

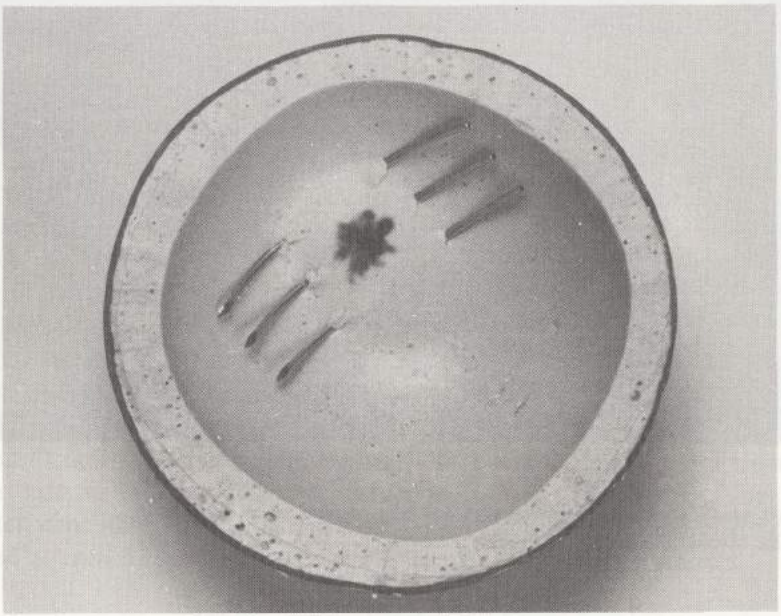
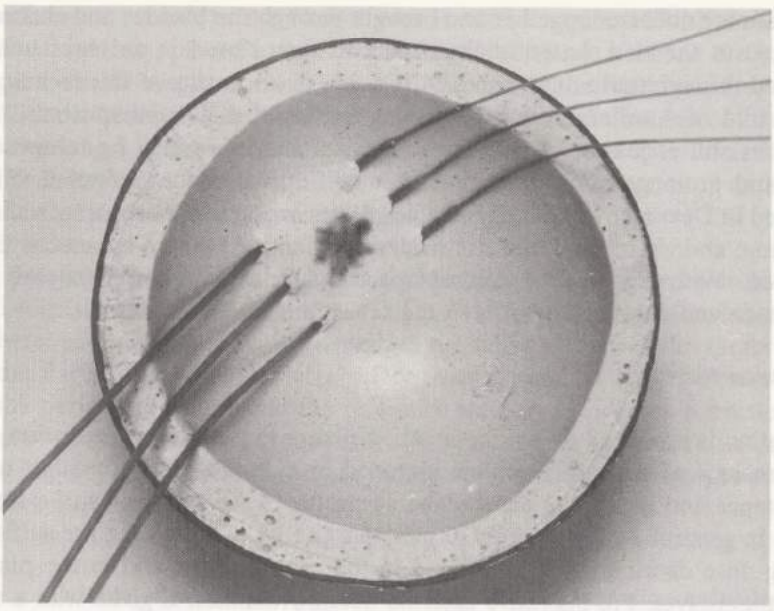


Fig 4.4 Slightly bended needles with an external diameter of 1.6 mm are placed in the target area at regular distances from each other.



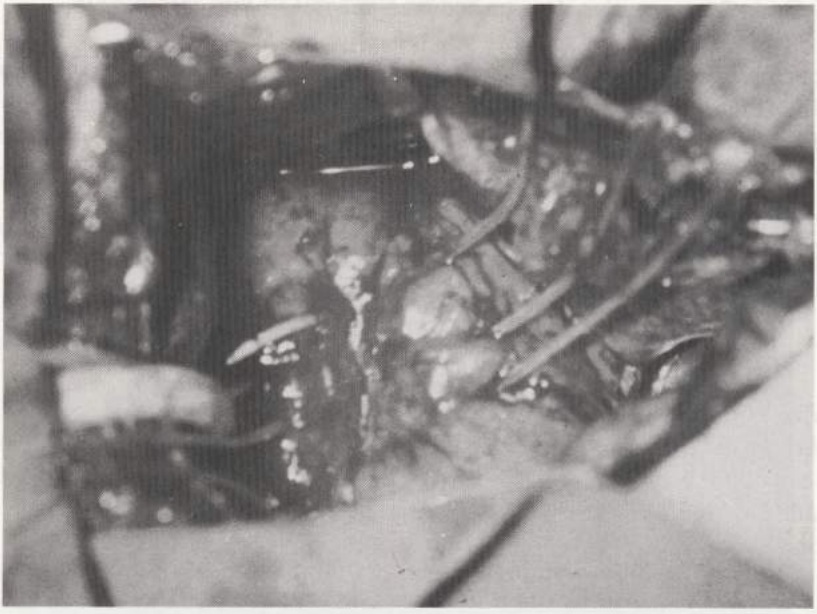


Fig 4.5 Each needle is replaced by an outer nylon tube (double leader tube). (a) shows the tumour model (b) the in vivo situation.

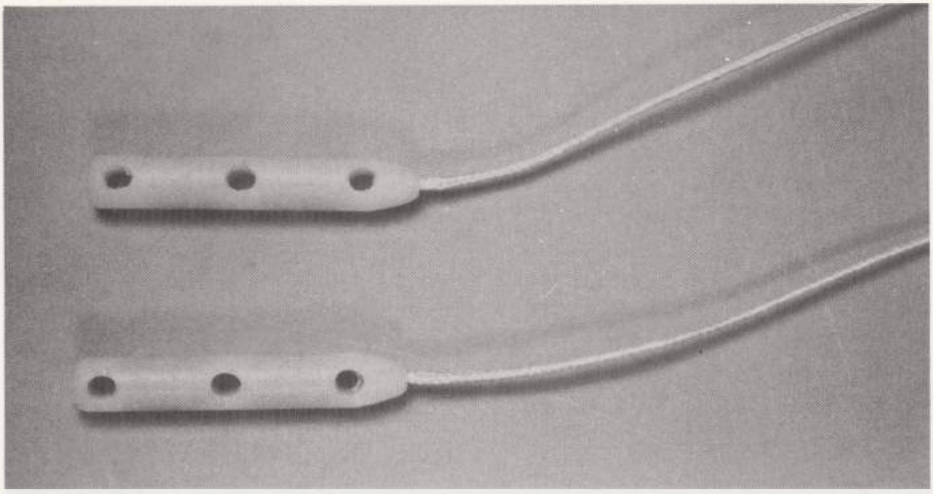


Fig 4.6 Conically shaped leaders ("spacer") with openings every 10 or 12 mm are used to ensure parallelism of the tubes.

a specially constructed needle-holder. The number and length of the needles is determined by the size of the tumour. The distance between the needles is determined using the Paris system as a guide. Once the needles are properly introduced, each one is replaced by an outer nylon tube of 1.6 mm external diameter with a leader at both ends whose external diameter is 0.7 mm (fig. 4.5).

To ensure the parallelism after closure of the bladder the nylon outer tubes are conducted through spacers specially designed for this purpose (fig. 4.6). These conically shaped leaders have a diameter of 4.5 mm with conducting openings every 10 or 12 mm, as desired. A metal nucleus permits radiological localization (fig. 4.7). From the top of the cone a thread is led outside through the urethra (fig. 4.8).

The two ends of the nylon tubes are led separately through the bladder and abdominal wall via a straight needle, paying special attention to the maintenance of parallelism. In this way a number of small openings are made in the bladder and abdominal wall instead of one large opening (fig. 4.9). Both ends are fixed by a button and sutured to the abdominal wall, on one side the thin leader and on the other side, after cutting the leader, the outer tube. A lead dummy sealed in an appropriate length of inner nylon tubing is placed into the outer tube to mark the target volume (fig. 4.10). Having confirmed that all dummies are properly situated, the bladder and the abdominal wall are closed. Orthogonal photographs (fig. 4.11) of the lead dummies in situ are made and with this information a special reconstruction is made (fig. 4.12) of the implant. Thereafter, depending on the configuration of the reconstruction, dose distributions are calculated at each 0.5 cm or 1 cm in planes at right angles to the sources.

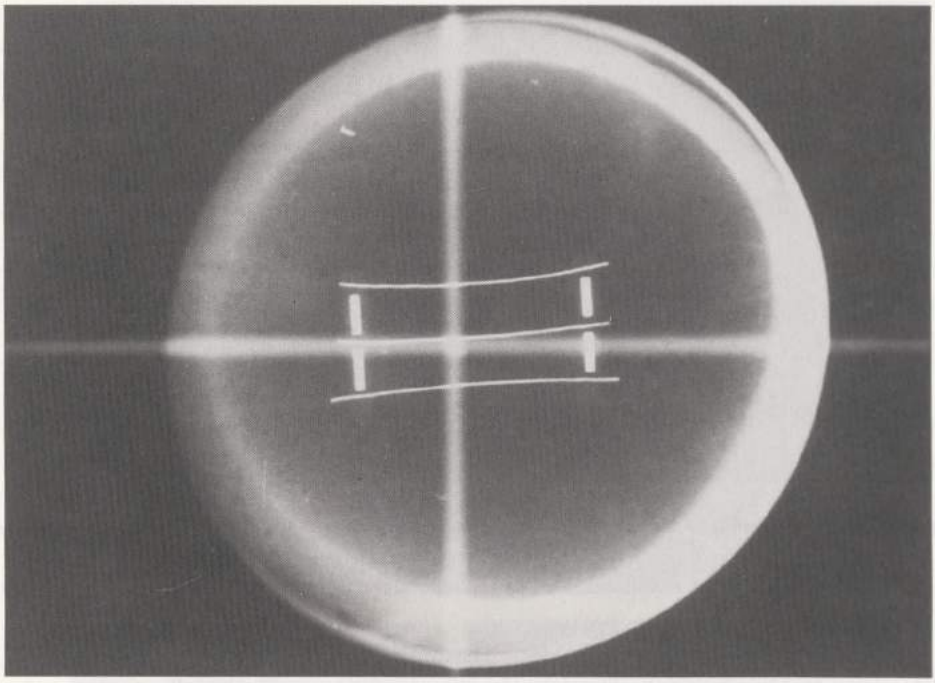


Fig 4.7 The metal nucleus in the spacers permits X-ray visualization.

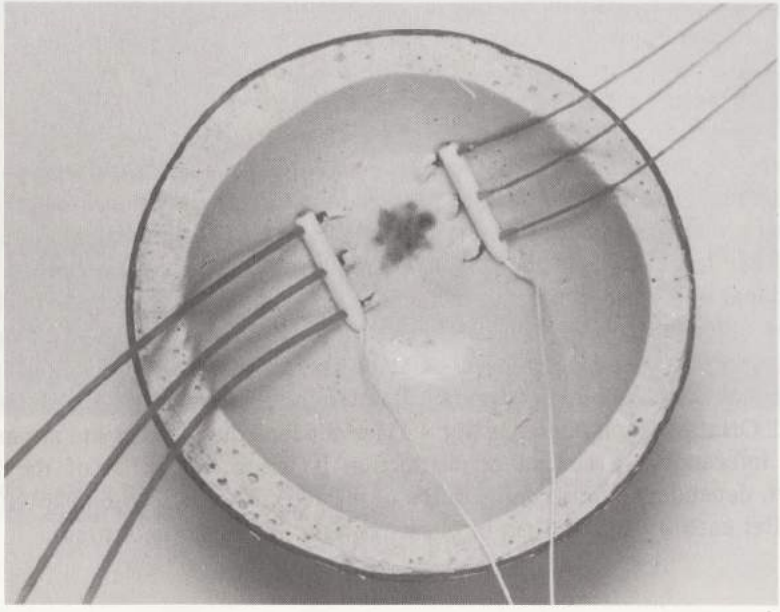


Fig 4.8 The threads from the spacers are led outside through the urethra.

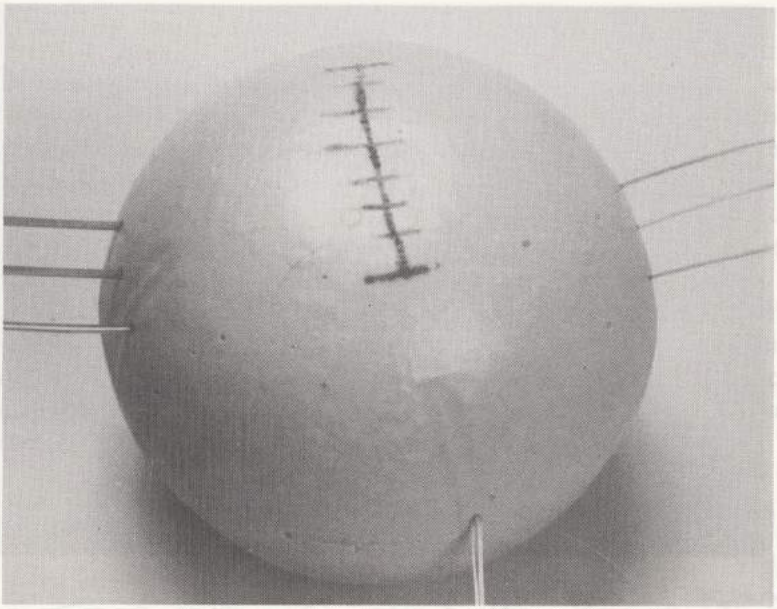


Fig 4.9 The tubes are conducted separately through the bladder and abdominal wall.

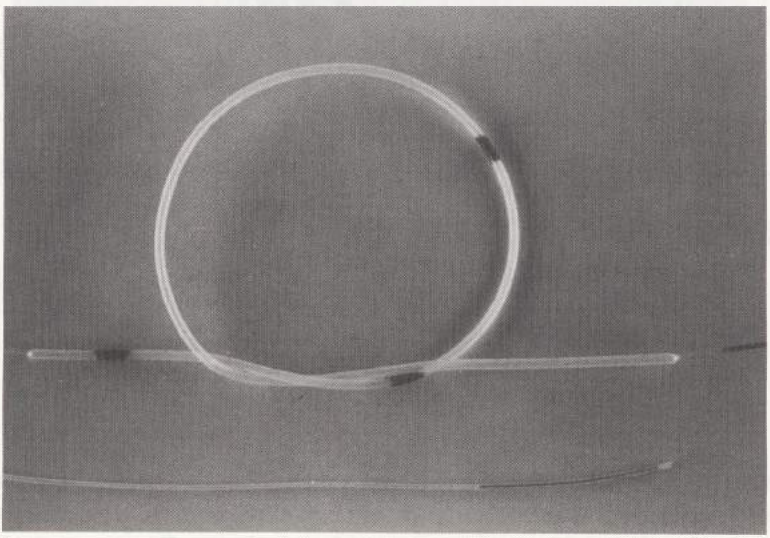


Fig 4.10 A double leader outer tube and a lead dummy sealed in inner nylon tubing.

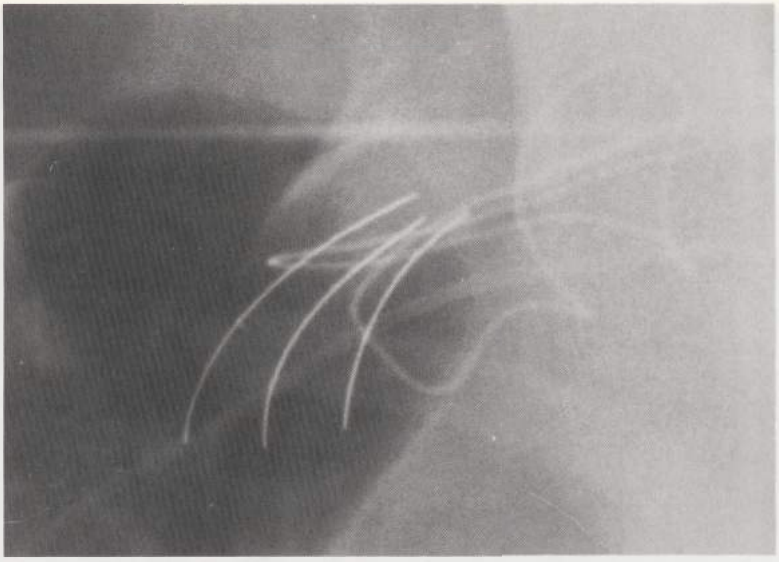


Fig 4.11 Localization film of the dummy sources.

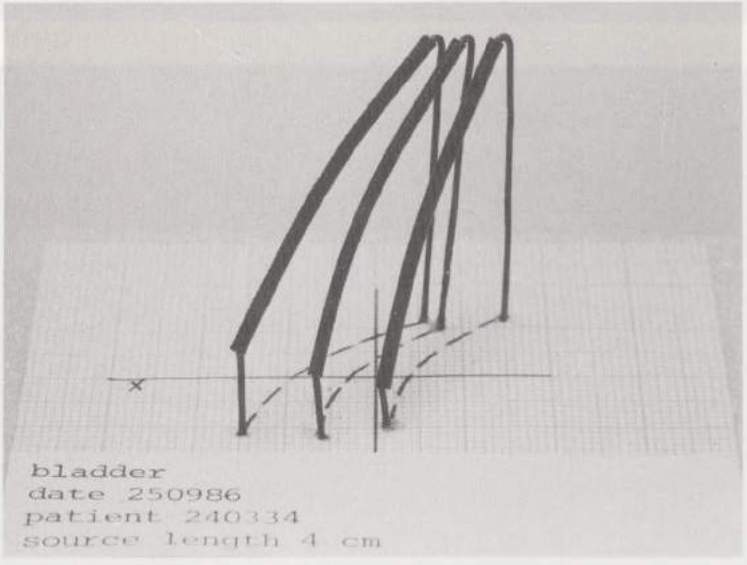


Fig 4.12 Reconstruction of the implant.

Dosimetry

The three-dimensional representation of the dose distribution round the sources (fig. 4.13) obtained in this way provides information regarding the dose-homogeneity in the implanted volume and leads to determinaton of the reference isodose. Thereafter the treatment time is calculated. The reference isodose varied from 60 cGy/hr to 90 cGy/hr which means for a dose of 6000 cGy a radiation time from almost 3 days to a little more than 4 days. Finally the dummies will be replaced by iridium wires, either by hand or by remote afterloading.

At the end of the treatment time, after removal of the radioactive wires, the nylon tubes are removed by a slight traction on the outer tubes once the sutures have been cut and the protruding parts desinfected. After complete healing of the bladder incision the conical leaders are pulled out of the bladder through the urethra after removal of the Foley catheter.

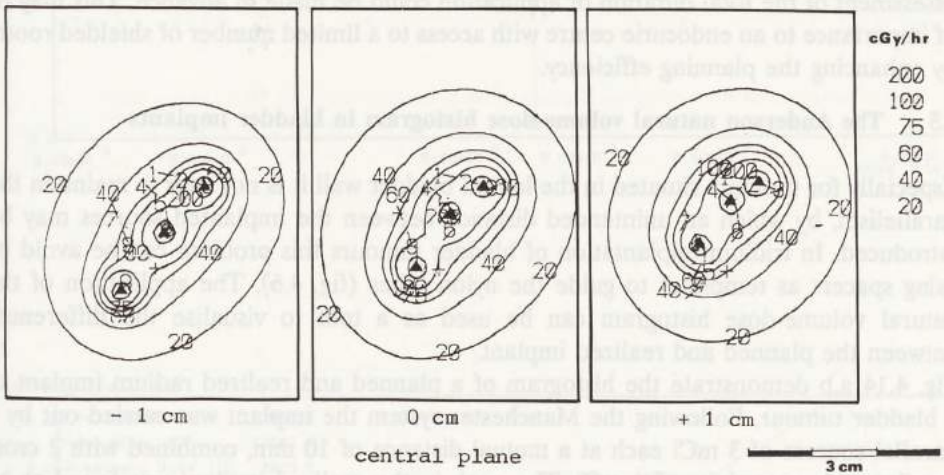


Fig 4.13 Typical dose distribution of a single plane implant with 3 sources.

Results

Of 15 patients treated during the years 1984 - 1987, one died 6 months after implantation as a result of disseminated blood-borne metastases. At autopsy the bladder was free from tumour. One patient underwent cystectomy 10 months after implantation at her own request because of the adverse influence of the diminished bladder capacity to her social life. This patient had undergone extensive intra-vesical treatments with Mitomycin on account of bladder papilloma. In this case, the bladder was also found to be free from tumour on histological examination. The remaining 13 patients are well and free from tumour or side effects. In no patient the period of hospitalization exceeded 14 days. No complications related to delayed wound healing were seen. The

soft and fine nature of the materials allowed them to be removed easily at the end of the treatment period.

Of course the period of follow-up is too short and the number of patients as yet to small to permit comparison with larger series such as those of Van der Werf-Messing [17,18] and Battermann [2,3]. We do not anticipate that the use of iridium will lead to a better tumour control. The aim here was to develop a reliable afterloading technique with less likelyhood of complications and, hence, reduced hospitalization. The average duration of hospitalization following radium implantation is four weeks [2], in our current series fourteen days. In addition to the short period of admission to the hospital, our modified technique is also suitable for the treatment of tumours of the bladder neck.
All of our patients experienced bladder cramps during the treatment period which responded to symptomatic treatment. In the majority of cases the value of the reference dose agreed with that forecasted by the pre-implantation plan, so an accurate assessment of the total duration of application could be made in advance. This may be of importance to an endocurie centre with access to a limited number of shielded rooms by enhancing the planning efficiency.

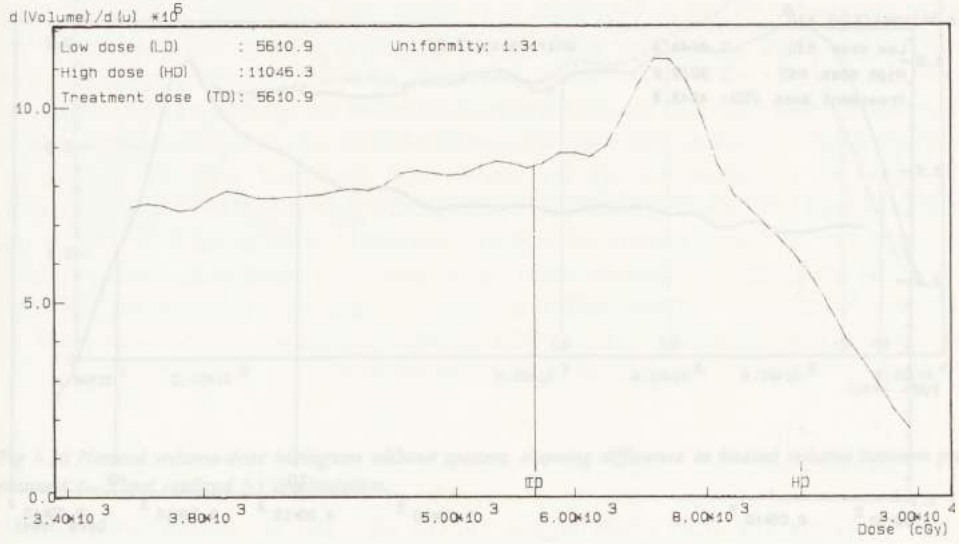
4.5 The Anderson natural volume-dose histogram in bladder implants

Especially for tumours situated in the lateral bladder wall it is not easy to maintain the parallelism, by which an unintended distance between the implanted sources may be introduced. In iridium implantation of bladder tumours this problem can be avoid by using spacers as templates to guide the nylon tubes (fig. 4.6). The application of the natural volume-dose histogram can be used as a tool to visualise the differences between the planned and realized implant.
Fig. 4.14 a,b demonstrate the histogram of a planned and realized radium implant of a bladder tumour. Following the Manchester system the implant was carried out by 4 parallel sources of 3 mCi each at a mutual distance of 10 mm, combined with 2 cross needles with an activity of 4 mCi. The peak in the realized implant was found to be much wider than the predicted one indicating less uniformity.

The reason of this may be the fact, that in spite of using rigid needles, during closing of the bladder wall a distortion of the needles with regard to each other cannot be avoided.

In fig. 4.15 a, b, and c in which the histograms are showed for a bladder implant using iridium afterloading technique without spacers, a remarkable difference between the planned and actual implant can be observed. These differences were caused by a distortion of the parallelism. The histograms of the implants when spacers were used, demonstrated in all cases almost complete agreement with the planned situation, as showed in fig. 4.16 and 4.17). The close agreement of the natural volume-dose histogram between the predicted and realized implant in bladder iridium implant using spacers as a template to guide the nylon tubes showes the benefit of it, making the clinical outcome of treatments more comparable [13].

a



b

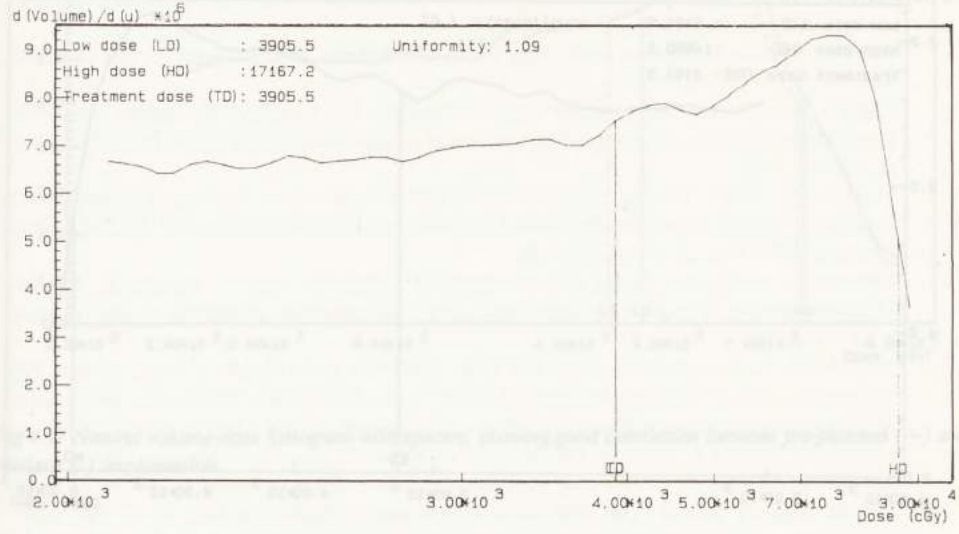
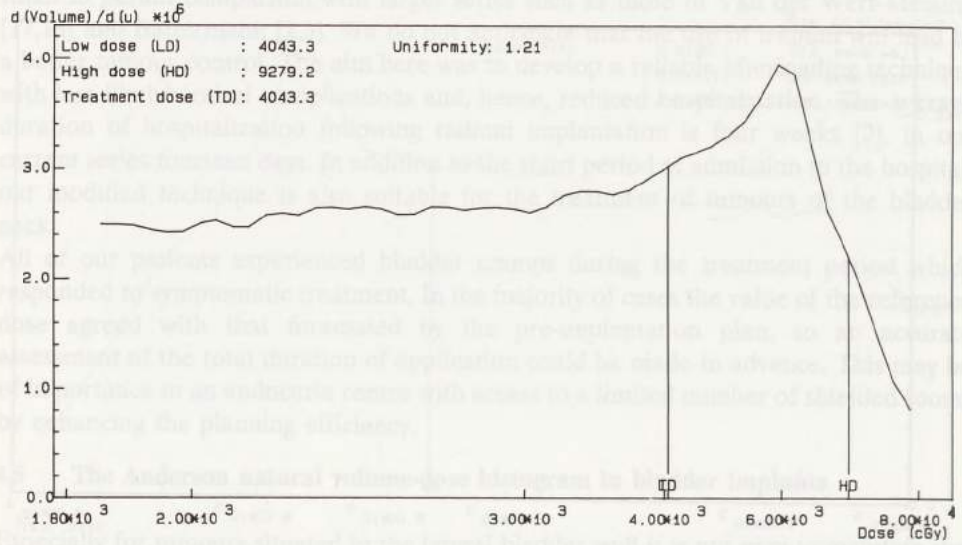


Fig 4.14 Natural volume-dose histogram of bladder implantation, using radium needles.
(a) pre-planned (b) realized implant.

a



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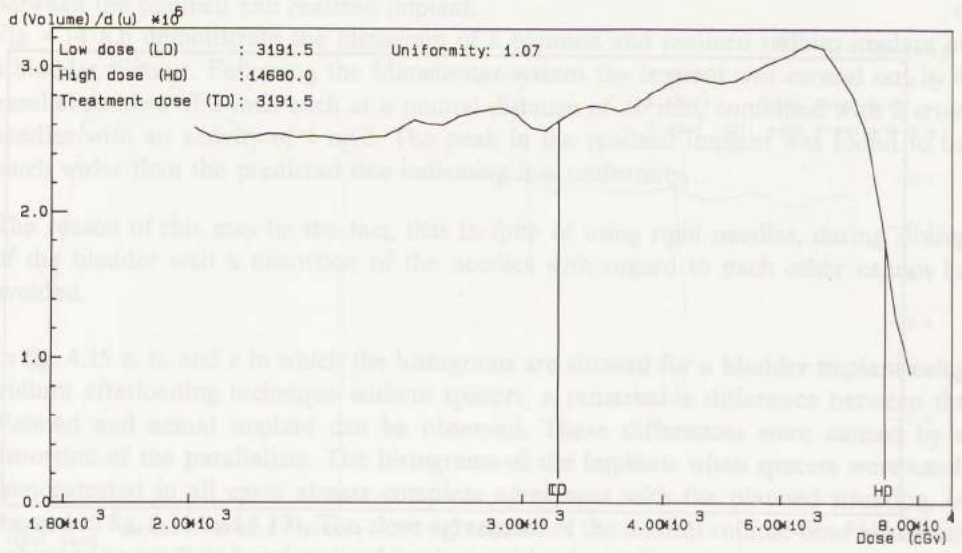

Fig 4.15 Natural volume-dose histogram of bladder implantation, using iridium wires. (a) pre-planned (b) realized implant.

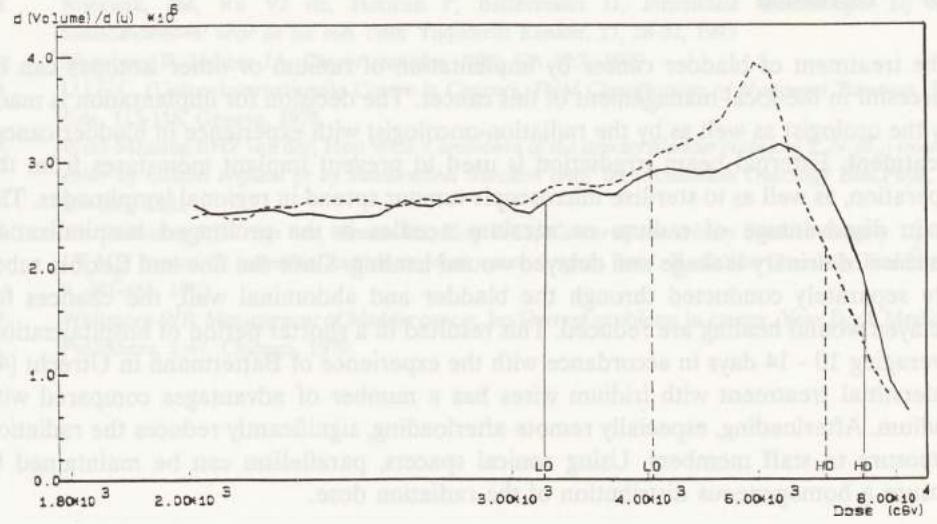

Fig 4.16 Natural volume-dose histogram without spacers, showing difference in treated volume between pre-planned (---) and realized (-) implantation.

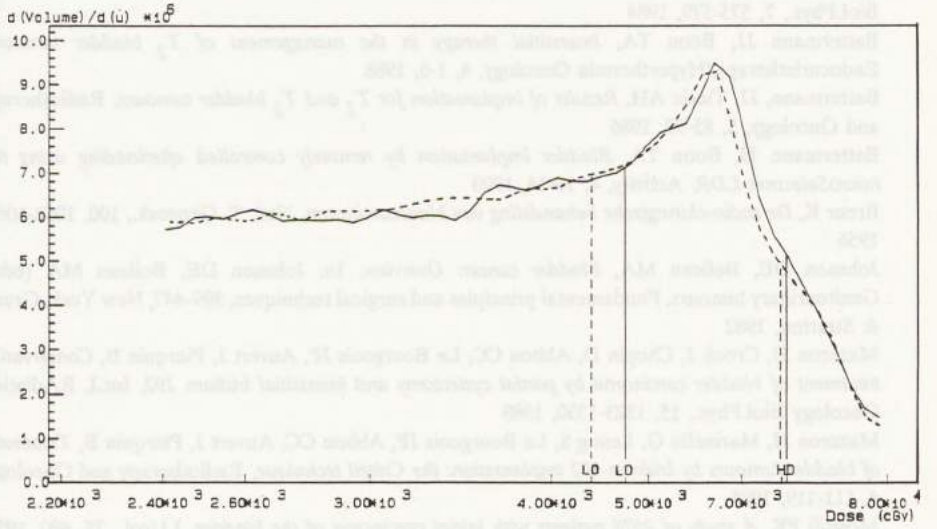

Fig 4.17 Natural volume-dose histogram with spacers, showing good correlation between pre-planned (---) and realized (-) implantation.

4.6 Discussion

The treatment of bladder cancer by implantation of radium or other isotopes can be succesful in the local management of this cancer. The decision for implantation is made by the urologist as well as by the radiation-oncologist with experience in bladder cancer treatment. External beam irradiation is used to prevent implant metastases from the operation, as well as to sterilize microscopic tumour spread in regional lymphnodes. The main disadvantage of radium or caesium needles is the prolonged hospitalization because of urinary leakage and delayed wound healing. Since the fine and flexible tubes are separately conducted through the bladder and abdominal wall, the chances for delayed wound healing are reduced. This resulted in a shorter period of hospitalization, averaging 10 - 14 days in accordance with the experience of Battermann in Utrecht [4]. Interstitial treatment with iridium wires has a number of advantages compared with radium. Afterloading, especially remote afterloading, significantly reduces the radiation exposure to staff members. Using conical spacers, parallelism can be maintained to ensure a homogeneous distribution of the radiation dose.

4.7 References

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CHAPTER 5

RADIOTHERAPY FOR CANCER OF THE VULVA AND LOWER THIRD OF THE VAGINA

5.1 Introduction and review of the literature

Carcinoma of the vulva is the fourth gynaecological tumour and accounts for 3 to 5% of all malignant gynaecological tumours [3]. For vaginal carcinomas the incidence rate is even lower, 1 to 2% [14]. The tumours occur most frequently in women aged 60 years and older, with a peak incidence around 70 years. Histologically, in about 90% of cases a squamous cell carcinoma is diagnosed [3,9].
Vulvar carcinoma may occur anywhere in the vulva, but most often in the labia, 70% [4]. When the tumour is located in the anterior part of the labia a "kissing lesion" is not seldom found. Vaginal cancers occur most commonly in the posterior wall of the upper third of the vagina; the next most common site is the anterior wall of the lower third [14].

The primary regional lymph nodes, both for the vulva and the distal part of the vagina, are the superficial inguinal lymph nodes. The second station is formed by the deep femoral nodes, further extending to the deep pelvic nodes. Cloquet's node is the last gland belonging to the deep femoral group and lies directly under the inguinal ligament of Poupart. Various authors describe a large variety of tumour-positive inguinal and pelvic nodes [3]. Franklin and Rutledge [5] found inguinal metastases in only one out of 18 patients with a vulvar carcinoma smaller than 1 cm in diameter. In contrast, 15% of 48 patients with a tumour process smaller than 2 cm already had spread to the lymph nodes. The incidence of lymph node metastases is not only associated with the size of the lesion, but also with the grade of histological differentiation. In literature the incidence of inguinal node metastases is found to be 35% (table 5.1). Morley [11] recorded an incidence of 21% tumour-positive nodes for T_1 tumours. This incidence was twice as high, 45%, in case of T_2 tumours. According to Curry [2] pelvic nodes are tumour-positive in 25% of proven metastases in the inguinal glands. The 5-year survival

Table 5.1 Incidence of inguinal and pelvic lymph node metastases in patients with vulvar cancer

Author	Patients	Inguinal Node Metastases	Pelvic Node Metastases
Taussig (1938)	65	25 (38%)	5 (8%)
Way (1960)	143	60 (42%)	23 (16%)
Merril and Ross (1961)	25	8 (32%	2 (8%)
Collins et al. (1963)	71	22 (31%)	6 (8%)
Rutledge et al. (1970)	101	48 (48%)	11 (11%)
Morley (1976	205	74 (36%)	6 (3%)
Krupp and Bohm (1978)	195	40 (20%)	9 (4%)
Green (1978)	142	54 (38%)	18 (13%)
T O T A L	947	331 (35%)	80 (8%)

Table derived from: Donaldson and Powel [4]

rate in women with tumour-positive inguinal nodes is 20% [4]. This is probably the reason of a valid reluctance to perform pelvic lymphadenectomy in conjunction with an inguinal node dissection. The surgical management of this catagory of patients, who are often of old age en suffering from concomitant diseases such as diabetes mellitus, circulatory disturbances of the lower limbs, cardiopathy and obesity, may be fairly drastic with a substantial risk of morbidity and even mortality. A long period of hospitalization is more the rule than the exception.
A retrospective analysis of 134 patients with carcinoma of the vagina was carried out by Perez and Camel [13]. No inguinal metastases were found in 83 patients with carcinoma of the cranial or middle part of the vagina. One of 20 women with a tumour in the distal third of the vagina and three of 20 women with a carcinoma extending throughout the entire length of the vagina, however, had metastases in the inguinal lymphnodes. This made the authors conclude that elective irradiation of the inguinal nodes is indicated when the carcinoma is localised to or penetrates into the distal third of the vagina. After a dose of 60 Gy not one of the patients with palpable inguinal metastases experienced a local recurrence.

Statements are made in literature with regard to the applicability of radiotherapy of vulvar carcinoma, because the tolerance dose of the vaginal mucosa is thought to be low [4,6,10]. Hintz et al. [8] postulated on the basis of vascularisation that the distal part of the vagina has a lower tolerance threshhold than the cranial part. In their series of patients in which a combination of intracavitary and interstitial techniques was applied, necrosis of the mucosa of the distal part of the vagina occurred in three out of every four patients. Radium or caesium needles were employed for the interstitial therapy.
In addition to the dose and the irradiated volume, other factors play a role in the occurrence of necrosis, including mechanical factors causing pressure of the vaginal applicator to the mucosa, anatomical factors of blood supply of the distal part of the vagina, microbacterial factors due to contamination of the irradiated mucosa, and hormonal factors.
Hacker et al. [7] described satisfactory tumour regression in 7 out of 8 patients who were irradiated pre-operatively with a dose of 44 to 54 Gy. In 4 out of 8 women no vital tumour was found in the operation specimen.
This suggests that one is dealing with radiosensitive tumours. In literature it is suggested that the therapeutical management of tumours of the vulva and the distal third of the vagina should be identical.

5.2 A retrospective analysis of the Deventer patient population with tumours of the vulva and distal part of the vagina

In our centre patients with a primary squamous cell carcinoma of the vulva or distal third of the vagina were treated by a combination of external radiotherapy and intracavitary/interstitial iridium implantation as a boost. Recurrent tumours following surgery were also treated according to the same protocol. During the periode November 1984 through December 1988, 14 patients with a tumour in the distal part of the vagina or vulva were treated. Tabel 5.2 summarizes the data of these patients.
Five patients had a primary carcinoma of the vulva, one had a primary vaginal

carcinoma and the others were treated for recurrences after surgery. Seven patients were treated with a combination of external and interstitial radiotherapy, the other seven patients received only interstitial radiotherapy because of their age and general condition.
External irradiation of the true pelvis included the entire vagina, vulva and pelvic nodes up to the promontory. The irradiation was given via two opposing fields with 12 MV photons. The inguinal nodes were irradiated with 12 or 15 MeV electrons depending on the desired depth. A total dose of 40 to 50 Gy was given in 2 Gy fractions. Palpable inguinal nodes received a booster up to a total dose of 66 to 70 Gy.

Implantation technique

For brachytherapy in this region of the body a special applicator is employed. The volume to be implanted and the treatment plan are determined prior to the external radiotherapy. Both intracavitary and interstitially placed sources are used in order to ensure a homogeneous dose distribution.

Intracavitary treatment is given, using a vaginal cylinder in which specially arranged rigid hollow needles can be placed. With this cylinder as a centre, templates are constructed to place hollow needles, parallel and at mutual equidistance according to the Paris method, in and around the target volume (fig. 5.1). The exact dimensions and localisation of the tumour are determined by inspection and by vaginal and rectal examination (fig. 5.2a, b). The external contour of the tumour is then drawn fullsize on a plastic template as is the vaginal countour, for placement of the vaginal cylinder (fig. 5.3). The course of the urethra is also traced to estimate the length of the sources at this place. The second step is to determine the length of the needles. Short needles, averaging 5 cm in length, are used on the ventral side because of the pubic bone and the bladder. Dorsally the length of the needles is determined by the tumour spread or target volume. With this information a source distribution can be determined to envelope the entire target volume. This results in an isodose distribution on the surface of the vulva as indicated in figure 5.4. The mutual source distance is kept small and never exceeds 15 mm.
In this way the volumes of the high dosage areas are kept as small as possible. The applicator is made and tested when the patient has just commenced the external irradiation. Having determined the actual length of all needles assessments of dose distribution at various levels are made in both transverse and longitudinal direction, as shown in figures 5.5a, b, c, d. In this way it is possible to see whether the volume to be treated can be sufficiently circumscribed at every level.
About three weeks after the end of external radiotherapy the application is carried out according to this previous plan. The procedure of implantion is shown in fig. 5.6 a, b, c. After introduction of a Foley catheter the applicator is placed in proper position. The template is sutured to the skin at various points. Thereafter, the vaginal cylinder is removed allowing placement one by one of the needles with the aid of the palpating finger. When vaginal examination confirms that the needles are correctly placed, the cylinder is re-introduced. Orthogonal photographs on the simulator are used to confirm the correct placement of the needles in the cylinder and those introduced interstitially

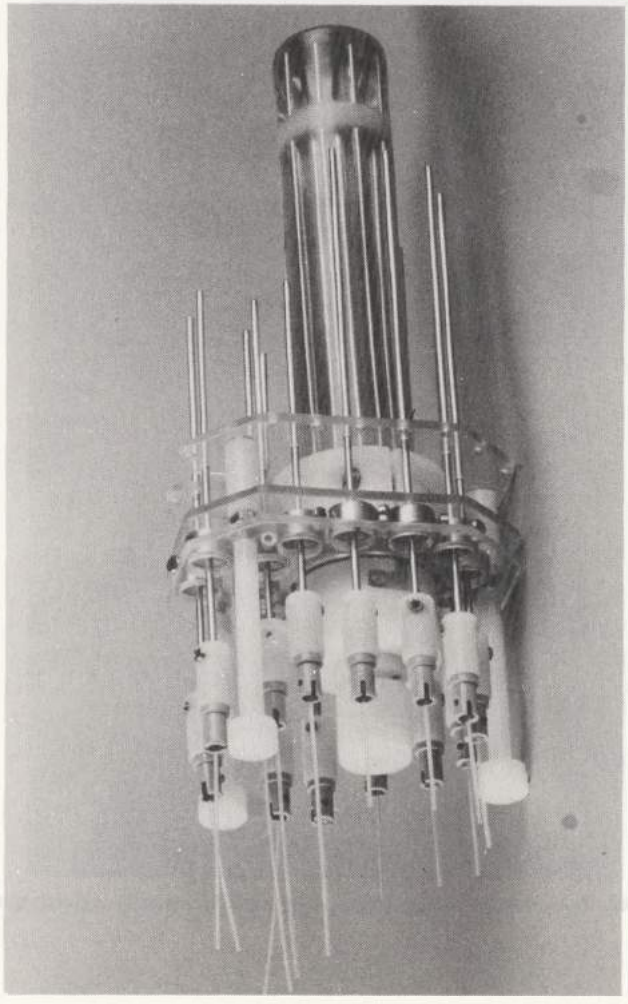


Fig 5.1 Deventer applicator for the treatment of tumours of the vulva and distal vagina, consisting of a vaginal cilinder for intracavitairy placement of sources and templates with pre-bored hooles at 12, resp. 15 mm distance for interstitial placement of sources.

with regard to their position and parallelism. The iridium sources are placed in the needles by afterloading. If implantation is the only treatment, a dose of 60 Gy is applied at the 85% isodose level. In one patient a dose of 65 Gy was applied. If the interstitial therapy was given as a boost to external radiotherapy, the interstitial dose varied from 20 to 30 Gy, to reach a total tumour dose of 65 to 70 Gy.

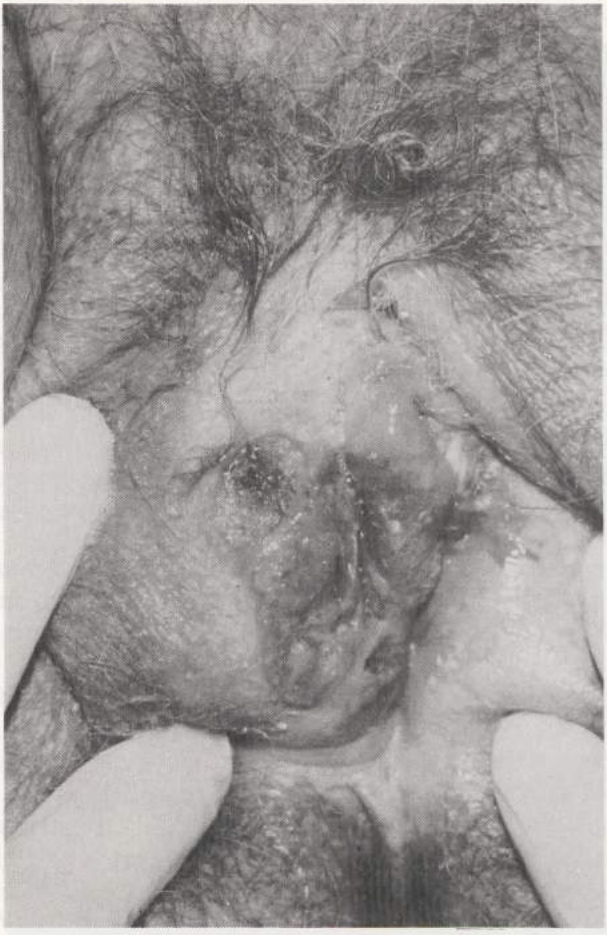


Fig 5.2 The exact localization and dimensions of the tumour are determined by inspection, and by vaginal and rectal examination.

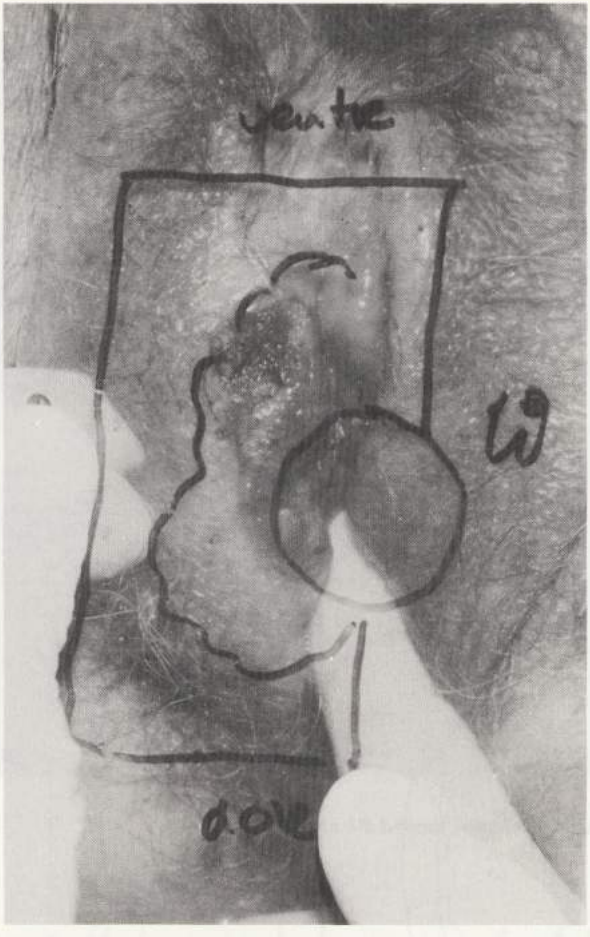


Fig 5.3 On a plastic template the tumour borders are indicated, with the vaginal cilinder as a marker point.

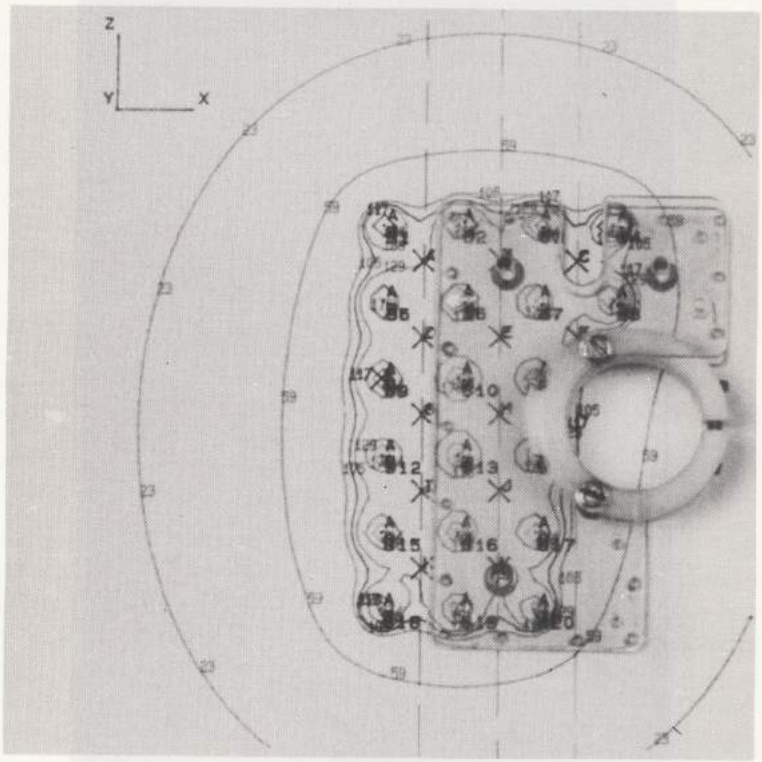


Fig 5.4 Preplanned dose distribution around the tumour.

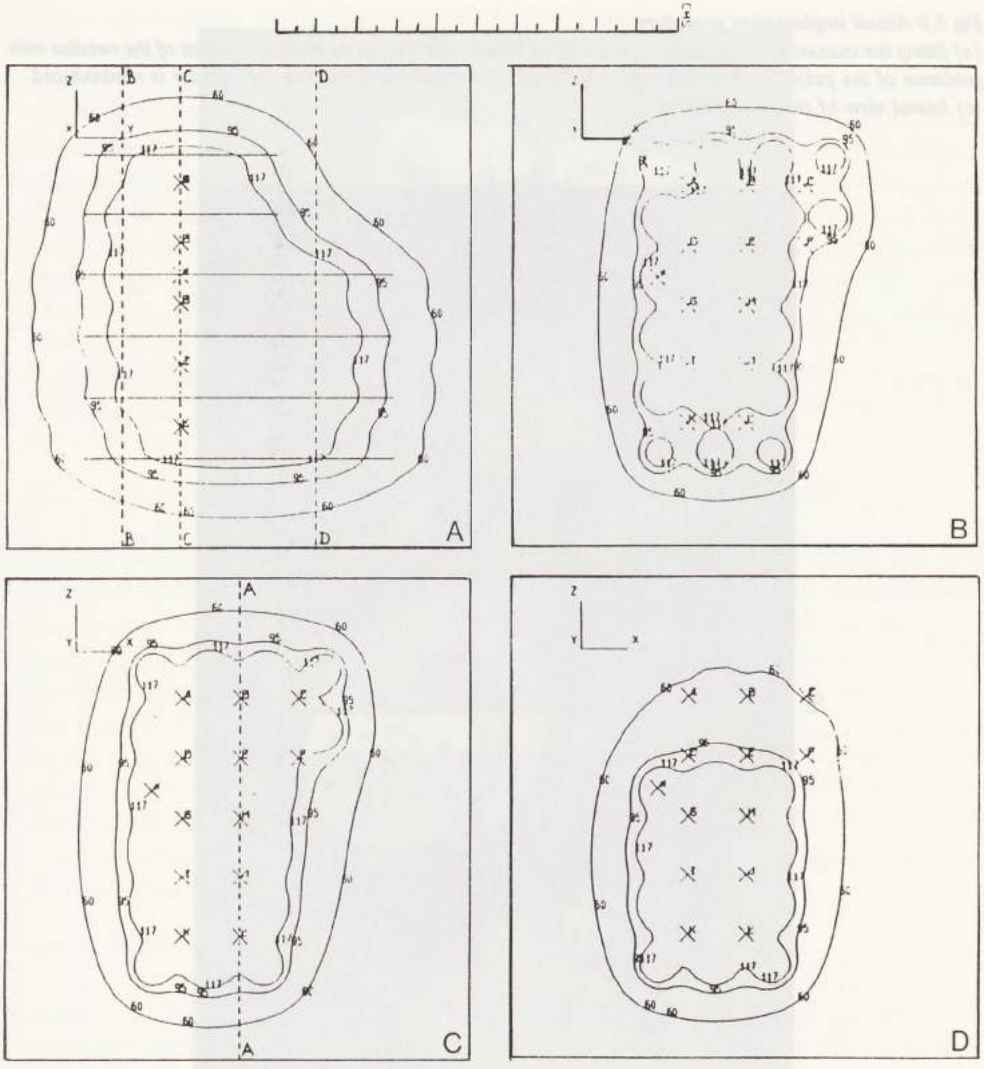
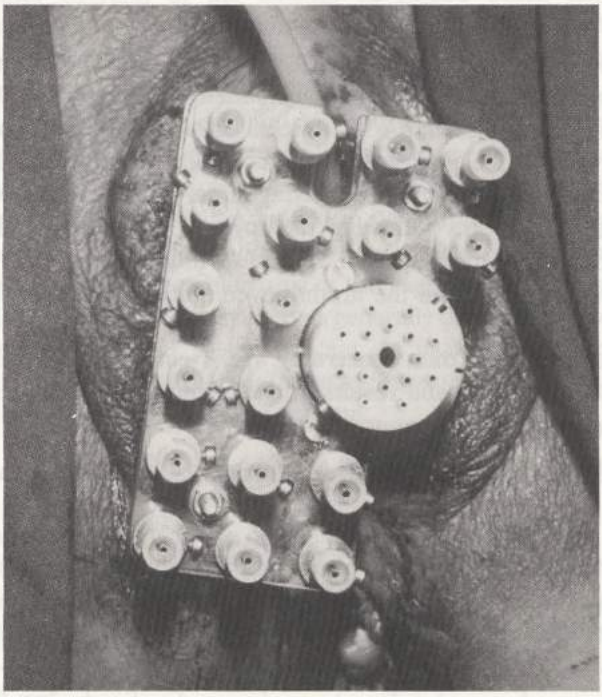


Fig 5.5 Dose distribution in different directions and at different levels of the preplanned implantation. Short needles will be used on the ventral side and around the urethra because of pubic bone and bladder. Dorsally the length of the needles is determined by the target volume.
(a) dose distribution in longitudinal direction through the midplane (b) dose distribution in transversal direction on the skin (c) dose distribution at 1 cm depth (d) dose distribution at 1 cm from the end of the sources.

Fig 5.6 Actual implantation procedure
(a) fitting the custom-made applicator. The vaginal cilinder is removed to allow placement of the needles with guidance of the palpating finger (b) after placement of the individual needles, the cilinder is reintroduced (c) lateral view of the final implant.

A



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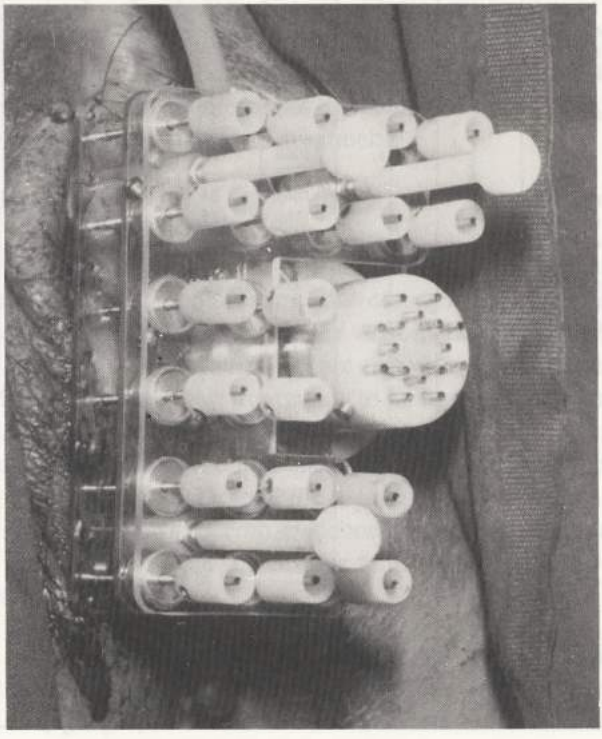

C

Results

With the exception of one patient (table 5.2, pat.no. 3) satisfactory tumour regression resulted already from external irradiation. One patient (pat.no. 4) died 10 months after treatment with bone metastases but without local or regional recurrence. Patient no. 5 developed a rcurrence in the right groin 24 months after treatment, and subsequently a local recurrence; she died 32 months following initial treatment. Patient no. 1 died of intercurent disease 15 months following therapy and without any signs of tumour activity. In patient no. 3 with a partial remission following external therapy, some residual tumour remained around the urethra even after iridium implantation.

Table 5.2 **Summary of data concerning age, T-category, external irradiation, implantation and results of treatment in the Deventer series of 14 patients with tumours of the vulva and distal vagina**

AGE AT TIME OF TREATMENT		TUMOUR STAGE	EXTERNAL RADIOTHERAPY		REMISSION		IRIDIUM IMPLANTATION		COMPLI-CATIONS		RECUR-RENCE		DEATH		N. E. D.
years			target volume	total dose cGy	par-tial	com-plete	dose cGy	hours	tem-por-ary	per-ma-nent	lo-cal	reg.	tu-mour months	inter-curr. months	months
1	89	T3N0M0	-	-	n. a.		6000	52	+		-	-		15	
2	79	T3N3M0	pelvis	5000		+	2000	22	+		-	-			48
			groinL	6600	+										
			groinR	7000	+										
3	72	T3N0M0	pelvis	4000	+		2500	30		+	+	+	30		
4	76	rec.			n. a.		6000	100	+		-	-	10		
5	67	rec. +	pelvis	4000		+	3000	25	+		+	+	32		
		abscess	groinR	5000	+		3000	25		(+)	+	+			
		10x15cm	groinL	4000			-								
	71	rec.	pelvis	4400		+	2100	34	+		-	-			31
			groinR	4400			-								
			groinL	4400			-								
7	66	rec.	pelvis	4000		+	2500	20	+		-	-			29
8	66	rec.					6000	46	+		-	-			3
9	77	rec.					6000	75	+		-	-			12
10	63	rec.					6000	64	+		-	-			8
11	80	T3N1M0	pelvis	4000			3000	26	+		-	-			7
			groinR	7000		+									
			groinL	4000											
12	85	rec.		4500		+	2500	24	+		-	-			6
13	84	T2N0M0					6500	72	+	+	-	-			13
14	98	T1/2N0M0					6000	92	+		-	-			8

Four weeks later necrosis of the mucosa developed which failed to respond to symptomatic treatment. Three months later a node was palpable in the right groin. This patient died 12 months following treatment with residual tumour and regional metastases. The remaining patients are well with a follow-up period of 6 to 48 months. Exsudative epidermolysis of the skin and mucositis of the vaginal mucosa were observed as reaction of external radiotherapy up to 4 weeks following completion of the irradiation. This caused complaints of frequent urgency, a burning sensation on passing urine and diarrhoea, all of which responded to symptomatic treatment. For this reason the implantation was postponed until 3 to 4 weeks after cessation of external therapy. Oedema of the labia and severe mucositis of the vagina were observed as a reaction of interstitial radiotherapy, but these symptoms generally disappeared spontaneously within 8 to 10 weeks after removal of the implant. In patient no. 13 radiation mucositis developed, which caused a rapid obliteration of the vagina. Probably this was influenced by a too long interval in the follow-up scheme.

5.3 The Anderson natural volume-dose histogram of vulvar implants

For the treatment of tumours in the distal part of the vagina and the vulva an appliator was used. Hence it can be expected that the realised implant is in close agreement with the predicted one. In our example (fig. 5.7) the source and dose configuration can be seen. Needle spacing in a square configuration is 16 mm. The reference dose is 85% of the basal dose with a calculated volume of 160 cm^3, and a high dose volume of 130 Gy ($2x\ D_{ref}$) of 10 cm^3.
In fig. 5.8 the natural volume-dose histogram of a pre-treatment calculated source configuration is shown. The uniformity from this histogram is 1.91. Since the shape of the implant did not vary widely between patients, spacing was kept 16 mm in all cases. The advantage of using an applicator is to guide the implant and to maintain its configuration throughout the course of treatment.

5.4 Discussion

Inspite of the negative selection of patients, the combined treatment of external radiotherapy and interstitial implantation offered a good alternative to surgery in the treatment of tumours of the distal part of the vagina and the vulva. Serious necrosis of the mucosa as suggested in literature was not observed in our series. All our patients were subjected, during and after treatment, to meticulous nettoyage of the vaginal mucosa with a soft desinfectant solution, thereafter a vaseline gauze tampon is left behind to avoid obliteration of the mucosa. This procedure is continued once or twice a week for about three months. Despite the high dose at the mucosa after intracavitary treatment with the vaginal cylinder no evidence of necrosis was found. We think that contamination of the irradiated mucosa is an important factor in the onset of complications such as necrosis.

Working with an applicator offers the possibility of a reproducible technique of implantation. Since the radiation volume and target volume are examined with the tumour still in situ, geograpical misses are avoided as the radiation-oncologist is not

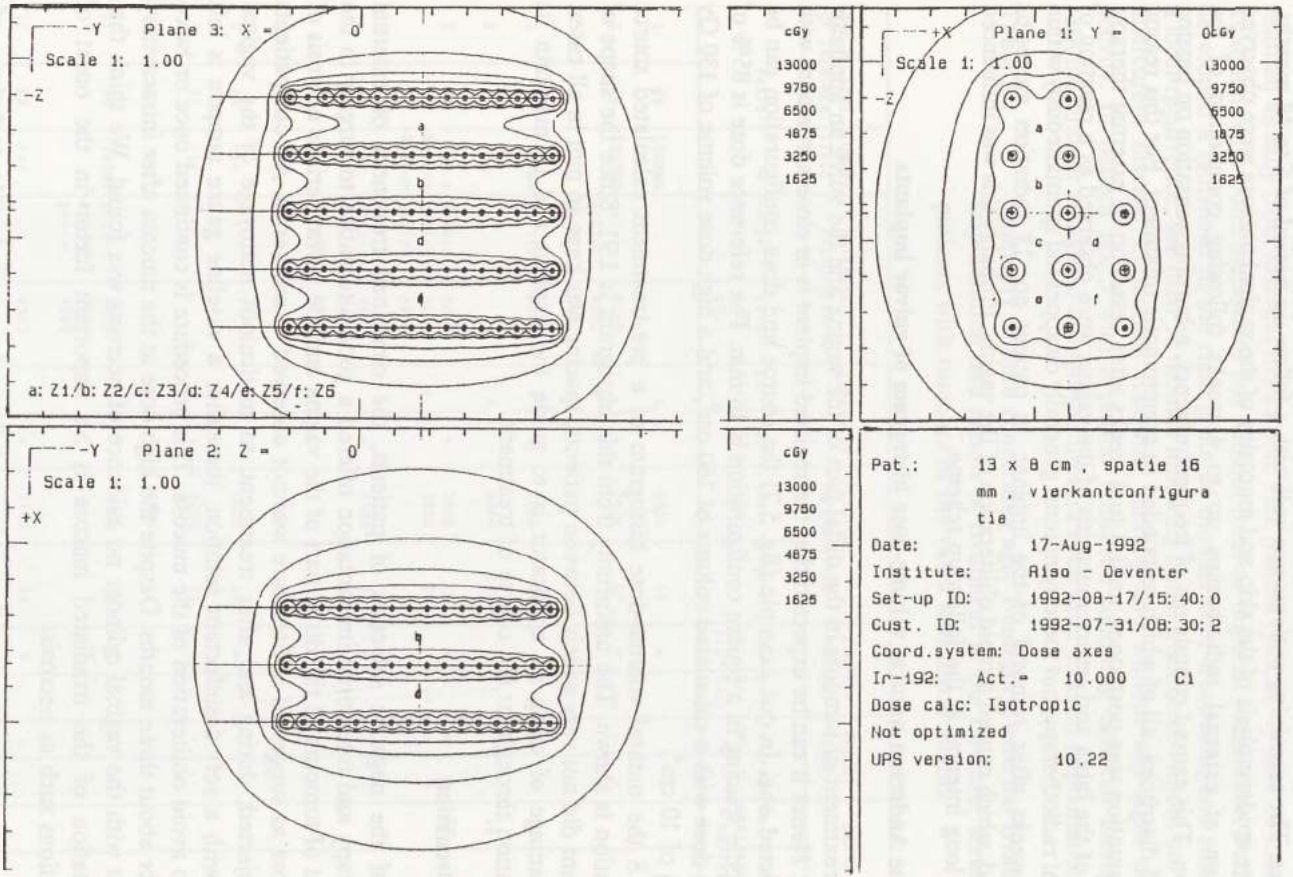

Fig 5.7 Dose distribution in X, Y, Z direction of the realized implant.

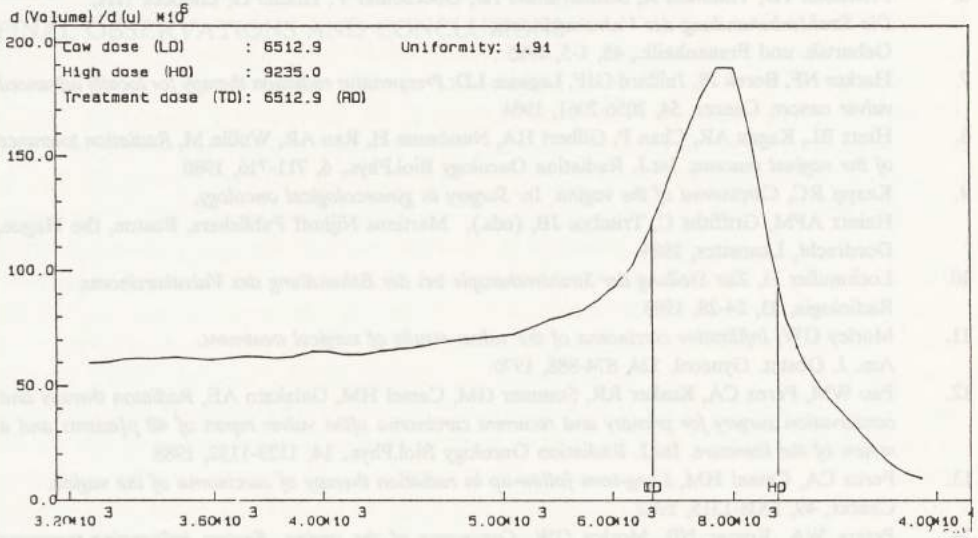

Fig 5.8 Natural volume-dose histogram of implantation
Since a custom-made applicator is used, there is no difference between the plots of the pre-planned and the realized implantation.

distracted by radiation induced alterations of the surrounding tissues or tumour regression. Implantation is performed rapidly and under regional anaesthesia. The application time is known, so the patient also has some idea about the duration of hospitalization. In general advanced age of the patient will not exclude treatment, nor concomitant disorders such as diabetes or obesity.
This form of treatment certainly should have a place in the management of tumours of the distal vagina and vulva, both for primary tumours [1,12,16] and for recurrences after surgery [15].

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CHAPTER 6

FINAL OBSERVATIONS AND CONCLUSIONS

6.1 Introduction

In the last decades interstitial radiotherapy made a comeback. This is partly due to the development of (remote) afterloading techniques, but also to the realisation that local recurrence remains a considerable problem in many tumours [3]. The unique advantage of implantation is the delivering of the highest possible dose of radiation to the tumour without exceeding the tolerance of surrounding normal tissues.
An other main advantage of endocurie therapy is the short overall treatment time. It is generally accepted, especially in head and neck tumours, that radiotherapy should be completed as rapidly as possible and it is better to delay treatment initiation than to introduce delay during treatment [9]. Clonogenic repopulation occurs after a lag period of the order of 30 days after initiation of external radiotherapy and a dose increment of about 0.6 Gy is required per day to compensate for this phenomenon [14]. However, we should realize that in combination of beam therapy and curie therapy (e.g. breast conservation), the interval between the two modalities might become critical [6].
Brachytherapy also has its disadvantages, in comparison to external beam therapy hospitalisation is required for almost all patients. A complex implantation may take even an experienced radiotherapist an hour or more. Although in some cases patients can be treated under local or regional anaesthesia, general anaesthesia is often required. Furthermore, pre-treatment evaluation is necessary in all patients to exclude patients with severe bleeding disorders, claustrophobic patients, etc. Since interstitial radiotherapy is very localized in comparison with external irradiation geographical misses are a serious problem. Corrections are not always possible and hence an implantation may result in an underdosage of the target volume, or an overdosage in the normal tissues.

For small, well localized tumours without signs of pathological lymph nodes, radical treatment by interstitial implant alone may be performed. For larger tumours the implant technique can be used as a boost in combination with external beam irradiation or as treatment modality following surgery. In this latter situation we prefer to perform an implant first, under direct vision of the tumour margins, followed by external beam irradiation. In all cases a pre-planning should be made to identify the target volume and to decide on the number and distribution of sources to be used. To reduce volumes of high doses, we have chosen for short distances between the sources and therefore more sources per implant, against less sources with a larger mutual distance between the sources. Simon et al. [13] noted a significant difference on local control and complication rate in tongue tumours with an interspacing of 9-14 mm versus 15-20 mm. Brachytherapy is not only applied in the treatment of primary tumours and regional lymph nodes (neck), but also one of the few options for the management of second primaries in pre-irradiated areas, especially in the head and neck [11]. Levendag [8] showed a clear advantage of the use of brachytherapy in local control of these tumours, although the complication rate remains relatively high and the overall survival relatively low.

Table 6.1 Pre-treatment procedures for beam irradiation and for interstitial radiotherapy

Beam irradiation	*Endocurietherapy*
1. define target volume (localization)	1. define target volume
2. computer treatment planning determination of fields (number, sizes, directions)	2. computer treatment planning determination of sources (number, mutual distance, activity)
3. treatment simulation	3. localization with (dummy) sources in situ
4. position verification (megavolt X-rays, verification, devices)	4. position verification
5. improvements if necessary (eg. better fixation, etc.)	5. improvements if necessary (eg. source position, number of sources, unequal loading, etc.)
6. actual treatment	6. actual treatment

As is shown in table 6.1, the pre-treatment procedure for endocurietherapy is identical to that for beam irradiaton. In external radiotherapy generally accepted criteria are defined to judge a treatment planning. The dose and the target volume should be less than +/- 10% of the specified dose. For larger discrepancies maximum and minimum dose in the target volume have to be documented separately. If it is assumed that the actual irradiation is in agreement with the simulation and planning, this means that it is possible to judge the treatment plans according to their homogeneity. Also for interstitial radiotherapy such a generally accepted criterium would be useful. In the Paris system, it is required that the dose in none of the basal dose points is more than 10% different from the mean basal dose [7]. Hence, a heterogeneity factor (FH) can be defined:

$$FH = \frac{Db_{max} - Db_{min}}{\overline{Db}} \times 100\%$$

Following this formula an implantation can be judged as good if the FH is less than 20%. However, since FH is related only to one direction of the implant, a criterium based on a dose volume histogram would be preferable.

In this thesis the Anderson natural volume-dose histogram [1] is used to show discrepancies in uniformity. A uniformity index (UI) is defined, see Chapter 1. Since this

parameter is related to the chosen treatment dose (TD), a quality factor (QF) is defined:

$$QF = \frac{UI\ planned - UI\ realized}{UI\ planned} \times 100\%$$

An implant is good when the QF is less than 10 %. The planned peak dose should be in agreement with the realized peak dose. In modern brachytherapy units, a dedicated computer planning system is available to visualize the isodose lines around sources. More and more a reference isodose line is chosen instead of the guide lines of the Paris system to chose the basal dose. A poor implantation will never be a good implantation by changing the reference isodose lines. Of special interest in this matter is the introduction of a single stepping source as with HDR or PDR. To optimize the homogeneity the treatment time can be changed along the line of a catheter. However, this optimization of the homogeneity might result in overdosage of normal tissues.

Furthermore we have to realize that the longest experience is with low dose rate brachytherapy. New modalities such as HDR and PDR still have to prove their clinical significance in most tumour sites [2], except cancers of the uterine cervix [12].

In order to attain uniformity of treatment and to implant accordingly to a pre-conceived plan, a number of applicators was developed to be used at various sites. These applicators should meet certain criteria, such as: it should be simple and the implantation should be reproducible. Pre- and post-treatment planning should be in close agreement with each other. To avoid geographical misses, the plan of the interstitial treatment should be made before the start of external irradiation.

6.2 The Anderson volume-dose histogram

In Chapters 2-5, the Anderson natural volume-dose histogram is used to visualize the discrepancies between the planned and realized implantation. It was shown (Chapter 2) that the use of an applicator optimized the implantation in tumours of the floor of mouth. As an example a looping technique is shown in fig. 6.1. In this example the lesion was treated with three loops and a single straight source. For all three loops it is found that the height of the curved portion is less than one half of the spacing between the lines and the length of the line measures more than 1.5 times the spacing. Therefore it may be concluded, that all three loops are properly positioned [10]. However, because of differences in the spacing between the loops, the actual source arrangement is not in agreement with the predicted arrangement. In fig. 6.2 a typical example is shown, using the oral cavity applicator. As can be seen, the actual dose distribution is almost completely in agreement with the pre-planned distribution.
Fig. 6.3 summarizes the results of 10 patients treated in the period of 1984 - 1986 in our Deventer institute. A comparison is shown between the dose distribution pre-planned and actually achieved in the central plane. Specially with the looping technique, the pre-planned dose distribution differed significantly from the actual distribution. For this

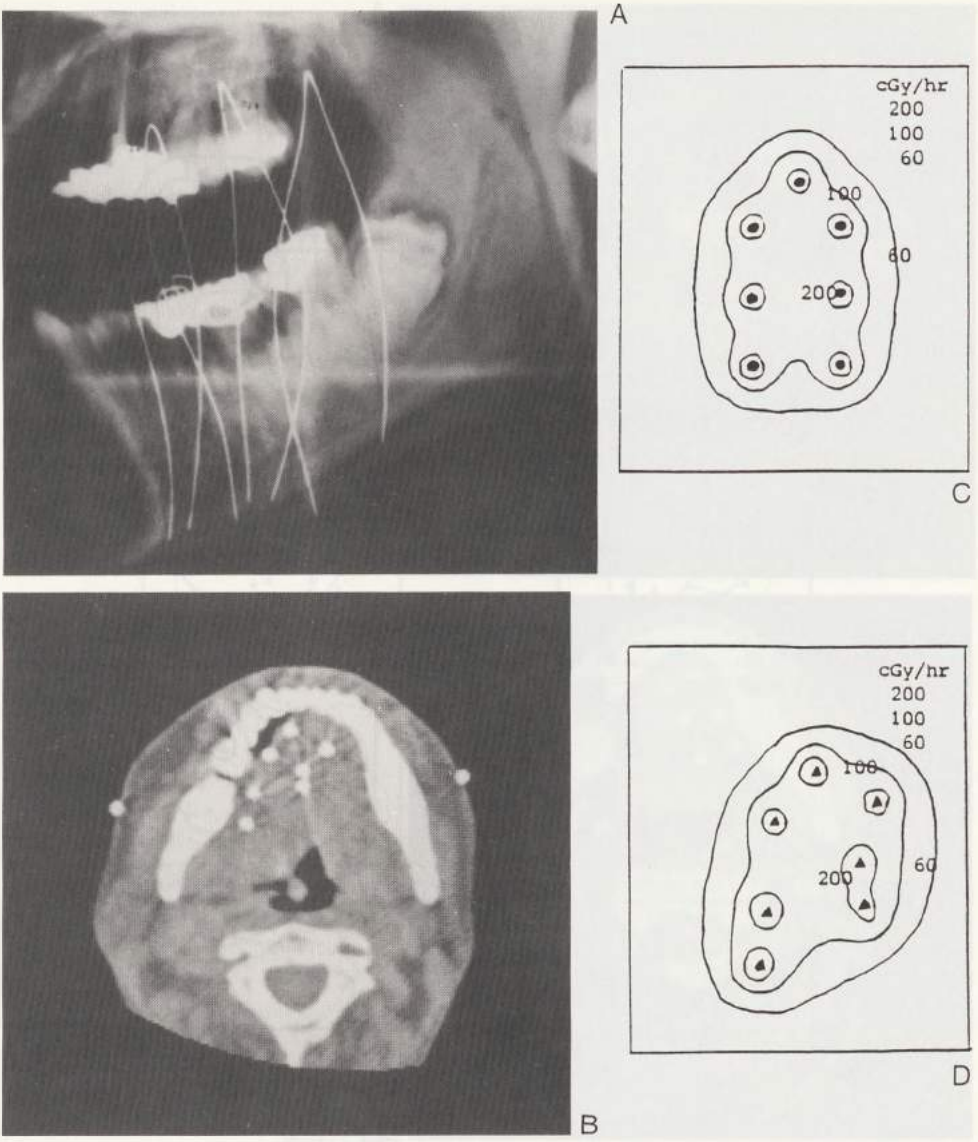

Fig 6.1 Implantation of three loops for the treatment of a tumour in the floor of mouth
(a) Lateral radiograph (b) CT image (c) Dose distribution pre-planned. The mutual distance between the sources is 12 mm (d) Dose distribution of realized implantation to allow for X-ray and CT-imaging, the lead shielding to protect part of the mandible is temporarily removed.

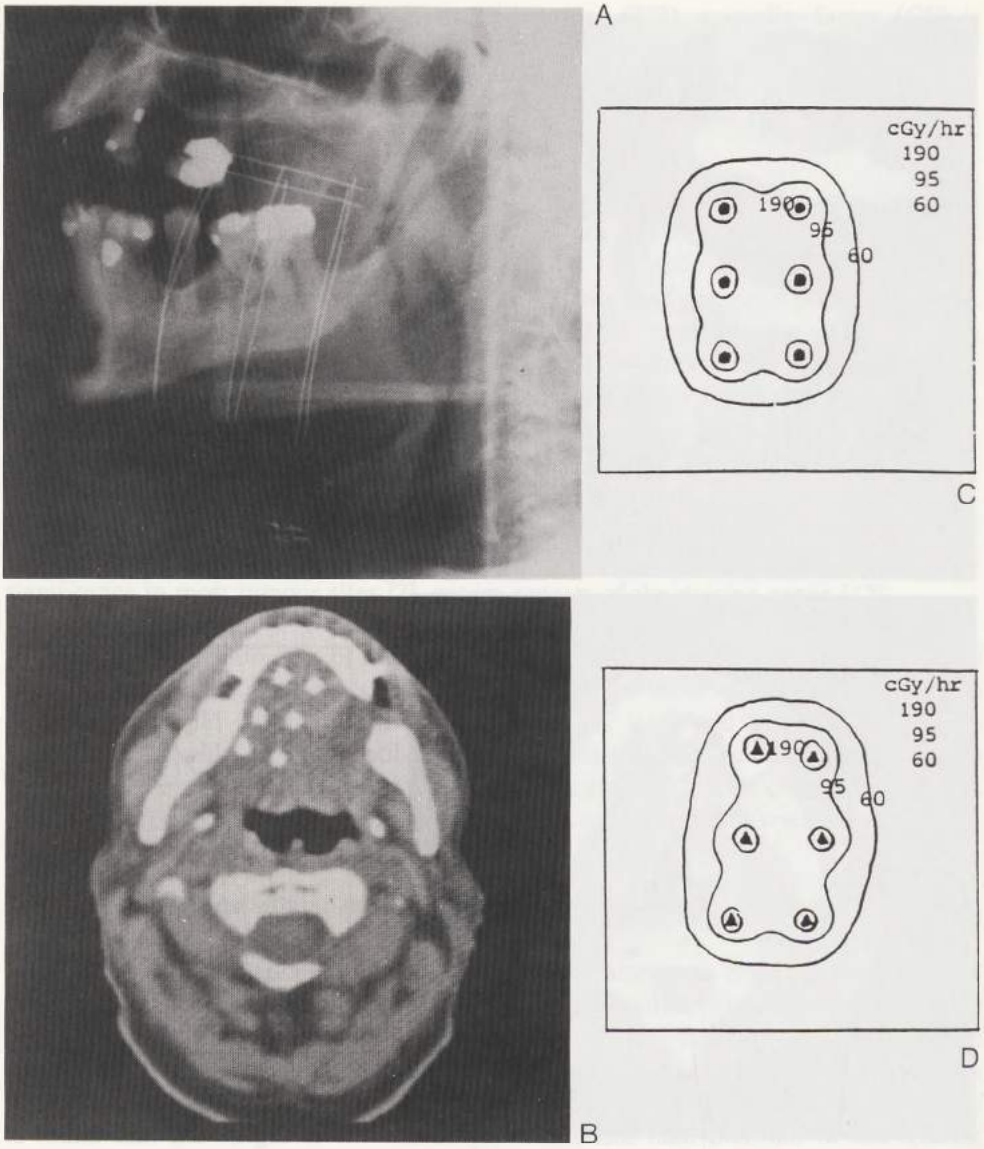

Fig 6.2 Implantation of three loops in the floor of mouth, using the oral cavity applicator
(a) Lateral radiograph (b) CT-image (c) Pre-planned dose distribution. Distance between sources is 12 mm (d) Dose distribution of realized implantation. To allow for X-ray or CT-imaging, the lead shielding to protect the palate and part of the mandible is temporarily removed.

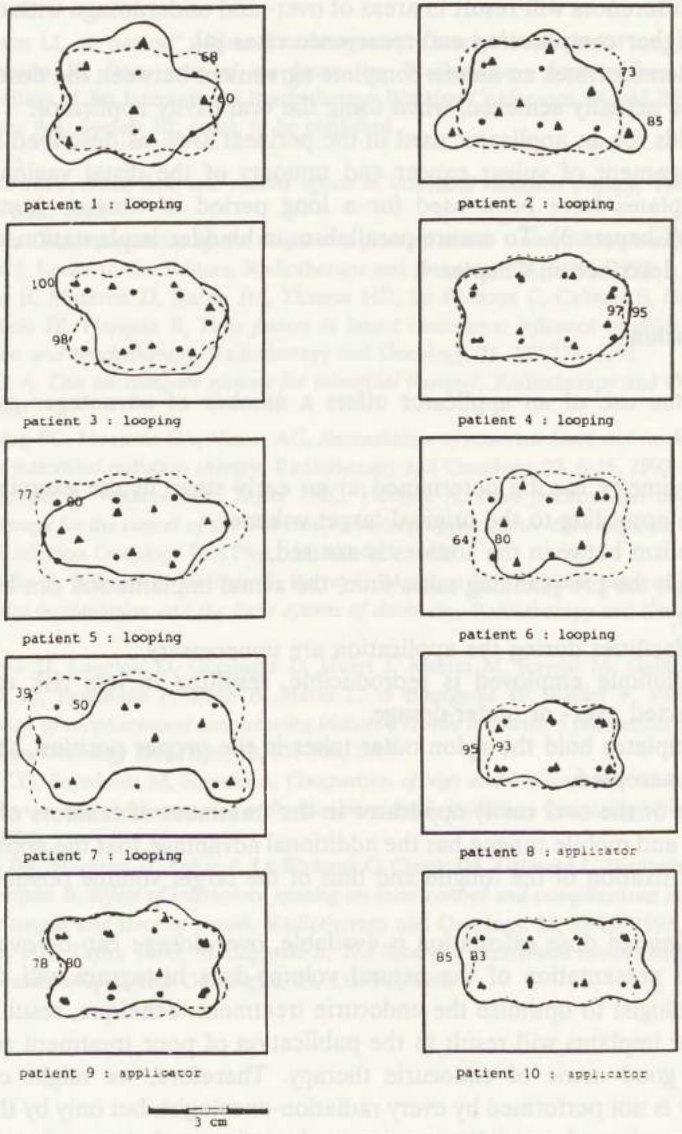

Fig 6.3 Comparison between pre-planned and realized implantation in the interstitial management of 10 patients with lesions of the floor of the mouth or mobile part of the tongue. Patients 1-7 are treated using the looping technique, while in patients 8-10 the oral cavity applicator is applied. In the central plane the shape of the actual chosen isodose (-) is shown in comparison with the pre-calculated reference dose (--). The positions of the radioactive lines as pre-planned and realized are depicted in solid dots and triangles. The numbers in the figures represent the dose rate (cGy/h). The mandible is protected by lead shielding, 2 mm thick, in all patients. The use of the applicator further permits the employement of lead shielding to protect the palate when dealing with lesions of the mobile part of the tongue. In the dose distributions presented the lead shielding is not taken into account.

reason, in some cases an other reference dose had to be chosen than forecasted. These geometrical differences will result in areas of over- and underdosage within an implant, resulting in higher complication and recurrence rates [4].
Fig. 6.3 also demonstrates an almost complete agreement between the dose distribution forecasted and actually achieved, when using the oral cavity applicator.
The same holds for an applicator used in the perineal area, as described in Chapter 5 for the management of vulvar cancer and tumours of the distal vagina. For breast implants templates have been used for a long period of time to homogenize the implantation (Chapter 3). To ensure parallelism in bladder implantation, spacers were developed as described in Chapter 4.

6.3 Conclusions

In summary the use of an applicator offers a number of advantages over freehand implantations:

* the dosimetry can be determined at an early stage in the examination and is chosen according to the original target volume,
* parallelism between the sources is assured,
* although the pre-planning takes time, the actual implantation can be carried out quickly,
* X-ray facilities during the application are unnecessary,
* the technique employed is reproducible, resulting in less risk of areas with unexpected over- or under-dosage,
* the templates hold the nylon outer tubes in the proper position, their presence is well accepted,
* the use of the oral cavity applicator in the treatment of tumours of the floor of mouth and mobile tongue has the additional advantage that the apparatus makes a good fixation of the tongue and thus of the target volume possible.

Since a pre-planned dose calculation is available, over-dosage can be avoided. In our opinion visual presentation of the natural volume-dose histogram will stimulate the radiation-oncologist to optimize the endocurie treatment technique, resulting in better implants. Poor implants will result in the publication of poor treatment results, hence affecting the good name of endocurie therapy. Therefore, we might consider that brachytherapy is not performed by every radiation-oncologist, but only by those who are trained by experienced specialists, using implantation techniques that improve the quality of implantation.

6.4 References

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SUMMARY

Chapter 1

A survey is given of the development of brachytherapy and especially the interstitial radiotherapy. After the discovery of radium in 1898, the first report about the treatment of malignant tumours appeared in 1905. With the rise of megavolt therapy in the 1960's with its greater penetrating power, deep seated tumours were better reached than with orthovolt machines, resulting in a decline in the use of brachytherapy. The long half-life of radium is an obvious hazard in the event of loss as well as the danger of leakage of a needle or tube. The development of artificial isotopes like caesium-137, iodine-125 and iridium-192 as well as the development of afterloading machines increased the interest for brachytherapy a second time. Brachytherapy, especially at a low dose-rate, has some physical and radiobiological advantages, too, over fractionated external beam irradiation.
After calculating systems as the Manchester system and the Quimby system, a new set of rules was designed by Pierquin and Dutreix in 1966, the so-called Paris system. Because of its small diameter and its flexibility, application of iridium-192 is gaining popularity especially in implants for tumours of the head and neck.

The aim of this study is to get an uniformity in implantation techniques by using technical aids during implantation. The Anderson "natural" volume-dose histogram (NVDH) gives us a tool to compare the planned and realized result of an implant in an objective way.

Chapter 2

The treatment results of patients with tumours in the mobile tongue, floor of mouth and base of tongue are discussed. In literature good local tumour control after a combined treatment of external and interstitial radiotherapy has been described, comparable with the results of surgery. In general, the complication rate is acceptable and the risk of radionecrosis of the mandibule could be avoided by keeping the mandibule out of the high dose areas.
In a retrospective study the treatment results of patients with tumours of the mobile tongue treated in Deventer in the period 1977 to 1984 were examined. For tumours of the mobile tongue an overall tumour control of 57% was reached. No complications were seen. The latter suggested that the given dose was too low in relation to the overall treatment time. Based on these experiences, there was a strive to give a higher tumour dose with respect to external as well as interstitial radiotherapy.
Since 1984 iridium-192 has been used with the Paris system as a guideline. The search for uniformity in treatment techniques has led to the development and the use of applicators in the interstitial treatment of oral cavity tumours.

Source arrangements and dose distributions were determined in an early phase of the treatment to avoid geographical misses by tumour shrinking and tissue reactions after external irradiation. The use of an applicator offers a number of advantages in the treatment of oral cavity tumours, especially when there are no X-ray facilities in the application room, resulting in a close agreement between the forecasted and realized implant. This can be demonstrated by the NVDH.

Chapter 3

The results of a retrospective study of breast conserving therapy were compared with data from literature. In the period 1981 to 1986, 113 patients with a maximum tumour diameter of 3 cm underwent breast conserving therapy. After lumpectomy and external irradiation, a boost was given by interstitial iridium implantation. A 5-year actuarial disease free survival of 89% was reached. No differences were found in cosmetic outcome between a boost dose of 25 Gy and 20 Gy. However, the cosmetic outcome in our series was less good in comparison to literature (good in 57%). Referring to calculations of the volumes of the reference dose (D_{ref}) and the volumes of the high dose areas ($2x\ D_{ref}$) it was shown that working with short spaces between the sources and more sources per implant may lead to a similar volume for D_{ref} but smaller volumes for the high dose areas $2x\ D_{ref}$.
Furthermore, an implantation in a square-configuration gives a more adequate dose distribution around the target volume than an ordinary implantation in triangles. The use of an applicator, also in breast conserving therapy, offers the advantage of a pre-planned implantation. The NVDH is a usefull parameter to express the degree of dose homogeneity within the target volume.

Chapter 4

The technique of radium implantation in solitary bladder cancer was introduced in 1951 in the Netherlands by Breur. Later on the technique was applied by Van der Werf-Messing on a large scale. In the period 1974 through 1984, 46 patients were treated in Deventer by interstitial radium implant after a short course of external radiotherapy on the pelvis. A minimum follow-up of 5 years was obtained. The results of local tumour control for tumour stages T_1 and T_2 were in agreement with the results of Van der Werf-Messing and Battermann. The complication rate was 24% and consisted of a delayed wound healing and urine leakage, because of the materials used.

A comparison of the Manchester system and the Paris system for a one-plane implantation showed that no differences were seen in respect to the volumes of the D_{ref} and $2x\ D_{ref}$ if the rules of implantation were respected.
The use of iridium in the interstitial therapy of bladder tumours offers a number of advantages over the treatment by radium needles. The material is fine and smooth and therefore less traumatic to tissue. By leading the nylon tubes, in which the iridium can be placed by afterloading, through conical "spacers" parallelism is ensured.

Since each nylon tube is led separately through the bladder and the abdominal wall, wound healing is not delayed and hospitalization does not exceed 14 days.
Using spacers to guide the tubes leads to a close agreement between the planned and realized implant in bladder iridium treatment, as can be shown by the NVDH.

Chapter 5

Carcinoma of the distal part of the vagina and vulva is a rare disease of elderly woman in the seventies and eighties. These tumours ordinarily follow a predictable way of spread to the regional lymphatic nodes depending on tumour size and histological grading. In literature it was suggested that radiotherapy often leads to necrosis of the mucosa of the vagina. However, good tumour regression was described after a pre-operative dose of 44 - 55 Gy.
In the period 1984 through 1988 fourteen patients with a tumour of the distal part of the vagina or vulva were treated in Deventer. Treatment consisted of a combination of external irradiation and iridium implantation. Before starting the external irradiation an applicator was made on the basis of the primary tumour extensions. The source configuration was determined first in both transversal and sagital directions. All data were copied on mm-paper. The guide needles in the applicator were constructed according to the disired source configuration. The preplanned implantation was carried out 3 weeks after conclusion of external irradiation.

The impression was that complications as radionecrosis of the mucosa may be due to contamination of irradiated tissue. This could be avoided by cleaning the mucosa of the vagina with a soft, desinfectant soap solution. Despite the negative selection of patients good local control was obtained. The advantage of using an applicator is expressed by the NVDH, since the histogram shows a great standing for dose homogeneity.

Chapter 6

A survey was given of the advantages of working with applicators and other tools like templates and spacers to ensure parallelism of the source carriers. By copying all source configurations on mm-paper in some cases a universal applicator might be constructed for the most occuring tumour sites. When a reliable enclosure of the target volume is ensured, the applicator can be prepared and tried out on the patient with the tumour still in situ. This avoids geographical misses and areas of under- and overdosage. Furthermore, the total treatment time can be predicted in advance. The most important in brachytherapy interstital implantation is the agreement between a predicted source arrangement and the realized implant. The use of applicators will lead to more uniformity and the NVDH gives us a tool to evaluate this.

SAMENVATTING

Hoofdstuk 1

Er wordt een overzicht gegeven van de verschillende aspecten van de brachytherapie, in het bijzonder de interstitiële therapie. Na de ontdekking van radium in 1898 werd in 1905 voor het eerst melding gemaakt over de toepassing ervan voor de behandeling van maligne tumoren. Met de ontwikkeling van de megavolttherapie, waarmee, in tegenstelling tot orthovolttherapie, ook diep gelegen tumoren konden worden behandeld, nam de belangstelling voor brachytherapie in de jaren vijftig en zestig af. De bezwaren die aan radium worden toegeschreven, vooral van stralings- hygiënische aard (o.a. angst voor het vrijkomen van radon bij lekkage) hebben hiertoe bijgedragen. Door de ontwikkeling van kunstmatige radioactieve isotopen, zoals het caesium-137, jodium-125 en iridium-192 en afterloading technieken, waardoor onder betere stralings-hygiënische omstandigheden kon worden gewerkt, nam de belangstelling voor brachytherapie weer toe.

Naast bestaande rekensystemen, zoals het Manchester en het Quimby systeem, werd in 1966 door Pierquin en Dutreix de grondslag gelegd voor een nieuw systeem voor dosimetrie, het zogenaamde Parijse systeem. De referentie dosis, gebieden van hoge dosis en te bestralen volume worden hierin nauwkeurig gedefinieerd. Uitgangsregels zijn: iridium van gelijke lineaire activiteit, gelijke bronlengtes, evenwijdig aan elkaar geplaatst en op onderling gelijke afstanden. Door flexibiliteit en geringe diameter is de toepassing van iridium-192 populair, vooral bij de behandeling van tumoren in het hoofd/hals gebied.
De radiobiologische voordelen van low dose-rate brachytherapie t.o.v. gefractioneerde uitwendige bestraling worden weergegeven bij de bespreking van de basisprincipes van low dose-rate bestraling. Met het doel verschillende behandelingsmodaliteiten met elkaar te kunnen vergelijken, wordt het α/β-model besproken en de relatie met de zogenaamde Extrapolated Response Dose (ERD) formulering.

Centraal in deze studie staat de toepassing van hulpmiddelen om te komen tot optimale implantaties. Het natural volume-dose histogram (NVDH) biedt vervolgens de mogelijkheid om de kwaliteit van een implantaat op objectieve wijze aan te geven en verschillen met andere technieken zichtbaar te maken.
In Deventer heeft men zich er op toegelegd te zoeken naar reproduceerbare implantatie technieken, met het Parijse systeem als leidraad. Hoewel meerdere tumorlocalisaties met behulp van interstitieel iridium werden behandeld, zijn slechts die technieken beschreven waarvoor speciale ervaring in de behandeling en zorg van een patiëntengroep is opgedaan.

Hoofdstuk 2

De behandeling van patiënten met tumoren in het mobiele deel van de tong, mondbodem en tongbasis wordt besproken. Mondholte tumoren zijn in Nederland zeldzaam en worden voornamelijk gezien bij mannen vanaf het zestigste jaar. Volgens de literatuur wordt bij een gecombineerde behandeling, bestaande uit uitwendige en interstitiële radiotherapie, een goede locale tumorcontrôle bereikt, vergelijkbaar met de resultaten van chirurgie alleen.
Retrospectief werd gekeken naar de behandelingsresultaten bij 14 patiënten met een tongcarcinoom die in de periode 1977 tot 1984 met uitwendige bestraling plus radium implantatie werden behandeld. Er werd een locale tumorcontrôle bereikt van 57%. Complicaties als gevolg van de behandeling werden niet gezien. Dit wordt toegeschreven aan een relatief lage dosis in relatie tot de totale periode van behandeling.

Op grond van deze gegevens wordt sinds 1984 gestreefd naar een hogere dosis, zowel van de uitwendige als van de interstitiële radiotherapie. Iridium-192 wordt toegepast met het Parijse systeem als leidraad. Het zoeken naar uniforme behandelingstechnieken heeft geleid tot de ontwikkeling en toepassing van applicatoren bij de behandeling van tumoren van de mondholte. Bronarrangementen en dosimetrie worden bepaald voor aanvang van de uitwendige radiotherapie om geografische missers te voorkomen. Het gebruik van een applicator biedt duidelijke voordelen boven een implantatie uit de vrije hand. De, voorlopige, resultaten laten een betere tumorcontrôle zien met aanvaardbare kans op complicaties.
Mucositis als gevolg van de bestraling werd bij alle patiënten gezien. Deze genas binnen 3 tot 4 weken na symptomatische behandeling. Radionecrose van de mandibula kan worden voorkomen door de bronnen niet te dicht bij de mandibula te plaatsen.

Het NVDH van een implantaat volgens de looping-techniek (implantatie uit de vrije hand) toont een opvallend verschil tussen gepland en gerealiseerd implantaat. Het NVDH van een implantaat met behulp van een applicator laat echter een goede overeenstemming zien tussen het geplande en gerealiseerde implantaat.

Hoofdstuk 3

Het streven naar uniformiteit in de interstitiële therapie komt vooral tot uiting bij de mammasparende behandeling. De resultaten van een retrospectieve bewerking van 113 patiënten die mammasparend zijn behandeld tussen 1981 en 1986 worden beschreven en vergeleken met gegevens uit de literatuur. Patiënten met tumoren tot een diameter van 3 cm ondergingen een sparende behandeling. Er werd een goede locale tumorcontrôle bereikt met een 5-jaars actuariële ziektevrije overleving van 89%.
Bij de beoordeling van het cosmetisch effect lijkt er geen verschil te bestaan tussen patiënten die 25 Gy of 20 Gy als surdosage op de uitwendige bestraling hebben gekregen. In vergelijking tot de literatuur werd echter een minder goed cosmetisch effect bereikt.

Aan de hand van volume berekeningen van de referentie dosis (D_{ref}) en de hoge dosisgebieden (2 x D_{ref}) bij een aantal modelimplantaten wordt aangetoond, dat werken met meerdere bronnen bij een kortere onderlinge bronafstand leidt tot kleinere volumina van 2 x D_{ref} dan bij een grotere onderlinge bronafstand en minder bronnen met behoud van gelijke volumina van de D_{ref}. De kans op grote gebieden van fibrose, als late reactie op de bestraling, wordt daardoor in evenredigheid teruggebracht.

Bij een peroperatieve implantatie, waarbij de richting van de incisie mede wordt bepaald door de richting van de te plaatsen naalden en door gebruik van een applicator, kan het doelvolume van de implantatie tot een minimum worden beperkt. Vervolgens wordt aangetoond, dat een implantatie in een vierkant-configuratie tot een betere dosisverdeling rondom het doelvolume leidt dan een implantatie in een driehoek-configuratie. De onderlinge bronafstand kan dan kleiner worden gekozen bij gelijke volumina van de D_{ref} met een geringer volume voor de hoge dosisgebieden van 2 x D_{ref}.
Significante verschillen voor wat betreft de dosishomogeniteit tussen de vierkant- en driehoek-configuratie doen zich niet voor (vergelijking van het NVDH van een driehoek-configuratie bestaande uit 7 naalden, bronlengte 7 cm en spatie 15 mm en een vierkant-configuratie van 8 bronnen, bronlengte 7 cm, spatie 15 mm laat zien, dat de kwaliteitsindex van de vierkant-configuratie een iets hogere waarde heeft dan de kwaliteitsindex van de driehoek-configuratie). Bij gebruik van templates en starre naalden kan met behulp van het NVDH de dosishomogeniteit binnen het doelvolume worden aangetoond.

Hoofdstuk 4

Na het literatuur overzicht wordt een retrospectieve bewerking beschreven van patiënten met een solitaire blaastumor die in de periode 1974 tot en met 1983 in Deventer met een radium implantatie zijn behandeld. De minimum follow-up periode bedroeg 5 jaar. De behandelingsresultaten van 46 patiënten bleken voor de tumorstadia T_1 en T_2 conform die van Van der Werf-Messing en Battermann. Het aantal complicaties was met 24% hoog en het verbijf in het ziekenhuis lang conform de literatuur. Dit wordt voornamelijk toegeschreven aan een vertraagde wondgenezing als gevolg van het gebruikte materiaal.

Een vergelijking van het Manchester systeem met het Parijse systeem voor een éénvlaks implantaat laat zien, dat, mits de regels worden gerespecteerd, geen verschillen bestaan ten aanzien van de volumina voor D_{ref} en 2x D_{ref}. Het gebruik van iridium biedt echter voordelen boven radium. De dunne, flexibele nylon slangen voor nalading met iridium zijn minder traumatisch voor het weefsel. Door deze elk afzonderlijk door blaas en buikwand naar buiten te leiden, werd geen vertraagde wondgenezing gezien, waardoor de opnameduur kon worden bekort tot gemiddeld 12 dagen. Bovendien biedt deze techniek het voordeel van afterloading.

Door gebruik te maken van konische geleiders (spacers), waardoor de nylon tubes worden geleid, worden parallelisme en onderlinge bronafstand behouden na sluiten van de blaaswand.
Met behulp van het NVDH wordt het verschil tussen het geplande en gerealiseerde implantaat weergegeven. Het gebruik van spacers om de nylon tubes op de plaats te houden en parallelisme te garanderen, kan met behulp van het NVDH worden aangetoond door de goede overeenkomst tussen gepland en gerealiseerd implantaat.

Hoofdstuk 5

De behandeling van tumoren in het distale deel van de vagina en vulva wordt beschreven. De kans op verspreiding via de lymfeklieren, waarvan de oppervlakkige liesklieren de eerste stations vormen, hangt samen met de grootte en de differentiatiegraad van de tumor. In de literatuur wordt gesteld, dat radiotherapie op de vagina gemakkelijk kan leiden tot necrose van het slijmvlies. Een aantal auteurs beschreven echter goede tumorregressie na een relatief lage (44 Gy - 55 Gy), pre-operatief gegeven dosis.
In de periode 1984 tot en met 1988 werden 14 patiënten met een tumor in het distale deel van de vagina en vulva in Deventer behandeld. Voor elke patiënte werd aan de hand van de tumoruitbreiding een applicator gemaakt, zodat voor aanvang van de uitwendige radiotherapie een bronconfigruatie kon worden bepaald. Conform de literatuur werd na de uitwendige radiotherapie een goede tumorregressie gezien en drie weken na beëindiging ervan werd de implantatie volgens plan uitgevoerd. De indruk bestond, dat complicaties, zoals necrose, zijn terug te voeren op contaminatie van het bestraalde weefsel. Door regelmatige nettoyage van het vagina-slijmvlies met een zachte desinfecterende zeep-oplossing, vooral in de periode na de applicatie, kon dit worden voorkomen. Ondanks de negatieve selectie van het ons aangeboden patiëntenmateriaal werd een goede locale tumorcontrôle bereikt.

Met behulp van het NVDH wordt een goede overeenkomst tussen gepland en gerealiseerd implantaat aangetoond. Dit is toe te schrijven aan het gebruik van een applicator en starre naalden.

Hoofdstuk 6

Door in de interstitiële therapie gebruik te maken van applicatoren en hulpmiddelen, zoals templates en spacers, kunnen de regels van het Parijse systeem worden gerespecteerd. De afmetingen van de primaire tumoruitbreiding worden op mm-papier gereconstrueerd. Het doelvolume wordt in kaart gebracht, waarna met geschatte bronlengtes de dosisverdeling wordt bepaald, zowel in dwarse als sagitale richting. Is een goede omsluiting van het doelvolume bereikt, dan kan de applicator gereed worden gemaakt en vervolgens bij de patiënt worden gepast, met de tumor nog in situ. De kans op geografische missers wordt voorkomen en de kans op over- of onderdoseringen beperkt. Van te voren kan een goede schatting worden gemaakt van de implantatieduur.

Bij het geven van interstitiële radiotherapie als surdosage wordt men niet afgeleid door tumorreductie of weefselreacties als gevolg van de uitwendige radiotherapie. Het gebruik van applicatoren leidt tot uniformiteit in de interstitiële technieken. Van groot belang is, dat er een goede overeenkomst bestaat in de uitkomst tussen een gepland en gerealiseerd implantaat. Met behulp van het Anderson NVDH wordt dit voor een aantal tumorlocalisaties aangetoond.

DANKWOORD

Het onderzoek en de bewerking van resultaten heeft tot stand kunnen komen door de medewerking en het enthousiasme van de medewerkers van het Radiotherapeutisch Instituut te Deventer en de Deventer Ziekenhuizen. Bij de bewerking van de resultaten van de retrospectieve studies van radium implantaten bij tong- en blaascarcinomen, evenals de resultaten van iridium implantaties bij het mammacarcinoom werd gebruik gemaakt van gegevens van patiënten die zijn behandeld door de collegae Dr. C. Stam, A.C.A. Mak en F.H.S. van Slooten. Ir. A. van 't Riet en Ing. P.W. Stam hebben een onmisbare rol gespeeld bij de realisatie van dit project. Het is dan ook met hun hulp, dat de uitvoering van dit project tot stand heeft kunnen komen. De medische staf van de Deventer Ziekenhuizen, waaronder de collegae Bos en Ypma, alsmede de collegae Donkers en Lamping ben ik dank verschuldigd voor hun steun en medewerking.

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Joke van Randwijk heeft met veel geduld diverse versies van het manuscript in de computer ingevoerd, waardoor het uiteindelijk drukklaar kon worden opgeleverd.

Prof.Dr. L.A. Ravasz gaf de eerste aanzet tot het bewerken van dit proefschrift.

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CURRICULUM VITAE

De schrijver van dit proefschrift werd op 1 februari 1941 te Meester Cornelis (Indonesië) geboren. De lagere en middelbare school werden in Zwolle gevolgd. In 1959 werd de studie scheikundige technologie te Delft aangevangen. Er bestond echter meer interesse voor een antropologisch georiënteerde studierichting en de studie werd aan de Medische Faculteit te Leiden voortgezet. Na het doctoraal examen was hij geruime tijd werkzaam als assistent op de afdeling Fysiologie. In 1971 werd het arts-examen afgelegd, waarna hij zich vestigde als huisarts te Den Haag. In 1979 werd begonnen met de specialisatie tot radiotherapeut (opleiders Prof.Dr. K. Breur en Mw.Dr. J.M.V. Burgers) in het Antoni van Leeuwenhoekhuis te Amsterdam. Na zijn inschrijving in het Specialisten Register bleef hij aldaar als staflid verbonden. Een speciale opleiding in de brachytherapie werd gevolgd in het Centre Alexis Vautrin te Nancy (opleider Mw.Dr. M. Pernot). Vanaf 1984 was hij gedurende 5 jaar als radiotherapeut-oncoloog werkzaam in Deventer. Thans is hij verbonden aan het St.Elisabeth Hospitaal te Willemstad, Curaçao.