MEDICAL APPLICATIONS OF ELECTRON LINEAR ACCELERATORS

A.Wambersie and R.A. Gahbauer***

* Service de Radiothérapie - Oncologie, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium
** Division of Radiation Oncology, Ohio State University Hospitals, Columbus, Ohio, USA

Abstract

The role of radiation therapy in cancer management is first defined: today among the cancer patients who are cured (≅ 45 %) about one half are cured by radiation therapy applied alone or in combination with surgery or chemotherapy. The experience accumulated in decades shows that, to be efficient, the radiation treatment must be delivered with a high physical selectivity. At present, electron linear accelerators are the primary equipment of a modern radiotherapy department, and a large proportion of the patients are treated with a linear accelerator for at least part of the treatment. Photon beams of about 6-20 MV have, in general, a sufficient penetration in the tissues to treat most of the tumours with an adequate physical selectivity. A single beam is never used alone, but a combination of several beams adequately oriented allow the radiation-oncologist to deliver the prescribed dose to the target volume without exceeding the tolerance of the surrounding normal tissues. Modern linear accelerators also allow us to apply electron beam therapy. Electron beam therapy is suitable for the treatment of superficial lesions (e.g., skin tumours) and is also the best available irradiation treatment for Intra-Operative-Radiation-Therapy (IORT). Finally, conformation therapy, which is developed in many well-equipped and well-staffed centres, will probably further improve, in the near future, the efficiency of linear accelerators at least for some tumour locations.

1. INTRODUCTION — ROLE OF RADIATION THERAPY IN CANCER MANAGEMENT

Electron linear accelerators today constitute the core of the equipment of a modern radiation therapy department. Nowadays, the majority of the patients referred to a radiation therapy department are treated with a linear accelerator for at least part of their treatment. It is likely that this will remain true for the foreseeable future. Linear accelerators thus play, and will keep playing, a significant role in cancer management in general and are responsible for the therapeutic success obtained in many tumour treatment. To illustrate the situation, Table 1 gives the number of linear accelerators at present used in France for radiotherapy applications (their type and energy). The numbers of the other radiotherapy units are also given for comparison [1].

Cancer has an increasing impact on the death rates in the Western world, as well as in the developing countries. For example, in 1980, 730 000 deaths were attributed to cancer in the countries of the European Union and there were 1 186 000 new cancer cases diagnosed in that year alone [2, 3]. These estimates exclude non-melanoma skin cancer, which, although a rare cause of death, nevertheless demands medical care. Even with the current prevention programs, the numbers will further increase within the next two decades. Similar figures have been published for North America.

Table 1

Number of radiotherapy units in France, on 1 January 1994 [1)]

A. LINEAR ACCELERATORS					
	GECGR Mev		Other companies		Total
4-6 MV	NEPTUNE 6	18	Philips (SL 75/5)	8	
	ORION 5		Clinac 600 C	4	31
10 MV	NEPTUNE 10	27			
	SATURNE 1M	3			30
15 MV	SATURNE 15	5			
	SATURNE 1	9	Philips (SL 18)	4	34
	SATURNE 41	16			
20 MV	SATURNE 20	9	Philips (SL 75/20)	3	
	SATURNE 11	9	Siemens Mevatron	19	
	SATURNE 42	4	Clinac 2100 C	4	48
25-40 MV	SAGITTAIRE 32 MV	10			
	SAGITTAIRE 40 MV	2			17
	SATURNE 25 MV	5			
20-25 MV	SATURNE 111	4			4
25 MV	SATURNE 43	35	Philips (SL 75/25)	9	44
Total Linear Accelerators		157		51	208 (+ 19)

B. OTHER TYPES OF RADIATION THERAPY UNITS		
RX 50-100 kV	116	(-6)
RX 150-305 kV	34	(-8)
Cobal Units (including 1 gamma knife)	144	(-19)
Betatrons	1	(-2)
Cyclotron neutron therapy	1	
Cyclotron neutron + protontherapy	1	
Synchrotron protontherapy	1	

1) The differences since 01.01.1993 are given (+) or (-)

Today, at the first consultation, approximately 65% of the patients have apparently localized tumours. About 2/3 of these are cured either by surgery, radiotherapy, or a combination of both treatments. In this group of patients with probable but unproved subclinical metastatic disease, chemotherapy used as an adjutant treatment may prolong life and maybe cure some additional patients.

Among the other 35% of patients arriving at the first consultation with already inoperable or metastatic disease, only about 5% will be cured by combined treatment including chemotherapy and immunotherapy as well as radiotherapy and/or surgery (Table 2). Although there is promising progress in the field of medical oncology, this cure rate is largely limited to solid paediatric tumours, leukaemias, lymphomas, and testicular tumours. These tumours represent only about 5% of all cancers seen in a general population [4-6]. Although these percentages [5] are useful as an indication of the contribution of the different techniques to cancer cure, they will become progressively less relevant to the extent that combination of these different techniques is more and more successfully applied.

It is axiomatic that one must control the local disease if one aims ultimately at curing any cancer patient. In fact, it has been shown that 1/3 of the patients who die of cancer had uncontrolled local disease. If local failure could be reduced by 50%, one could expect a 10-15% improvement in cure rate [7].

Surgical techniques have already reached a very high level. Further improvement will be seen in a reduction of mutilating procedures (limb-sparing operation, breast-conserving therapy, reduction of colostomies, and urinary diversions). On the other hand, wider excisions are still

foreseeable as a result of safer anaesthesiology, intensive care support, and improvement in reconstructive surgery.

Table 2
Summary of the present situation concerning cancer cure rate

Patients	Cure rate %	
With localised tumour:	65	
cured by surgery		22
cured by radiotherapy		12
cured by combination of surgery and radiotherapy		6
With inoperable or metastatic disease:	35	
cured by combined treatment including chemo- and immunotherapy		5
Total	100	45

Furthermore, the combination, on a wider scale, of surgery with irradiation will help to increase the local control rate. In that respect, Fletcher (M.D. Anderson Hospital, Houston) has shown that, after radical surgery, doses of 50 Gy given over 5 weeks are able to eradicate expected occult infestation ("subclinical disease") in the lymphatic nodes for cancer of the breast, upper respiratory and digestive track and some pelvic tumours, in more than 90% of the cases. Doses of 50 Gy do not exceed the tolerance limit of many normal tissues.

Today, about 70% of the cancer patients are referred to a radiation therapy department, either for a radical treatment (aiming at a local control) or after surgery (also aiming at a local control) or for a palliative treatment often in combination with chemotherapy (e.g., a painful bone metastasis) [8].

2. RATIONALE FOR RADIATION THERAPY

Soon after the discovery of x-rays by Röntgen in 1895 and of radium by Marie Curie in 1898, it became evident that ionizing radiations could sterilise malignant tumours and thus cure cancer patients. It also became rapidly evident that, above a certain dose level, x-rays induce damage to the normal tissues they traverse.

The effects produced by radiation are not instantaneous. In particular, tumour shrinkage after irradiation is a process extending over weeks or even months. This is due to the fact that cells, doomed to die, do not disappear immediately: they remain present for hours or days; sometimes they are able to undergo a few divisions before disintegration and elimination. This progressive tumour shrinkage reduces the risk of acute complications, such as haemorrhage after electro-coagulation. It is a major advantage of irradiation for cancer management [9].

Since local control probability increases with dose, radiation must reach the whole volume(s) of tissues invaded by malignant cells at a sufficiently high dose level to be effective. This goal must be reached without inducing severe and irreversible sequelae in the surrounding normal tissues. A first approach to reach this goal is the improvement of the physical selectivity.

2.1 Physical selectivity of a therapeutic irradiation

The physical selectivity of irradiation is defined as the ratio of the dose to the "tumour" relative to the dose to the surrounding "normal tissues". It can be improved by varying the nature and energy of the radiation or the beam arrangement (number and orientation of the beams, and their size and shape as in conformation therapy).

The best historical illustration of the importance of the physical selectivity in radiation therapy is the impressive improvement in the clinical results achieved in the 1950's–60's when 200 kV x-rays (orthovoltage) were replaced by cobalt-60 gamma rays and high-energy x-rays, as shown in Table 3. The high-energy x-rays mentioned in this table are x-rays (≥ 2–3 MV) produced by Van de Graaff machines, betatrons or electron linear accelerators. Linear accelerators have played an important role in the improvement of the physical selectivity in radiation therapy in the last decades, as will be discussed in detail in the following sections.

Table 3

Improved survival of patients with several types of cancer treated with megavoltage radiotherapy

Type of cancer	Survival (%) after	
	200 kV x-rays	High-energy x-rays
Hodgkin's disease	30–35	70–75
Cancer of the cervix	35–45	55–65
Cancer of the ovary	15–20	50–60
Cancer of the bladder	0–5	25–35
Cancer of the prostate	5–15	55–60
Seminoma of the testis	65–70	90–95
Embryonal cancer of the testis	20–25	55–70
Cancer of the nasopharynx	20–25	45–50
Cancer of the tonsil	25–30	40–50
Retinoblastoma	30–40	80–85

From the Conquest of Cancer, Report of the National Panel of Consultants of the Committee on Labor and Public Welfare United States Senate, November 1970, p. 51 [9].

Today, with modern techniques, most critical normal tissues such as brain, eyes, spinal cord, kidneys, liver, etc. may be completely avoided or at least irradiated at levels well below tolerance (except, of course, in special cases depending on the tumour location: e.g. the normal brain is the normal tissue at risk when a brain tumour is treated, similarly the spinal cord is the normal tissue at risk when some cervical or mediastinal tumours are treated, etc.).

Physical selectivity is a second specific advantage of radiation therapy compared to chemotherapy in which all the tissues in the body are exposed to the toxic drug.

The real situation is however more complex. Outside the limits of the detectable tumour (i.e. the "gross tumour volume" as defined below), there is in general some "subclinical" involvement. A larger tissue volume must then be irradiated: not only the gross tumour volume itself but also a surrounding safety margin and, in some cases, the regional lymph node areas. Several types of volumes thus have to be defined and identified.

2.2 Concepts and definitions of volumes used in radiation therapy

Gross Tumour Volume (GTV)

Radiation oncologists first identify the gross tumour volume (GTV), which is the gross palpable or visible extent and location of the cancer disease (ICRU Report 50, [10]). The shape, size and location of the GTV is determined by means of different diagnostic methods such as clinical examination (e.g., inspection, palpation, endoscopy) and various imaging techniques (e.g., x-ray, CT, ultrasound, MRI, etc.). The gross tumour volume consists mainly of malignant cells, connective tissue and blood vessels, and necrotic areas.

Clinical Target Volume (CTV)

Clinical experience has shown that around the GTV there is in general "subclinical involvement", i.e., individual malignant cells, small cell clusters, or microextensions which cannot be detected by the clinical or imaging procedures. Thus a safety margin surrounding the GTV must be irradiated to ensure local control of the disease. The size of the safety margin depends on the type of tumour, its location, and its tendency to invade the surrounding normal tissues (histology, grading, etc.). The GTV together with this safety margin consisting of tissues with presumed or proven subclinical involvement is defined as a Clinical Target Volume (CTV).

In addition to the safety margin around the tumour, other volumes with presumed or proven subclinical spread (such as regional lymph nodes) may also require irradiation. The Clinical Target Volume is thus the tissue volume that contains a demonstrable GTV and/or presumed/proven subclinical microscopic malignant disease. This volume must be treated at an adequate dose level (and time-dose pattern) to achieve the aim of therapy, cure, or palliation.

Planning Target Volume (PTV)

To ensure that all tissues included in the CTV receive the prescribed dose, one has, in principle, to plan to irradiate a volume geometrically larger than the CTV. It is the Planning Target Volume or PTV.

The additional safety margin, included in the PTV, results from a number of factors:

- movements of the tissues which contain the CTV (e.g., with respiration), as well as movements of the patient.

- variations in size and shape of the tissues that contain the CTV (e.g., different fillings of the bladder, rectum, stomach).

- all variations and uncertainties in beam geometry and patient-beam geometry. There are some uncertainties in the beam sizes, shapes and directions, as well as in the relative position of the beam with respect to the patient, the CTV and the normal tissues.

- all uncertainties in dose distribution, especially in or close to the penumbra region, or where inhomogeneities have to be taken into account (e.g., beam penetration for electron beams).

Delineation of the PTV is a matter of compromise and depends upon the judgement of the radiation-oncologist, who ultimately bears the responsibility for this decision. In particular, too-large safety margins will result in unnecessary side effects and complications.

2.3 IMPROVEMENT OF THE DIFFERENTIAL EFFECT. A PROBLEM FOR THE RADIOBIOLOGIST

As defined above, the safety margins contained in the CTV and in the PTV consist primarily of normal tissues and, only for a small proportion, of invading cancer cells. Because of the presence of these cells, the safety margin should be irradiated in principle to the highest possible dose to prevent a local recurrence, but the tolerance of the normal tissues included in the safety margin limits the dose which can be prescribed.

The difficulty cannot be solved by improving the physical selectivity of the irradiation; it requires an improvement of the differential effect, and this brings us from the field of physics to the field of radiobiology. Improvement of the differential effect implies, for a given (physical)

dose, increasing the effect of the cancer cell population and/or reducing the effects on the normal tissues [11, 12].

The possibility of improving the differential effect by adequately selecting the irradiation parameters is the third advantage of radiation therapy for cancer management.

Historically the first, and presently the most efficient, method for improving the differential effect was the fractionation of the dose, as initiated in 1919 by Regaud, Ferroux and Coutard at the Fondation Curie in Paris. Today, five fractions of 2 Gy each per week are used as the conventional fractionation for most treatments.

As a further refinement, the fractionation could be adapted to the growth characteristics of the individual tumour (such as, the tumour doubling time, or better the potential doubling time, T_{POT}). In that respect, an EORTC study has shown that a shorter overall time brings a benefit for some head and neck tumours with short T_{POT}. This implies the administration of several small ($\leq$ 1.5 Gy) fractions per day, since large fraction sizes are known to be harmful.

Combination of radiation with radiosensitizers is another method to improve the differential effect. Drugs such as misonidazole are used to sensitize selectively hypoxic cancer cells. Other drugs, such as actinomycin D, bleomycin, adriamycin, 5-fluorouracil, and, more recently, cis-platinum have been used as radiosensitizers in the treatment of oesophagus, lung, or intestinal tumours. Besides any synergistic effects, radiation and drugs have several complementary actions which further justify their therapeutic association.

A third possibility for improving the differential effect is to replace x-rays (and other low-LET radiations) by high-LET radiations (ICRU Report 45 [10]). High-LET radiations bring a benefit for well-differentiated, slowly growing tumours and/or for tumours containing a large proportion of hypoxic cancer cells [13-15].

2.4 ACCURACY REQUIRED IN RADIATION THERAPY

Whatever the improvement in the radiobiological differential effect, the doses which are needed to control a malignant tumour are often of the same order of magnitude as the tolerance doses for the normal tissues. In addition, radiobiological and clinical evidence indicates that the dose-effect relations for tumour control are steep (Table 4) [16–18]. For some tumours, a dose variation of a few percent can modify significantly the observed local control rate. The dose-effect relations are even steeper for normal tissue complications (Table 5) [17]. For these two reasons, accurate dosimetry is needed, and, in 1976, the ICRU made the following recommendations: "the available evidence for certain types of tumours points to the need for an accuracy of $\pm$ 5% in the delivery of an absorbed dose to a target volume if the eradication of the primary tumour is sought" (ICRU Report 24 [10]). More recently (1987), Mijnheer et al. [17] recommended an accuracy in absorbed dose delivery of 3.5% (one standard deviation, for the dose at the specification point, for radical treatment).

Over the years, the ICRU has played an important role in the world-wide improvement of dosimetry in radiation therapy. An important step in that direction was the definition of quantities and of a system of units (ICRU Report 33 [10]). Besides quantities and units, the ICRU has focused a great part of its efforts on the selection of procedures suitable for the measurement and application of these quantities. This implies a critical review of the existing procedures, value judgement, and finally the recommendation of selected procedures. These should be well described and codified, and widely accepted in the different countries.

Several ICRU Reports have dealt with dosimetry protocols for photon therapy: Reports 14, 17, 23, 24 and 42 [10]. For electron beam therapy, Report 35 remains a world-wide reference. Other ICRU Reports have contributed to a better accuracy and uniformity of dosimetry procedures in radiation therapy: Reports 44, 46 and 48.

Table 4

Relative steepness of the dose-effect curve for local tumour control. The steepness is expressed as the relative increase in absorbed dose (in %) producing a change in tumour control probability from 50 to 75%.

Site of tumour	Steepness (%)
Supraglottic larynx T_2 and T_3 (Shukovsky)	5
Larynx T_3 (Stewart and Jackson)	6
Supraglottic larynx all stages (Hjelm-Hansen et al.)	11
Larynx all stages (Hjelm-Hansen et al.)	12
Bladder T_{4B} (Battermann et al.)	13
Epidermoid carcinoma head and neck (Cohen)	13
Supraglottic larynx T_1 and T_2 (Ghossein et al.)	13
Skin and lip (Strandqvist)	17
Supraglottic larynx T_2 and T_3, revised analysis of the Shukovsky date (Thames et al.)	17
Nasopharynx T_1 and T_2 (Tokars and Griem)	18
Nasopharynx (Moench and Philips)	19
Lymphoma (Fuks and Kaplan)	21
Retromolar trigone/anterior faucial pillar T_1 and T_2 (Thames et al.)	21
Bladder all stage (Morisson)	26
Base of tongue T_1 and T_2 (Thames et al.)	31
Tonsillar fossa T_3 and T_4 (Thames et al.)	32
Hodgkin (Kaplan)	46
Base of tongue T_3 and T_4 (Thames et al.)	50

Table 5

Relative steepness of the dose-effect curve for normal tissue reaction The steepness is expressed as the relative increase in absorbed dose (in %) from 25% to 50%

Normal tissue reaction	Steepness (%)
Major chronic complications of the larynx (Harwood and Tierie)	2
Peripheral neuropathy (Stoll and Andrew)	3
Late skin damage (Battermann et al.)	4
Late intenstinal damage (Battermann et al.)	4
Brachial plexus (Svensson et al.)	5
Radiation pneumonitis (van Dijk et al.)	6
Skin reaction (Turesson and Notter)	7
Major complications of the intestine and bladder (Morrison)	9
Skin and lip (Strandqvist)	10
Myelitis (Phillips and Buschke)	15
Major and non major complications of the larynx (Ghossein et al.)	17

3. SHORT DESCRIPTION OF A MEDICAL LINEAR ACCELERATOR

In medical linear accelerators, the charged particle is an electron and the RF accelerating electric field oscillates at about 3000 MHz. For comparison, radio waves in standard amplitude modulation broadcast channels oscillate at about 1 MHz [19].

The electrons are thermo-ionically emitted from a concave metal cathode at 1000 ˚C and accelerated in the gun to about 1/4 the velocity of light by a pulsed dc electric field. They are then formed (coalesced) into a pencil beam by a convergent electric field between the gun electrodes. The RF electric field in the accelerating tube then forms the electron stream into bunches and accelerates them to more than 99% of the velocity of light, increasing their mass (e.g., by a factor of 13 at 6 MeV). The electrons then bombard the target (e.g., tungsten). When an electron enters a tungsten target, the positively-charged nuclei of the tungsten atoms pull on the negatively-charged electron, shaking it violently as it passes by one such tungsten atom after another. These high-energy electrons give up a portion of the energy at each successive atom that they penetrate and emit hard, penetrating x-rays in the forward direction. Two sets of tungsten blocks allow the sizes of the radiation beam (square or rectangular sections) to be adjusted.

All modern medical electron linacs employ an isocentric gantry. The accelerator wave guide is mounted in the gantry, either (relatively) parallel to the gantry axis if a beam bending magnet is employed, or perpendicular to the gantry axis if a beam bending magnet is not required (low energy, e.g. 4 MV x-ray beam). A simplified block diagram of a medical linear accelerator is presented in Fig. 1.

More and more modern linear accelerators are equipped with a multileaf collimator which typically consists of two sets of 20 leaves which can be moved independently allowing the application of irregularly-shaped beams better adapted to the complex shape of the target volume (Fig. 2) [20].

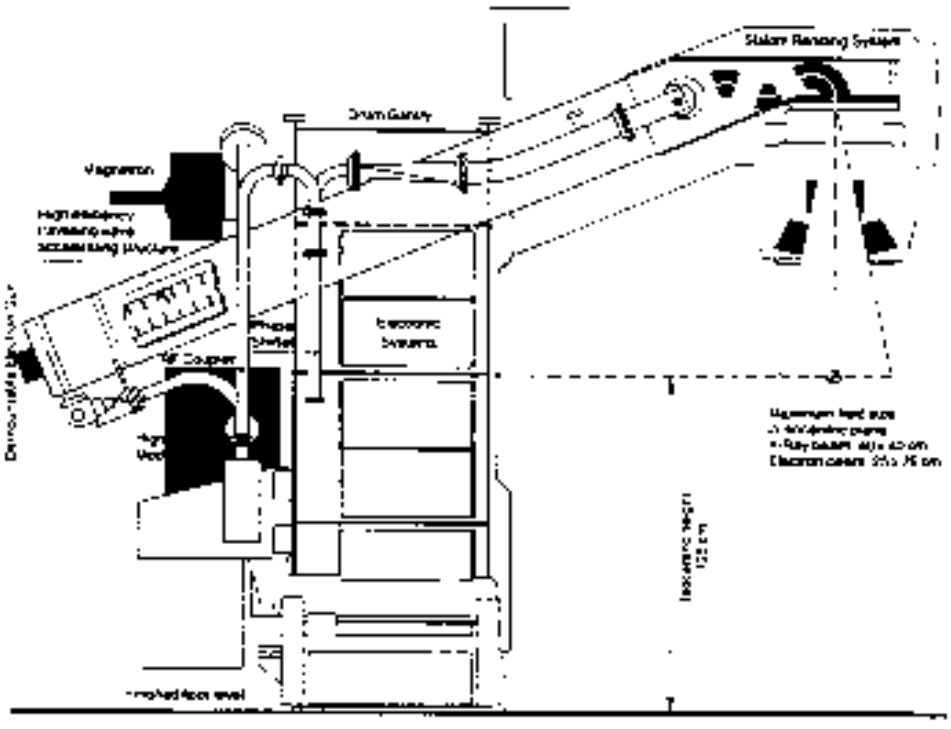


Fig. 1 Simplified block diagram of a medical linear accelerator

4 THERAPY WITH HIGH-ENERGY PHOTON BEAMS

The most important characteristics of a therapeutic photon beam are the penetration in the irradiated tissues (depth/dose curve), the skin sparing effect and the penumbra. For clinical applications, a single beam is seldom applied; and, for each patient, the optimal combination involving several (or many) photon beams has to be selected.

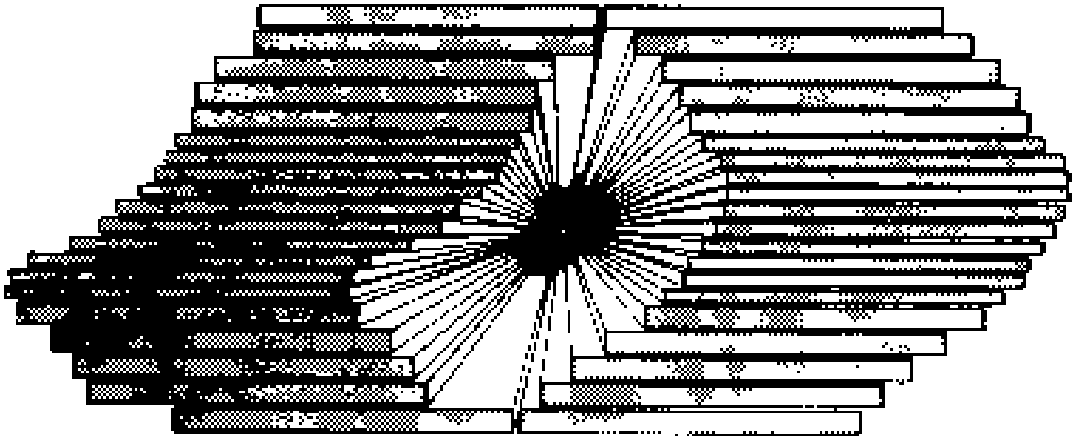


Fig. 2 Principle of a multileaf collimator. It consists of two sets of 20 leaves which can be moved and adjusted independently. As a result, beams of any shape can be applied to closely match the shape of the target volume. Target volumes with complex shapes can be treated with minimum irradiation of the surrounding normal tissues [20].

4.1 Beam penetration — depth/dose curves

The penetration of the beam increases with energy (Fig. 3). The depth/dose curves describe the variation of absorbed dose (relative to the maximum dose) as a function of depth, in the irradiated medium, on the beam axis.

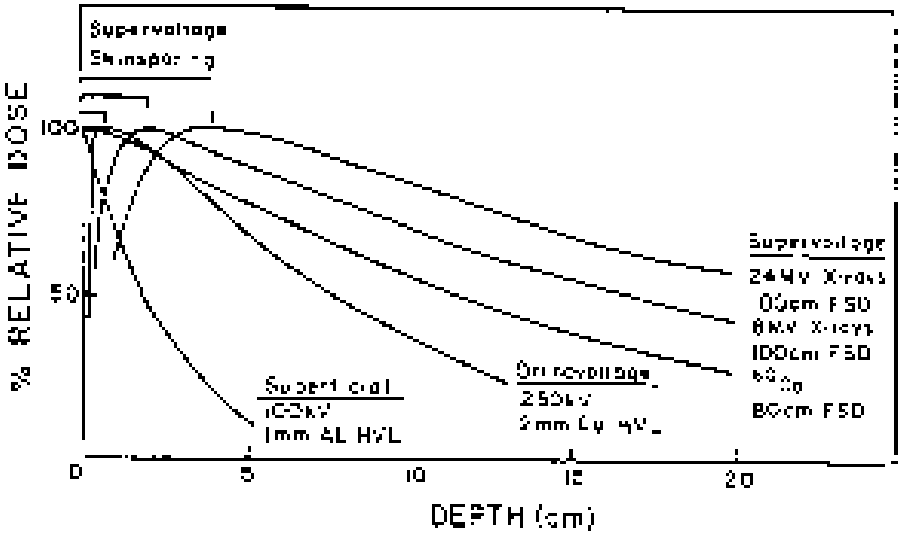


Fig. 3 Depth/dose curves for therapeutic photon beams of different energy. Low-energy x-ray beams (100 kV) are still in use and are suitable for treating skin lesions. Orthovoltage x-rays (200-500 kV) are totally inadequate to treat deep seated tumours; they are nearly completely abandoned. Cobalt-60 is satisfactory for many clinical situations but x-ray energies between 8 and 24 MV are needed to obtain adequate depth dose/curves. In addition to an improvement of the beam penetration with energy, there is a sparing effect which also increases with energy. Epidermis only is spared with cobalt-60 but the subcutaneous tissues are also protected with 8-24 MV photons.

X-rays of about 100 kV ("low-energy" x-rays) are still in use, but only for the treatment of superficial (skin) lesions. Conventional x-rays ("orthovoltage", 200-250 kV) were the only treatment available up to 1955–1960, before cobalt-60, betatrons and linear accelerators were available.

Cobalt-60 provides irradiation conditions which are satisfactory for a large proportion of clinical situations. Cobalt-60 emits gamma rays at 1.17 and 1.33 MeV respectively. Due to the simple construction of the machine, cobalt units are the ideal equipment for developing countries.

Linear accelerators of about 8 MV and above allow most of the tumours to be treated with good physical selectivity. There is no clear advantage in increasing the x-ray beam energy beyond 20-24 MV.

The importance of beam energy in irradiating deep seated tumours is better illustrated on Fig. 4, where the doses are normalized at the depth of the centre of the target volume.

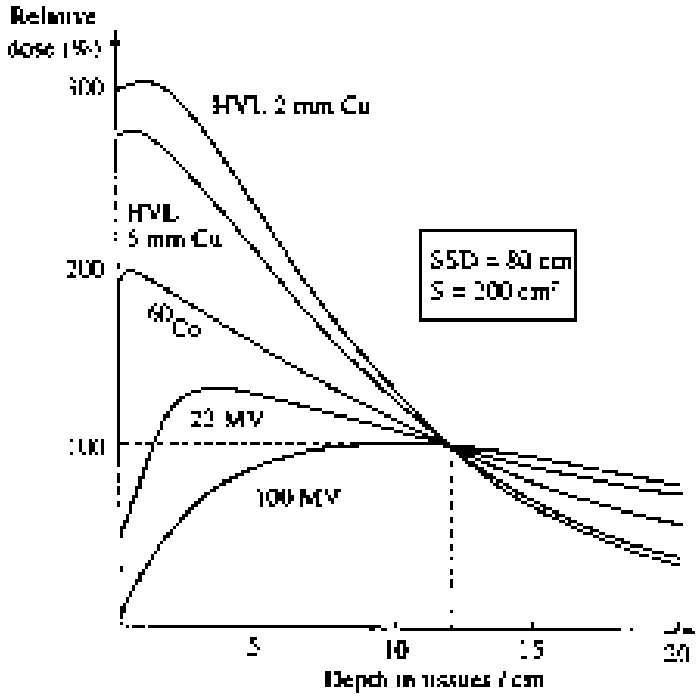


Fig. 4 The depth/dose curves for different photon beam energies are normalized at 12 cm in depth (e.g. difficult situation for an obese patient). This presentation better illustrates the excessive dose delivered to the normal tissues located in front of the PTV when 200 kV x-rays or (to a lesser extent) cobalt-60 are used.

4.2 Skin sparing

When only 200 kV x-rays were available, the acute skin reactions often prevented the radiation-oncologist from delivering the appropriate dose to the deep seated tumours.

For photon energies higher than 2–3 MV, the maximum absorbed dose is not observed at the surface of the irradiated medium, but a few millimetres below the surface. This skin sparing effect is due to a lack of "electronic equilibrium" (ICRU 24 [10]).

For cobalt-60, the acute skin reactions are dramatically reduced. Furthermore, for photon energies of about 8 MV and above, there is a significant reduction of the absorbed doses at the level of the subcutaneous tissues which reduces the risk of late fibrosis. A reduction of the absorbed dose at the level of the subcutaneous tissues also facilitates healing of the surgical wound if surgery is needed after irradiation.

4.3 Penumbra

Ideally, the absorbed dose within the geometrical limits of the photon beam should be homogeneous and the absorbed dose outside the beam as low as possible. Unfortunately, at the border of the beam, there is a narrow region with a steep dose gradient: it is the "penumbra region".

The penumbra width is defined, at a given depth, as the distance between two selected isodose levels, i.e., between the 80% and 20% isodoses or between the 90% and 10% isodoses (100% being the maximum absorbed dose on the beam axis at that depth). In all cases, the two isodose levels used for defining the penumbra should be specified (Fig. 5).

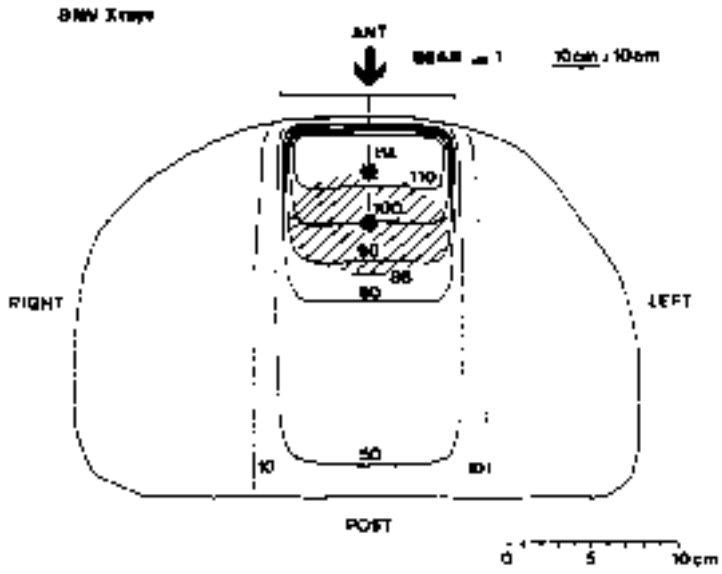


Fig. 5 Dose distribution obtained with a single 8 MV photon beam (beam size 10 cm x 10 cm). Transverse section through the patient body; the planning target volume (PTV) is indicated by the hatched area. The dose is specified at the centre of the PTV (100%), it varies within the PTV from 114% to 86%. From ICRU 50 [10].

4.4 Beam combination

An acceptable dose distribution cannot be achieved with only a single photon beam. The normal tissues in front of the target volume receive too high a dose, and the normal tissues behind the target volume also receive a significant dose (see again Figs 3 and 4).

In the "cross-fire" technique, several beams that intersect at the level of the target volume are used; as a result, the surrounding normal tissues at risk are irradiated only by one beam. The number and the orientation of the beams are selected by the radiation-oncologist; it is a matter of judgement and experience to select the optimal beam arrangement for each particular patient. Some examples of treatment schemes are presented in Figs 6–9.

5. ELECTRON-BEAM THERAPY

Besides photon-beam therapy, modern linear accelerators allow electron-beam therapy to be applied. For that purpose, in the accelerator head, the target is removed and the beam of accelerated electrons is directly oriented towards the patient and the PTV.

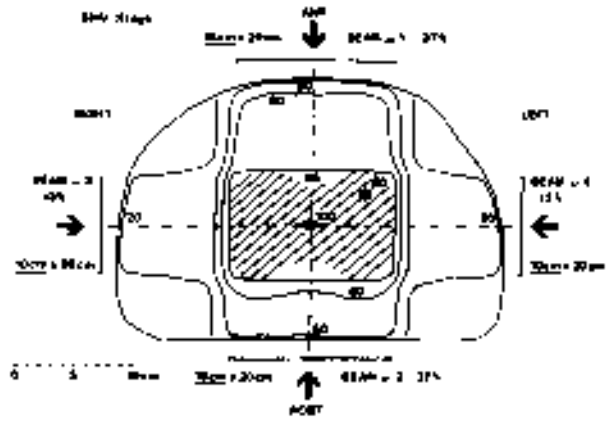


Fig. 6. Transverse section through the pelvis, with the display of the dose distribution resulting from four beams: two sets of two parallel opposed beams orthogonal to each other ("box technique"). The PTV is indicated by the hatched area. The dose is specified (100 %) at the centre of the PTV and on the beam axes. The dose within the PTV ranges from 103 % to 95 %. This beam arrangement can be used for the treatment of a locally-extended cervix carcinoma. From ICRU 50 [10].

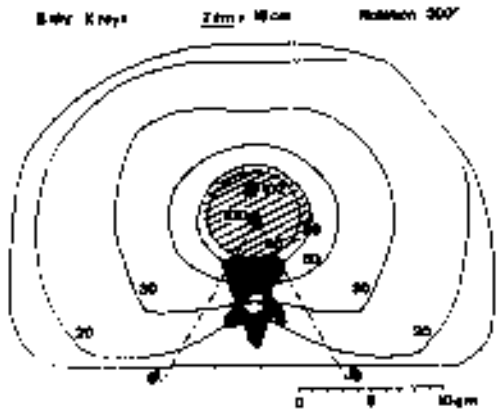


Fig. 7. Transverse section through the thorax, with the display of the dose distribution resulting from a moving beam treatment with an 8-MV photon beam (large arc 300°). The PTV is indicated by the hatched area. The dose is specified at the centre of the target volume (100 %) and on the central axis of the moving beam. The dose variation within the PTV ranges from 102 % to 80 %. This irradiation technique can be used e.g. for the treatment of a mediastinal tumour (oesophagus as presented in the figure) or a prostatic tumour. From ICRU 50 [10].

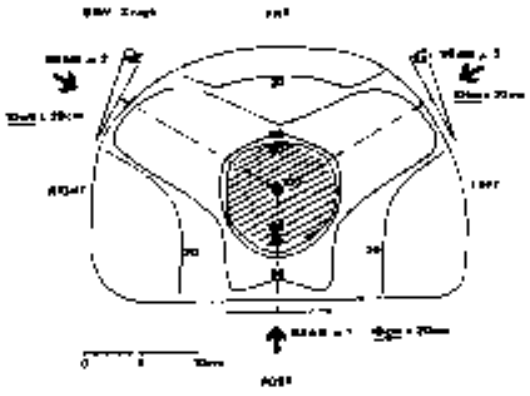


Fig. 8 Three equally weighted 8-MV photon beams are converging towards the centre of the PTV. Wedge filters (45 °) are used for beams # 2 and 3 to achieve a homogeneous dose distribution throughout the PTV. From ICRU 50 [10].

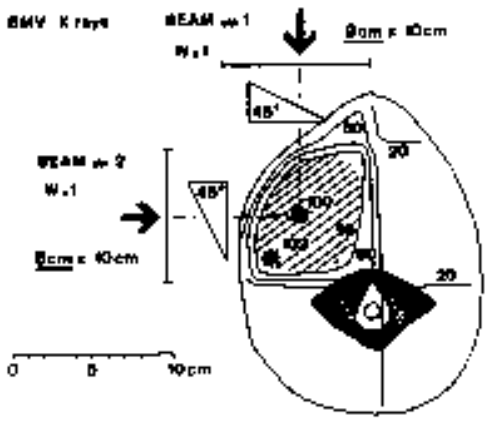


Fig. 9 Irradiation of a lateral lesion (e.g. floor of the mouth). Two orthogonal 8-MV beams with 45° wedge filters are used. From ICRU 50 [10].

5.1 Electron beams

The penetration of the electron beams in the tissues is much shallower than that of the x-ray beams and, in addition, can be adjusted by varying the energy of the incident electrons (Fig. 10). Therefore, electron-beam therapy is used to treat superficial or semi-deep-seated tumours extending (close) to the skin surface. Beyond the depth of the maximum, the dose falls off rapidly (but to a lesser extent when the initial energy increases). Figure 11 presents, as an example, the dose distribution for a 20 MeV electron beam. Treatment energies range from about 4 to 20–25 MeV, but some accelerators reach higher energies (e.g., 35 MeV for a Sagittaire and 50 MeV for the race-track microtron).

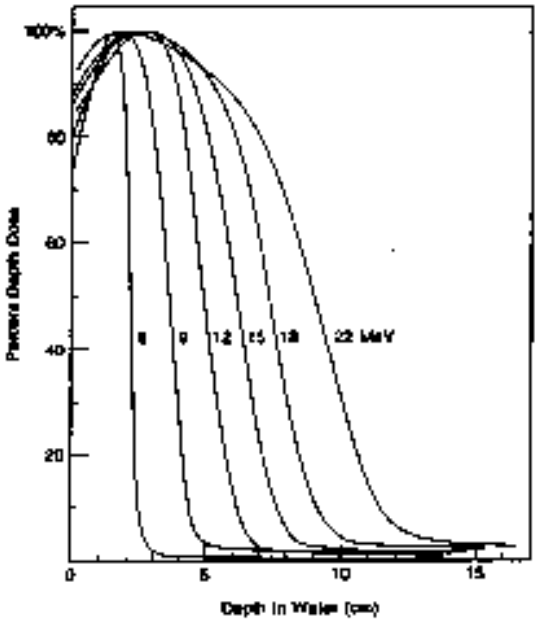


Fig. 10 Central-axis depth/dose curves for electron beams of different energy, from 6 to 22 MeV (field size: 10 cm x 10 cm; source/skin distance: 100 cm). The steep fall-off of the dose, especially at the low energies, protects the normal tissues located beyond the PTV.

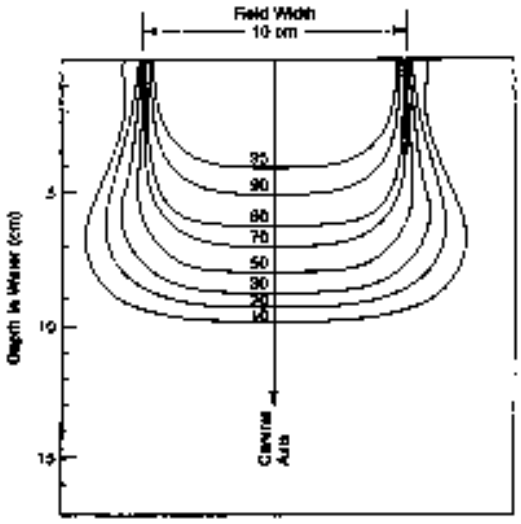


Fig. 11 Isodose curves for a 20 MeV electron beam in a water phantom (10 x 10 cm; source/skin distance: 100 cm). Scattering of the electrons in the medium is responsible for the widening of the isodose curves with increasing depth.

Electron beams are used for 10–25 % of the patients referred to the radiation therapy department, this proportion varying from country to country and from centre to centre depending on the local treatment policy. Electrons are often used in combination with photon beams (e.g., as a boost against the residual tumour). Two specific applications of electron beams deserve to be mentioned.

5.2.1 Total skin electron therapy

A skin cancer, mycosis fungoides, is most often treated in this way. The aim of the basic treatment is to irradiate the total skin envelope as homogeneously as possible. The depth of the lesions suitable for this type of treatment varies with the stage and type of disease and/or the body surface. This may lead to the use of different beam penetrations. When tumourous lesions are present, there may be a need for a special boost and/or shielding.

The maximum depth of the PTV varies from approximately 5 to 15 mm in most of the lesions. For the most frequent indications, with localised and even generalized plaques, the

PTV is located within the first 5 mm. Infiltrated plaques, ulcerations, and tumourous lesions justify an individual estimate of the thickness of the lesions whenever possible.

Different technical approaches have been developed using multiple fields, arc therapy, patient rotation, patient translation, according to the available local equipment and facility (Figs 12, 13) [21]. In the past, low-energy x-rays were the only possibility, but they tend to be less frequently used since the implementation of low-energy electron beam techniques using linear accelerators. As a general rule, the integral dose should be kept as low as possible. Usually, the incident electron beam energy at the level of the patient skin ranges from 3 to 7 MeV with nominal energy ranging from about 4 to 10 MeV (i.e., accelerator energy at the exit window). Such energy losses are due to the material in the treatment head, the air gap between the exit window and the patient, and the use of scattering screens. The use of scatter energy degrader (typically a 1 g. cm^{-2} lucite panel) close to the patient improves dose uniformity, particularly on oblique body surfaces, and results in a higher surface dose and shallower depth dose due to the increase of the angular spread of the original electron beam.

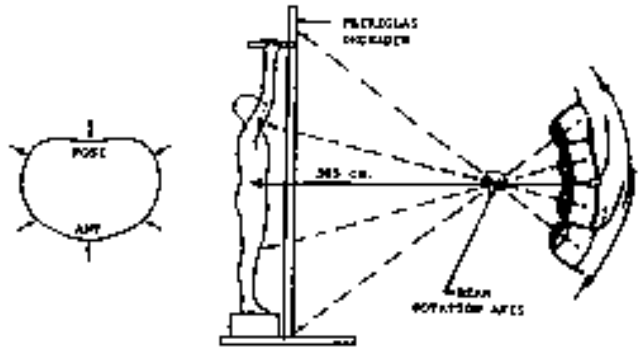


Fig. 12 Total skin electron therapy – six field arc therapy. Geometry of the treatment set-up of electron arc therapy, showing the arc direction. Distribution of the six fields for full circumferential coverage is also indicated on a typical transverse section.

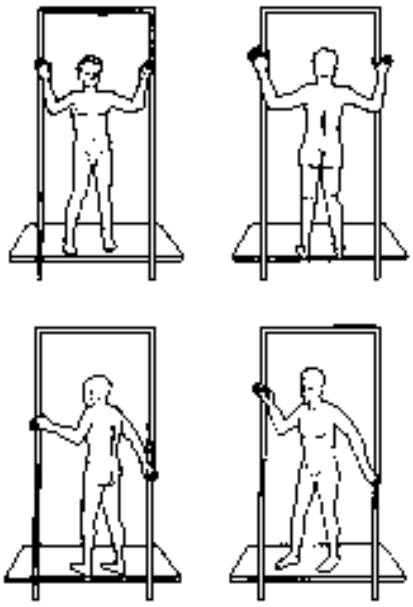


Fig. 13 Total skin electron therapy. Patient stances for the anterio, posterior, and two of the angled dual-field exposures.

5.2.1 Intra-operative radiation therapy (IORT)

With this technique, electron beams are used to deliver a large single-dose fraction during surgical procedure to a well defined PTV. The dimensions of the CTV are defined accurately by the surgeon and the radiation oncologist together. During the procedure, mobile sensitive tissues are displaced out of the beam using localizers, in order to decrease normal tissue toxicity.

The purpose of the procedure is usually to treat presumed subclinical disease after macroscopically radical resection. The exact shape, size and location of the CTV can thus only be defined during surgery.

Different types of localizers have been described, according to the local equipment and facilities. The dose distribution depends strongly on the design of such localizers, applicators, and other accessories, as well as on patient/beam positioning accuracy. Most irradiation techniques involve lucite applicators linked physically to the head of the treatment machine (docking system), but systems using laser beams and an optical set up (non-docking system) are also in use (Figs 14, 15).

In general, the nominal incident electron beam energy ranges from 6 to 20 MeV (beam energy at the exit window), giving energies between 3 and 15 MeV at the patient surface. Flattening filters are used to provide a homogeneity of ± 10 % within the geometrical beam; they also act as scattering foils leading to additional decrease in the beam energy at the patient level. Nominal energy thus becomes irrelevant, and beam quality can only be described using depth/dose distribution on the geometrical axis of the beam (assuming an homogeneous phantom parallel to the applicator end). In some cases, combination of adjacent beams has to be used to treat a PTV larger than the available localizers.

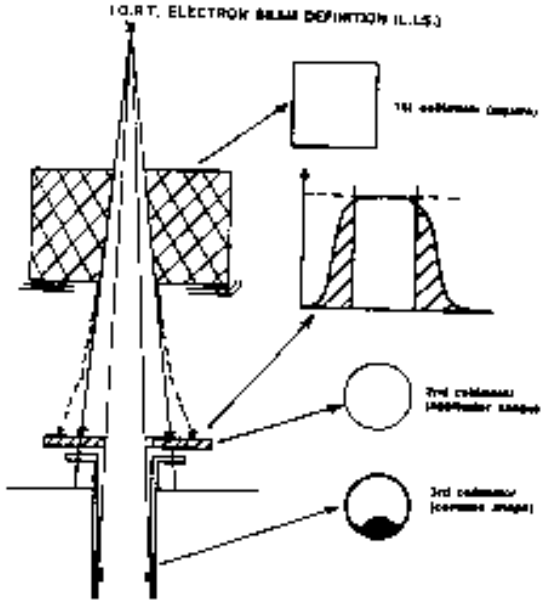


Fig. 14 Shematic drawing of the Lyon IORT system

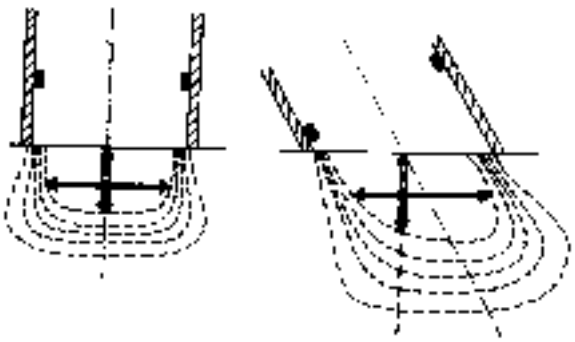


Fig. 15 Electron beams for IORT. The dose distribution varies with the localizer, in particular with the angle between the localizer (or beam) axis and the distal plane of the localizer (perpendicular or oblique, left and right figure respectively). With an oblique beam, a higher electron energy is needed to treat a given tissue thickness.

6. THE FUTURE: NEW DEVELOPMENTS AND TRENDS IN RADIATION THERAPY

As mentioned above, the efficiency of radiation therapy may be improved either by increasing the differential effect, the physical selectivity, or both.

Several attempts have been made to improve the "radiobiological differential effect":

- optimizing the fractionation scheme as a function of the characteristics of the individual tumours;
- combining radiation with new radiosensitizing drugs, but also selecting their optimal combination (e.g., time schedule for administration of both radiation and drugs).

However, it is probably through the development of new irradiation techniques that the most significant progress may be expected. An increase in total dose to the target volume, without exceeding the tolerance dose of the surrounding normal tissues, has always been the key to a better clinical result [7, 16, 18].

A promising approach is the replacement of conventional x-rays by new types of radiation, at least for some tumour sites. Among them, fast neutrons and protons are the most commonly used, and, to a lesser extent, heavy ions.

Fast neutrons, which are high-LET radiation, aim at improving the differential effect (ICRU Report 46 [10]). Radiobiology has shown that they are specifically efficient against hypoxic (cancer) cells or against cells which accumulate in the resistant phases of the mitotic cycle.

Recently, clinical observation has shown that neutrons bring a benefit for the treatment of some well-selected types of tumours [13, 14, 22]. The most convincing results were obtained for locally-extended inoperable salivary-gland tumours for which the conclusions of a NCI study are summarized as follows: "fast neutron radiation therapy alone is the treatment of choice for salivary-gland tumours that cannot be completely resected and/or where the surgical risk of facial nerve damage is high" [15, 23]. Also, for locally extended prostatic adenocarcinoma, two randomized trials, initiated by the RTOG in the US, have shown the superiority of fast neutrons (used alone or as "mixed schedule") compared to conventional x-rays [23, 24].

Proton-beam therapy improves the physical selectivity of the irradiation, but no benefit is to be expected from an improved differential effect [7]. However, the impressive clinical results obtained for selected tumour sites (in particular, uveal melanoma) by the pioneer centres have encouraged several other centres to initiate proton therapy programs. The number of proton-therapy facilities is increasing: 4 in 1980, 6 in 1985, 10 in 1990, and 16 in 1994. Other facilities are planned.

Technological development has allowed the engineers to offer cyclotrons that are compact, reliable, and affordable. These compact cyclotrons, superconducting or based on conventional technology, can be installed within the hospital. They will soon certainly facilitate the development of neutron- and proton-beam therapy.

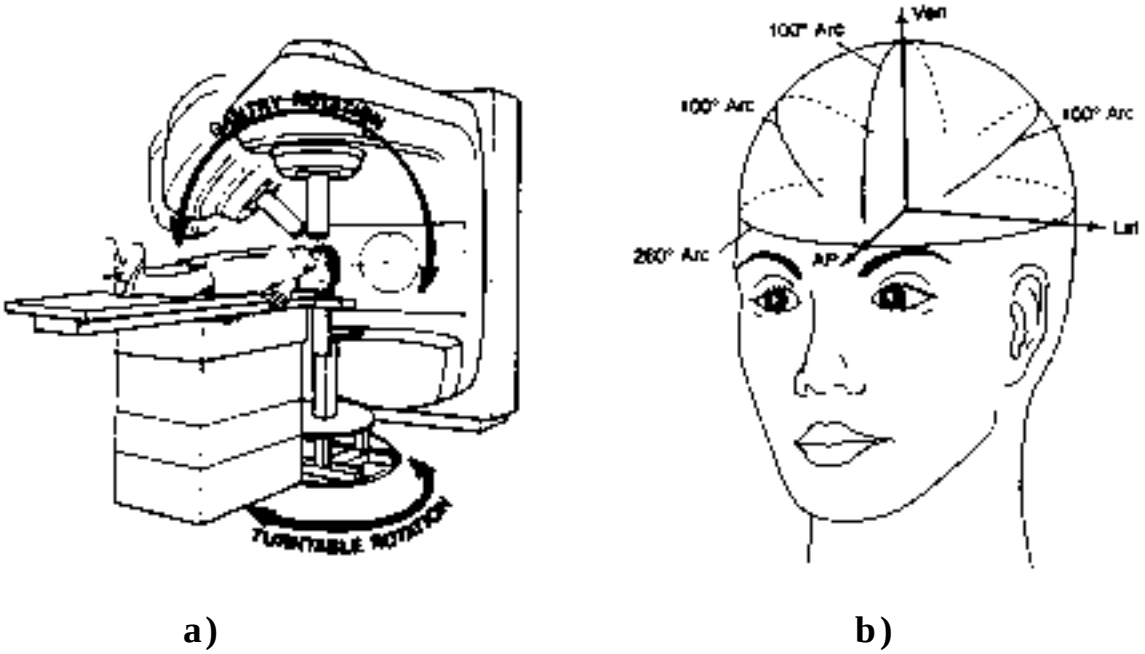
Heavy ions combine the advantages of neutrons and protons: they enable the radiation oncologist to deliver a high-LET therapeutic irradiation with an excellent physical selectivity comparable to that of proton beams. Heavy ions were applied at the Lawrence Berkeley Laboratory, where 299 patients were treated with neon ions. Unfortunately, the facility was closed recently. However, an ambitious heavy-ion therapy program was started at the NIRS in China, Japan, in 1994. A third program will start at the GSI in Darmstadt, Germany, in 1996.

Unfortunately, for the present and the near future, the number of patients who could benefit from these new types of beams will be limited. Therefore, it is important to improve and to optimize the available techniques. In that respect, stereotactic radiosurgery, conformation radiotherapy, intra-operative radiotherapy, total skin irradiation, and modern developments in brachytherapy have already brought encouraging results for some tumour types. These techniques are being applied in an increasing number of large, well-equipped and well-staffed radiotherapy departments. Their safe application requires accurate dosimetry and careful quality control procedures. Some of these approaches (e.g., stereotactic radiosurgery and conformation radiotherapy) involve optimizing the use of linear accelerators and improving their technical characteristics.

Stereotactic radiosurgery is used mainly for the treatment of lesions limited in size and located in the head (e.g., tumours of the base of the skull). By using a large number of narrow beams intersecting at the level of the lesion or by using arc therapy, high doses can de delivered to the lesion while keeping the dose to the surrounding normal structures relatively low. This procedure requires accurate localization of the lesion, accurate dose computation, and accurate beam/patient positioning (Fig. 16) [25].

Conformation therapy can be defined as an effort to optimize the treatment by adequately selecting the number and orientation of the beams, their size and shape. In other words, the volume of tissues actually irradiated should match as closely as possible the PTV, even if it is complex in shape.

Since the early days of radiation therapy, some kind of conformation therapy was an objective. Impressive examples were given already in the forties, for example by Baclesse and his colleagues at the Fondation Curie in Paris, especially for some tumours of the head and neck area. However, the poorly penetrating beam available at that time prevented the full success of these efforts.



a) **b)**

Fig. 16 Stereotactic radiosurgery. a) Overview of patient treatment. A special collimator and an accurate head support system is added to the linear accelerator. Treatment uses both gantry and turntable rotation. b) Head schematic showing the three coordinate axes and the four arcs of a typical cranial treatment [25]

Today, four sets of new means are available to the radiation-oncologist:

a) complete patient data: typically in the form of a series of CT slices with detailed anatomical information (MRI or other imaging techniques). The location, extent and position of the target volume relative to the organs at risk or anatomical reference points can be known accurately.

b) with high-energy, penetrating x-ray beams, it is possible to reach any point in the body, even in depth. Furthermore, the beams are well collimated; their size and shape can be adapted to the target volume. With complex beam arrangements, different beam shapes can be applied.

c) with the modern treatment planning systems (3-D), it is possible, even for a complex treatment, to visualise rapidly the resulting dose distribution and thus to optimize the beam arrangement based on reliable information.

d) lastly, with some sophisticated equipment, the treatment machine can be driven automatically by the computer of the treatment planning system.

An example of the possible development in the field of conformation therapy is given in Fig. 17 where the target volume consists of the iliac and para-aortic lymph node areas. In different transverse planes, the shape of the target volume and its position relative to the patient contour and reference anatomical points vary significantly. This implies that the optimum beam arrangement (number and orientation of the beams) may be different within the different transverse planes. Furthermore, in a given plane, since the target volume is not spherical in shape, the size and shape of the beams should be different according to their orientation [26]. Other approaches are possible, combining for example beams which are no longer coplanar.

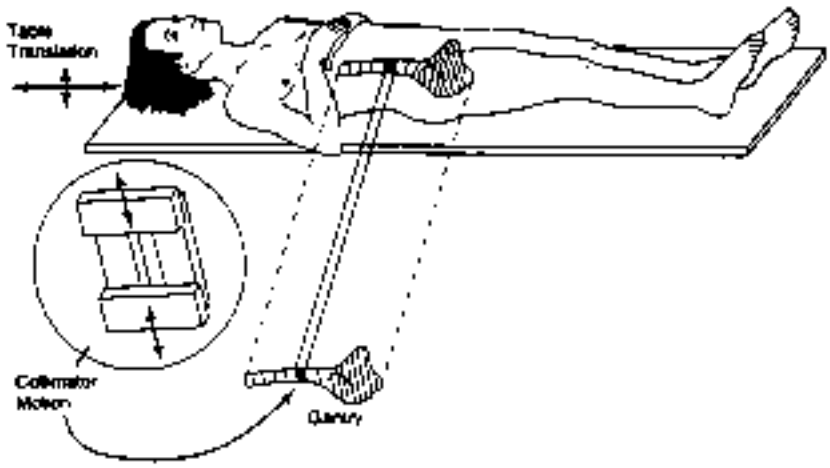


Fig. 17 Example of conformation therapy. Dynamic treatment is used to irradiate a PTV consisting of the retroperitoneal para-aortic lymph nodes as well of the iliaque lymph nodes. In each transverse section, the number, size, shape and orientation of the beams is optimized. Irregular-shaped beams can be used. The movements of the gantry, treatment head, and collimator are computer controlled. There is, in addition, a slow (computer-controlled) patient translation [26].

In conclusion, an optimal use of the available modern linear accelerators, in particular conformation therapy, will improve the outcome of the radiotherapy treatments in well-selected patient groups. The side effects and complications will certainly be reduced. Optimization of the treatments with linear accelerators will be facilitated by further improvement in their technical performance and reliability. In addition, several companies have designed specific types of linear accelerators for specific purposes (e.g. stereotactic radiosurgery) [25, 27].

Finally, the techniques of stereotactic radiosurgery and conformation therapy described above can be combined with the introduction of new beam qualities (e.g. protons, neutrons, heavy ions). The benefit of both approaches could then be added. Application of neutron, proton and heavy-ion beams using conformation therapy techniques has actually been achieved in some centres for certain well-selected tumour types [24, 27].

* * *

REFERENCES

[1] A. Laugier, ACRIM 1994, Annuaire de la Cancérologie/Radiothérapie et des Imageries Médicales en France, Hôpital Tenon, Paris 20, 1994.

[2] C.S. Muir and P. Boyle, The Burden of Cancer in Europe, Eur. J. Cancer, Vol. 26, no 11/12, 1111-1113, 1990.

[3] L. Davis, D. Hoel, J. Fox and A. Lopez, International trends in cancer mortality in France, West Germany, Italy, Japan, England and Wales, and the USA, The Lancet, 336, 474-481, August 25, 1990.

[4] V.T. Devita, Progress in cancer management, Cancer, 51, 2401-2409, 1983.

[5] V.T. Devita and D. Korn, Progress against cancer, New Engl. J. Med., 315, 964, 1986.

[6] R. Doll, Are we winning the fight against cancer? An epidemiological assessment, EACR - Mühlboch Memorial Lecture, Eur. J. Cancer, Vol. 26, No. 4, 500-508, 1990.

[7] H.D. Suit, Potential for improving survival rates for the cancer patient by increasing the efficacy of treatment of the primary lesion, Cancer, 50, 1227-1234, 1982.

[8] Commission of the European Communities, Concerted action: cancer treatment with light ions in Europe - EULIMA, Final Report - Part 1: General Feasibility Study; A. Wambersie, P. Chauvel, G. Gademann, J.P. Gerard, R. Sealy, Socio-economic study, pp. 2-39, CEC, rue de la Loi 200, 1049, Brussels, 1992.

[9] A. Wambersie and G.F. Whitmore, Radiation therapy, ICRU News, International Commission on Radiation Units and Measurements (ICRU), Inc., 1, 15-20, 1995.

[10] INternational Commission On Radiation Units And Measurements (ICRU):
- Report 14: Radiation dosimetry: x-rays and gamma rays with maximum photon energies between 0.6 and 50 MeV (1969).
- Report 17: Radiation dosimetry: x-rays generated at potentials of 5 to 150 kV (1970).
- Report 23: Measurement of absorbed dose in a phantom irradiated by a single beam of x or gamma rays (1973).
- Report 24: Determination of absorbed dose in a patient irradiated by beams of x or gamma rays in radiotherapy procedures (1976).
- Report 33: Radiation quantities and units (1980).
- Report 35: Radiation dosimetry: electron beams with energies between 1 and 50 MeV (1984).
- Report 42: Use of computers in external beam radiotherapy procedures with high-energy photons and electrons (1987).
- Report 44: Tissue substitutes in radiation dosimetry and measurement (1989).
- Report 45: Clinical neutron dosimetry - Part 1, Determination of absorbed dose in a patient treated by external beams of fast neutrons (1989).
- Report 46: Photon, electron, proton, and neutron interaction data for body tissues (1992).
- Report 48: Phantoms and computational models in therapy, diagnosis and protection (1993).
- Report 50: Prescribing, recording and reporting photon beam therapy (1993).

ICRU, Inc., 7910 Woodmont Avenue, Suite 800, Bethesda, Maryland 20814-3095, USA.

[11] M. Tubiana, J. Dutreix and A. Wambersie, Radiobiologie, Hermann Ed., Paris, 1986.

[12] M. Tubiana, J. Dutreix and A. Wambersie, Introduction to radiobiology, Taylor & Francis, London, 1990.

[13] A. Wambersie, Neutron therapy: from radiobiological expectation to clinical reality, Radiation Protection Dosimetry, 44, 379-395, 1992.

[14] A. Wambersie, F. Richard and N. Breteau, Development of fast neutron therapy worldwide, Acta Oncologica, 33, 261-274, 1994.

[15] G.E. Laramore, J.M. Krall, T.W. Griffin, W. Duncan, M.P. Richter, K.R. Saroja, M.H. Maor and L.W. Davis, Neutron versus photon irradiation for unresectable salivary, gland tumors: final report of an RTOG-MRC randomized clinical trial, Int. J. Radiation Oncology Biol. Phys., 27, 235-240, 1993.

[16] R.C. Ultrasun, Does improved depth dose characteristics and treatment planning correlate with a gain in therapeutic results? Evidence from past clinical experience using conventional radiation sources, Int. J. Radiation Oncology Biol.Phys., 22, 235-239, 1992.

[17] B.J. Mijnheer, J.J. Battermann and A. Wambersie, What degree of accuracy is required and can be achieved in photon and neutron therapy? Radiotherapy and Oncology, 8, 237-253, 1987.

[18] H.D. Thames, T.E. Schultheiss, J.H. Henry, S.L. Tucker, B.M. Dubray and W.A. Brock, Can modest escalations of dose be detected as increased tumor control? Int. J. Radiation Oncology Biol.Phys., 22, 241-246, 1992.

[19] C.J. Karzmark, S. Nunan and E. Tanabe, Medical Electron Accelerators, McGraw-Hill, Inc., Health Professions Division, New York, 1993.

[20] A. Brahme: Optimal setting of multileaf collimators in stationery beam radiation therapy. Strahlentherapie und Oncologie, 164: 343-350, 1988.

[21] AAPM, American Association of Physicists in Medicine, C.J. Karzmark (ed): Total skin electron therapy; technique and dosimetry, Report # 23, American Institute of Physics, New York, 1987.

[22] W.J. Koh, J.M. Krall, L.J. Peters, M.H. Maor, G.E. Laramore, C.M. Burnison, L.W. Davis, S. Zink and T.W. Griffin, Neutron vs. photon radiation therapy in inoperable regional, non-small cell lung cancer: results of a multicenter randomized trial, Int. J. Radiation Oncology Biol. Phys., 27, 499-505, 1993.

[23] National Cancer Institute (NCI), Fast neutron radiation therapy in the United States: a twenty-year NCI sponsored research program (NTCWG annual report, 1991), National Cancer Institute, Bethesda, MD 20892, USA, 1991.

[24] M. Austin-Sempour, R. Caplan, K. Russell, G. Laramore, J. Jacky, P. Wootton, S. Hummel, K. Lindsley and T. Griffin, Impact of a multileaf collimator on treatment morbidity in localized carcinoma of the prostate, Int. J. Radiation Oncology, Biol.Phys., 30, 1065-1071, 1994.

[25] W. Lutz, K.R. Winston and N. Maleki: A system for stereotactic radiosurgery with a linear accelerator Int. J. Radiation Oncology Biol.Phys., 14, 373-381, 1988.

[26] L.M. Chin, P.K. Kijewski, G.K Svensson, J.T. Chaffey, M.B. Levene and B. Bjarngard: A computer-controlled radiation therapy machine for pelvic and paraaortic nodal areas. Int. J. Radiation Oncology Biol.Phys., 7, 61-70, 1981.

[27] H.D. Kogelnik (Ed), Progress in Radio-Oncology V, International Proceedings Division, Monduzzi Editore, 40128 Bologna, Italy, 1995.