General Aspects
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1 History

Radioactivity was discovered by Becquerel (Fig 1.1) in 1896 after accidental exposure of a photographic plate to uranium. Two years later Marie Curie (Fig 1.2) extracted radium from pitchblende ore and recorded her findings in the proceedings of the French Academy of Sciences. In 1903 Becquerel, together with Marie and Pierre Curie, received the Nobel Prize for Physics. After the death of Pierre Curie, Marie Curie continued her researches and received the Nobel Prize for Chemistry in 1911. (10,14)

Fig 1.1: Henri Becquerel. Fig 1.2: Marie Curie.

During the first decade of the 20th Century the first treatments with radium were performed; Danlos and Bloc (1901) irradiated lupus at the St. Louis Hospital in Paris and Abbe (1905) performed radium implants in the USA. In 1906 Danne, Dominici, Degrais and Wickham created the Radium Biological Laboratory in Paris and in 1909 Finze started treating patients with radium in England. (22) The first radium therapy book was published by Wickham and Degrais in 1909, and this reference book was rapidly translated into English. (Fig 1.3,1.4)

After the first world war several different schools of brachytherapy were created: the Radium Hemmet in Stockholm, the Memorial Hospital in New York and with Regaud and Lacassagne the Radium Institute in Paris. Progressively the bases of brachytherapy were established. (31)

The Stockholm and Paris methods for intracavitary radiation were described in 1914 and 1919 and during the 1930s the rules of the Manchester System for interstitial radium therapy were published by Patterson and Parker (28) later by Meredith. (24)

In 1934, artificial radioactivity was discovered by Pierre and Marie Curie's daughter, Irene Curie and her husband Frederick Joliot and opened the possibility of a new era of brachytherapy using artificial radionuclides.
Cobalt needles were used for a short time after the second world war, but fell out of use later on. Radioactive tantalum and gold were then used for a short time but were overtaken by iridium, which was first used by Henschke in 1958. (Fig 1.5) This is still the most widely used artificial radioactive source in brachytherapy.

During the 1950s and 1960's the first developments in afterloading were made and other new radioactive sources were developed, such as iodine and cesium. New rules of implantation and dose calculation for interstitial brachytherapy of iridium wire sources were established in Paris by Pierquin, Chassagne and Dutreix. (Fig. 1.6) This Paris System of dosimetry became widely used and the clinical results of brachytherapy improved. [8,27,30,31] These wire sources introduced new possibilities for implantations as a result of their flexibility and adaptability.

During the last two decades, the development of remote afterloading machines has allowed complete radiation protection. (Fig 1.7) In addition, the ability to vary source positions and the time that a source is in that position (dwell time) has also improved the quality of treatment. Modern imaging
facilities allow more accurate definition of target volume and the localisation of adjacent normal tissue and can also be used to guide afterloading and sources devices. (2,21,35) This, together with computerised dosimetry and better knowledge of the radiobiology involved, have made brachytherapy much more accurate and safe. (4,6,18,33,36)

Fig 1.7: One of the first remote afterloading machines for gynaecological tumours: Curietron prototype (1965)

Fig 1.8: Modern Afterloading Machines (PDR/HDR). A: MicroSelectron HDR (Nucletron); B: GammaMed plus (MDS-Nordion), C: MicroSelectron PDR (Nucletron)
6 General Aspects

High Dose Rate (HDR) brachytherapy (Fig 1.8B and C) has been widely accepted over the past two decades, particularly for the treatment of gynaecological tumours and for tumours at other sites which are not easily accessible for Low Dose Rate (LDR) techniques because of the relatively larger size and lower strength of LDR sources.

Most recently Pulsed Dose Rate (PDR) brachytherapy (Fig 1.9) has been developed. (12,18) PDR brachytherapy like HDR brachytherapy utilises a single miniaturised source which moves step by step through implanted afterloading devices to achieve the desired dose distribution. In PDR such a sequence of steps, also called a pulse, is repeated a number of times to obtain the prescribed total dose. By choosing an appropriate number of pulses one can simulate, from a radiobiological point of view, a continuous low dose rate treatment. This and other newly developed techniques allow brachytherapy to be used in a very wide variety of tumour types and sites. (32)

![VariSource (Varian)](image)

More and more sophisticated treatment planning systems are used. They can be combined with modern image information; the dose distribution is more and more conformal to the PTV (Planning Target Volume). (2,20,32,34)

2 Brachytherapy Definitions

Brachytherapy consists of a very local irradiation. The dose is delivered by one or several sealed sources. Different kinds of brachytherapy have been defined: (13,14,15,16,17,19,34)

2.1 characterised by the positioning of the radionuclides:

- interstitial brachytherapy: radioactive sources are inside the tumour
- contact brachytherapy or plesiobrachytherapy: radioactive sources are close to the tumour. Contact brachytherapy is divided into four different kinds of brachytherapy: intracavitary, intraluminal, endovascular and surface brachytherapy.
2.2 characterised by the duration of the irradiation:

- permanent implant: sources are definitely implanted, the most common radionuclides used for permanent implants are iodine, palladium and gold encapsulated in seeds. These sources have a relatively short half-life (see table 1.1A in the physics chapter), and are left in the tissue implanted for gradually delivering the dose until the activity decays. The photon energy used in permanent seed implants is low so that radiation protection can be achieved with relatively simple measures. Permanent implants are not suitable for remote afterloading.

- temporary implant (removable implants): sources are implanted for a specific time duration. The majority of removable implants are performed with iridium and cesium. This approach requires that the sources or source carriers remain in the patient for the duration of the treatment and be removed once the prescribed dose has been delivered. Most of these implants can now be performed with remote afterloading machines.

2.3 characterised by the dose rate (ICRU definitions) (16,17):

- low dose rate (LDR) 0.4-2 Gy.h\(^{-1}\)
- medium dose rate (MDR) 2-12 Gy.h\(^{-1}\)
- high dose rate (HDR) >12 Gy.h\(^{-1}\)

That means broadly speaking: LDR 10 Gy/d, MDR 10 Gy/h and HDR 10 Gy/min (14).

3 Afterloading Devices: Indications, Presentations

Afterloading technique implies a meticulous implantation of non radioactive applicators, guides, catheters or tubes later loaded by radioactive sources. These systems allow a high quality of application, and effective radioprotection.

Two kinds of afterloading systems are used: (1,11,13)

- manual afterloading systems: plastic tubes, guide gutters, hypodermic and guide needles, plastic needles, silk threads (for interstitial brachytherapy); applicators (for intracavitary or surface brachytherapy); catheters (for intraluminal applications).
- remote afterloading machines: these projectors can be used with interstitial as well as with contact brachytherapy. Afterloading equipment is connected to various types of applicators and catheters. Remote afterloading is mandatory for MDR, HDR as well as PDR brachytherapy for reasons of radiation protection. (13)

3.1 Manual afterloading systems:

Different manual afterloading systems are presented according to the different types of implants (interstitial, intracavitary, intraluminal). For each device the primary indications, presentation and timing for loading are indicated. (1,27,30,31)

3.1.1 Interstitial implant

- plastic tubes:
  - indications: head and neck (Fig 1.11), breast, skin, soft tissue sarcoma, bladder, prostate,
8 General Aspects

gynaecology, paediatric malignancies.
- presentation: supple, adaptable; size: selected lengths, external diameter 1.6mm
- afterloading: delayed

Fig 1.10: Plastic tubes in an oral cavity carcinoma. Fig 1.11: Guide gutters in a lateral border of a mobile tongue carcinoma.

- guide gutters:
  - indications: head and neck (Fig 1.12), gynaecology, urology.
  - presentation: rigid, curved or straight, single or double; size: length 30 to 60 mm, external diameter 1.8 mm
  - afterloading: immediate replacement

Fig 1.12: Penis implant with hypodermic needles. Fig 1.13: Guide needles implant as a boost in an adenocarcinoma of the breast.

- hypodermic needles:
  - indications: nose, skin, lip, penis (Fig 1.13).
  - presentation: rigid, bevelled extremities; size: length 20-80 mm, external diameter 0.8 mm
  - afterloading: immediate
plastic needles (Fig 1.14):
- indications: anus, rectum, gynaecology, brain, head and neck
- presentation: semi-flexible, maximum length 200-294 mm, external diameter 2 mm, with or without template
- remote afterloading machine

Fig 1.14 : Plastic needles and tubes.

guide needles:
- indications: head and neck, breast (Fig 1.15), pelvis…
- presentation: rigid, bevelled extremity; size: 50 to 200 mm, external diameter 1.2 mm; often used with templates
- afterloading: immediate or delayed

silk threads:
- indications: head and neck, skin (Fig 1.15), lip, eye.
- presentation: braided surgical silk thread; size: total length 1 m, selective active length from 10 to 40 mm, external diameter (when loaded) 0.5 mm
- afterloading: preloading

Fig 1.15 : Silk thread technique for a basal cell carcinoma of the internal angle of the eye (cauthus).
3.1.2 Intracavitary brachytherapy: (13,30,31)

- Applicators from standardised to personalised, made of plastic or metal:
  - indications: gynaecology, nasopharynx
  - presentation:

Standardised: Fletcher-Suit-Delcos (Fig 1.16) (uterine catheter + vaginal catheters with ovoid), Nucletron (Fig 1.17) (uterine catheter + vaginal ring catheter or catheters with ovoids), Delouche (adapted plastic-made), Baillet (universal applicator)...

Personalised: Chassagne-Pierquin mould (customized applicator).

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*Fig 1.16*: Commercially available modern Fletcher-Suit-Delcos applicator for afterloading with Ir-192 (HDR or PDR).  
*Fig 1.17*: Commercially available modern Manchester applicator for afterloading with Ir-192 (HDR or PDR).
3.1.3 Intraluminal brachytherapy: (26,32)

- indications: bronchus (Fig 1.19), oesophagus (Fig 1.20), biliary duct, endovascular
- presentation: catheters +/- adaptators

Fig 1.18 : Chassagne-Pierquin mould.

Fig 1.19 : Intraluminal brachytherapy in a cancer of the bronchus.

Fig 1.20 : Intraluminal brachytherapy in a cancer of the oesophagus.
3.1.4 Surface brachytherapy: (26,30)

- indications: skin, soft tissue sarcoma
- presentation: standardized or adapted moulds

3.2 Remote afterloading systems:

A remote afterloading system is a machine to transfer the sources from the projector to the patient and vice versa. Different systems of transport exist according to the machine and the type of radioactive source: a pneumatic system or flexible cables. (25,26)

These projectors of sources can often be wheeled from one room to the other, for performing the irradiation of the patient. They contain a shielded source(s) container (safe) and can be loaded with sources of different type, length and activity. The sources are selected for each type of target to be irradiated (e.g. LDR gynaecological brachytherapy), and catheters can be temporarily loaded with for instance a miniaturized moving source (HDR or PDR implant). (25,26)

These machines ensure accurate source positioning, a time control structure and an automatic source removal. This provides complete radioprotection for the personnel and any visitors. The tolerance of the patient is improved and the irradiation is perfectly tailored case by case (Fig 1.21). (14,25,26)

Fig 1.21: Remote afterloading machine: good patient tolerance, total radioprotection for the medical staff.
4 From how to implant a Tumour to how to report Doses in Brachytherapy

The classical dosimetry systems for interstitial brachytherapy developed in Manchester, New York and Paris all consist of three main parts: (8,9,37)

- The first part is a set of rules to describe how the radiation sources should be distributed inside a defined volume to achieve an acceptable homogeneity of dose.
- The second describes a method for calculating the dose.
- The third defines a system for dose prescription. (8,16,17)

The methods were developed before computers were available to calculate and to display isodoses and before integration with imaging, which could show whether or not the chosen isodose covered the target volume. These new developments now make it possible to adapt the dose distribution much better to the volume to be treated. In addition, remote afterloading with optimisation of source positions and dwell times enables a better dose homogeneity to be achieved than in the past. (3,12,19,23)

All brachytherapy implants start with the evaluation of volumes: (37)

- GTV: from tumour volume consisting of the primary tumour volume (GTV primary), positive lymph nodes (GTV nodal). In brachytherapy the GTV primary is essentially defined by clinical examination and imaging techniques. To define the GTV staging is taken into account.
- CTV (Clinical Target Volume): knowing from experience the risk of subclinical extension around the GTV, a safety margin is allowed around the GTV, thus determining the CTV. The GTV as well as the CTV are clinical-anatomical concepts and their definitions correspond to the ones given for external beam irradiation.
- PTV (Planning Target Volume) the PTV by definition includes GTV and CTV. The PTV is a geometrical concept and in brachytherapy PTV and CTV are, in a “perfect” implant, identical.
- Treated Volume: this is encompassed by an isodose surface corresponding to the minimum target dose, the isodose ideally encompassing the CTV.
- Irradiated volume: this is encompassed by an isodose surface corresponding to 50% of the isodose surface of the treated volume.

There is thus a tendency to adapt established systems and rules. However, this means that if some centres prescribe and specify their dose in their own way, it is impossible for others to know what has been done or how it can be compared with other series. For this reason, international guidelines for reporting dose and volume for intracavitary irradiation (ICRU 38) (17) and for interstitial brachytherapy (ICRU 58) (16) have been developed. The guidelines are not intended to make anyone change their method of working, but to provide a common language by which different methods of dose and volume specification can be compared.

There is the additional assumption that if enough people use these guidelines much valuable information can be gained on the relationships between tumour volume and the dose required to achieve cure, and between dose and volume for normal tissue complications. (5,16,17,21)
5 Quality Assurance

The aim of quality assurance (QA) in brachytherapy is to maximise the probability that each individual treatment is administered consistently, accurately and safely. (25) A very important function in LDR, HDR and PDR brachytherapy is the correct geometric localisation of the afterloading device in order to treat the target volume adequately. (3) The consistent device placement is crucially dependent on the skill of the radiation oncologist. Following the application procedure, it is primarily the physicist's responsibility to ensure that the treatment is delivered accurately and safely in accordance with the radiation oncologist's prescription.

One needs to ensure that sources of correct strength and type are accurately positioned in the applicators, as determined from the reconstruction radiographs and the treatment planning procedure.

The following physical and technical QA criteria can be applied for LDR and HDR as well as for PDR to each device or individual step in the treatment delivery process:

- Geometric accuracy: 1 mm
- Temporal accuracy: 2 %
- Dose computation accuracy: 2 %
- Source strength calibration: 3 % of group average
  5 % of individual source

A QA program is needed to guarantee that the stated criteria are met. Such a program requires periodic verification of each device. In addition regular verification of the procedures used to implement the following steps: device insertion, treatment prescription, dose computation, source preparation, source insertion, radiation protection survey, source removal, is essential. (3,23,26)

6 Radiobiology

The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate, and treatment duration. These factors vary considerably for brachytherapy as compared to conventional external beam radiation therapy. In brachytherapy, a very high dose is delivered in a short time and a limited number of fractions. These doses and dose rates would not be tolerated by normal tissues in a volume as large as that commonly treated with external beam irradiation, because of the volume-effect relationship. (4,36)

The radiobiological processes involved in continuous (LDR), hypofractionated (HDR) and hyperfractionated (PDR) brachytherapies are however similar to those involved in fractionated external radiotherapy. (6,12)

Repair of sublethal damage, tumour repopulation, and the degree of tumour oxygenation (or reoxygenation), are the main factors determining the outcome of the treatment. Variations in the dose rate are equivalent to those in dose per fraction. Increasing or decreasing the dose rate in brachytherapy is equivalent to increasing or decreasing the dose per fraction in fractionated external beam radiotherapy. (33,36)

The role of dose rate is relevant only to radiobiological mechanisms and is quite independent of
implantation parameters, such as techniques of inserting devices and sources, methods of determination, and specification of delivered dose. Both radiobiological and clinical studies have provided data, which are useful for interpreting radiobiological mechanisms. The two most important biological factors are repair capacity and repair kinetics, which change from one tissue to another. Simple mathematical formulas allow a quantitative description of the role of dose rate, and can be applied to current clinical problems. (4,6,33)

7 Indications, Contra-indications

7.1 Advantages of brachytherapy:

As far as concerns matching the PTV to the GTV, the advantages of brachytherapy are:

- A rapid fall off of dose around the radioactive sources, making it possible to increase tumour control and sparing the surrounding structures
- A short overall treatment duration which reduces the risk of tumour repopulation. (1,7,11,13,26)

7.2 Indications for brachytherapy: (see table 1.1)

Beginning in the sixties new techniques made possible a considerable increase in the scope of brachytherapy. (11,13,29) Over the past two decades, technical developments, new radioactive sources, modern afterloading machines using different dose rates, and great progress in imaging have opened new fields for brachytherapy. (2,3,32,33)

Nevertheless, before starting a brachytherapy procedure, essential basic facts must be known: the dose distribution is not homogeneous, a displacement of the radioactive sources by few millimetres will create hot or cold spots, so a perfect geometry of each implant is mandatory. (13,14)

The tumour to be implanted should be accessible, and the tumour limits should be well defined.

If these conditions are not fulfilled brachytherapy should be combined with other treatments or replaced by other therapeutic approaches.

7.3 Brachytherapy can be combined with other treatments: (11,13,26)

7.3.1 Combination with external beam irradiation

For tumours which measure 40 mm or more, frequently because of poorly defined tumour limits, the first treatment should be external beam radiation, delivering 50 Gy in 5 weeks. The brachytherapy boost will follow as soon as possible after the end of the external beam therapy, delivering a dose of at least 20 to 30 Gy in 2 to 4 days for an LDR irradiation. In practically all cases treated with MDR or HDR brachytherapy, this is delivered combined with external-beam radiation therapy, during the latter or as a boost.

One important rule to be observed with this combination: the brachytherapy target volume should always take into account the initial tumour volume.

To meet this goal the best possible description of the tumour should be made by hand drawing, photography, interstitial markers at the tumour boundaries such as ink tattoo or metallic seeds,
precise measurement (in mm) and of course all the tools offered by modern imaging. (20)

With this combination, the safety margin between the dose needed to sterilise the tumour, and the dose which will produce a necrosis of normal tissue is very narrow. In certain circumstances, there is no safety margin and one should accept a calculated risk of late complications in order to cure the tumour.

7.3.2 Combination with surgery

A perioperative implant can be indicated when the surgeon can remove most of the tumour, but is unable to guarantee a safety margin in one part of the tumour bed.

If this area of possible remaining cancer cells can be precisely described and is easily accessible, it is the best indication for intraoperative brachytherapy.

A removable implant using the plastic tube technique is always preferable to achieve postoperative afterloading. In some deep situated tumours, only a permanent implant is possible, with intraoperative loading.

7.3.3 Combination with chemotherapy

Chemotherapy, more often combined with external beam radiotherapy, can be used in T3 cancers before brachytherapy implantation. Initially enormous tumours can thus be shrunk to permit implantation. As in the combination with external radiation, the initial infiltrating tumour volume should always be considered, whatever the shrinkage of the tumour.

The indications for brachytherapy are summarised in Table 1.1 (see overleaf), according to different tumour sites, depending on the tumour size, according to the dose rate to be used, and to the afterloading system to be chosen in case of temporary or permanent implant.

These different choices are only given as proposed indications and must be discussed according to the therapeutic protocols, to the possibilities of treatment combinations and of course to the technical possibilities and experience of each treatment centre. (11,13,14,18,26,29,30,34)
### Table 1.1: Main indications of Brachytherapy

<table>
<thead>
<tr>
<th>Tumour Site</th>
<th>Tumour Size</th>
<th>Dose Rate</th>
<th>Afterloading systems</th>
<th>Implant</th>
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- **Dose rate:** L: Low, H: High, P: Pulsed
- **Implant:** T: Temporary implant, P: permanent implant
To conclude, brachytherapy will continue to play an important role in the multidisciplinary approach in the treatment of cancer. Brachytherapy requires close collaboration, based on comparison but also on competition, between radiation oncologists and site specialised surgeons and medical oncologists in order to achieve the best outcome. It does, however, require a high level of training which should be organised in radiation oncology departments with the co-operation of radiation oncologists, physicists, technologists and engineers. (14,19,29)

The insertion of radioactive material into tumours rather than shining beams of radiation in from the outside has always been a most attractive proposition and results soon showed that it was very effective. The treatment was at first difficult, potentially dangerous and subject to geographic miss.

With the aid of new technologies it is now easier, safer and much more accurate. It is for these reasons that brachytherapy retains such an important role in the multi-disciplinary management of cancer. (14, 34)

Meetings, symposiums, courses, articles, books... allow more and more international exchanges, permitting progress but also compulsions. (14)

During the last decade a lot of progress has been made in implantation systems, afterloading machines and more conforming dose distribution to the tumour and healthy structures. This progress was possible as a result of new imaging facilities, radiobiological research and collaboration with specialised companies. Nowadays a lot of people think that there is a “true renaissance” of brachytherapy. (14,26,32,34,35)

Many technical innovations have made this change possible, based on a more frequent use of new dose rates: high dose rate, medium dose rate, and pulsed dose rate brachytherapy. The technological aspects of brachytherapy are more and more sophisticated, allowing the integration of 3D imaging data and 3D dose distributions. Examples are: 3D navigation for interstitial stereotactic brachytherapy, scanner simulation and 3D virtual planning, MRI- and ultrasound-assisted brachytherapy treatment planning, CT-based software for clinical evaluation. (2,19)

Other technologies are developed for adapted and effective brachytherapy when combined with other treatment modalities, such as: radiosensitizers, hyperthermia, external beam irradiation, chemotherapy, surgery. (26)

New integrated brachytherapy units are being installed in treatment centres.

Last but not least, there is a tremendous interest of the medical community in intravascular brachytherapy to prevent restenosis in peripheral and coronary vessels. We are leaving the field of malignant diseases here, but this kind of brachytherapy is a good example to show the necessity of collaboration, common language, technical progress, clinical trials, economical and ethical aspects… all these parameters constituting the necessary bases for the future of brachytherapy (Fig 1.22). (32)
Fig 1.22: The future of Brachytherapy. Integration of modern imaging (MRI, CT, US) computer assisted treatment planning with DVH analysis and stepping source technology for gynecology and prostate cancer.
9 References


33. Steel GG. *Basic Clinical Radiobiology* 1997; London: Edward Arnold.


