CHAPTER 2. RADIOTHERAPY OF MALIGNANT TUMORS

Malignant tumors are capable of boundless growth and to extent by metastases. There are next special methods for treatment of cancer and other malignant tumors:

- surgery;
- radiation therapy;
- chemotherapy.

Today, more than 50%of patients with cancer will survive.

2.1. Establishing the diagnosis

Treatment of a malignancy can begin only after the tumor has been diagnosed. Recent radiologic techniques have dramatically improved the assessment for cancer, and we are now in the era of techniques such as x-rays methods of research, computed tomography (CT), diagnostic ultrasound, magnetic resonance imaging and nuclear medicine. Imaging procedures are invaluable in the staging of most solid tumors. Although the staging procedures used to depend on tumor type and location, the underlying principle is evaluation of the local and distant extent. Local extent is usually evaluated by the primary diagnostic modalities discussed above; this section will deal with the evaluation of common areas of metastatic disease. However, the only sure way to establish the diagnosis of cancer is by pathologic confirmation.

Guide to Therapy. Accurate assessment of tumor volume and local extent is particularly important when surgery or radiation therapy is used. Generally, the imaging studies recommended for primary tumors described above and in the specific chapters will give adequate information for a surgeon or radiation therapist. In most instances, CT scanning of solid tumors will give adequate information, although, as noted, there are occasions when MRI may be more useful. However, if ultrasound has been satisfactory in delineating the primary tumor, this method should be used for following response to therapy since it is cheaper. Metastatic lesions are also best monitored using the same modality which demonstrated them at the time of presentation.

Nuclear medicine studies can be an effective diagnostic tool. Bone scintigraphy is of less value than either CT or MRI in the evaluation of the extent of involvement by primary bone tumors but continues to be the most sensitive and easily performed modality for the early identification of skeletal metastases. Positive bone scans can result from abnormalities other than metastases, however, and any area that is positive on bone scan should be studied further by radiography. Positron-emission tomography (PET) utilizes positron-emitting isotopes and has significant potential for evaluation of physiological and metabolic activity rather than just anatomic structure.

Labeling of antitumor agents may permit localization of neoplastic tissue. The necessity for a nearby cyclotron to produce the positron-emitting isotopes limits the availability of the technique.

Arteriography is rarely indicated other than in primary liver tumors, although it should be considered when questions of blood supply or preoperative vascular embolization are raised.

Detection of recurrences. Recurrent disease can be defined as reappearance of tumor in its original location or as metastases in distant sites. The primary site is usually best followed with the imaging modality used for the initial tumor. Adequate evaluation for metastatic disease requires knowledge of the natural history of the tumor; chest films, head and chest CT, bone scans, and abdominal ultrasound and CT are all reasonably used, depending on the organ of origin of the original tumor.

The vexing problem that has yet to be resolved is how often follow-up studies should be obtained.

*Staging of solid tumors.*The original concept of "stage" in solid tumors was a system designed to describe only the extent of disease at one point in the course, usually at diagnosis. A shorthand form was used, condensing the multiple types of possible extension of the disease into categories, exemplified by the TNM (T = tumor; N = nodes; M = metastases) system. They indicated which patients went to surgery or received irradiation and what type or dose. Surgeons, radiotherapists, and pathologists frequently modified (for different tumor types) the TNM staging system, and these modifications received the endorsement of national and international organizations. In some tumor systems, the TNM classification was divided into a clinical stage (before surgery) and pathologic stage (after surgery and histologic examination).

In the era of effective surgery, radiotherapy and chemotherapy, the staging of solid tumors is an absolute necessity for comparing multi-institutional therapy trials.

Radiation therapy plays a major role in the management of most cancers. Because of the potential for acute and chronic side-effects, radiation must be used cautiously in patients. The severity of the side-effects is directly related to dose. Acute morbidity, such as gastrointestinal dysfunction, bone marrow suppression, and skin reactions, is seldom a limiting factor when radiation therapy is used alone, and the changes produced are generally reversible.

By ionizing radiation in malignant tumor next changes take place:

–reduction of tumour size;

–development of granulation tissue;

–reduction of tumour vessels;

–destruction of all malignant cells and their substitution by connective tissue.

2.2. Principles of radiotherapy

1. To achieve a favorable therapeutic ratio without producing unacceptable damage to adjacent normal tissues.

2. The radiotherapy has to be started in time. So much the better in I or II stages, when tumor is small.

3. For a favorable therapeutic ratio we must irradiate all tumor cells in necessary dose and in optimal time. The first course of radiotherapy is very important.

4. The dose is necessary if it is enough to plan effect. For radical treatment total doses of 60-70 Gy conventional fractionation are used. Primary tumor must receive this dose. The regional lymphanodes must receive 50 Gy (in absence of metastases).

5. The favorable therapeutic ratio increases by using the factors which can increase radiosensitivity of tumour cells or radioprotect organs at risk.

7. Adequate diet, vitamins, giving up smoking and alcohol.

For favorable radiotherapy of cancer the tumor must be no more than 1 cm. Because for treatment of this tumor 60 Gy γ-ray conventional fractionation will be used.

The practical experience shows that result of radiotherapy depends more on radiosensitivity, oxygen enhancement ratio, immunity and some other factors. But the zise of tumor is the principal reason for favorable radiotherapy. The limit of tumor size is 6,0 cm for successful radiotherapy.

Contra-indications for radiotherapy:

- Disintegration of tumor with abscess or bleeding, sprouting into hollow organs.
- Presence of many distant metastases.
- Bad condition of a patient.
- Exhaustion.
- Anaemia, low level of leucocytes ($< 3\times10^9$/litre).
- Sepsis diseases, active tuberculoses of lung.
- Myocardial infarction (< 1 year ago).
- Heart, liver, kidneys insufficiency.

2.3. Variants of radiotherapy

Radiotherapy as an independent method of treatment can be performed according to a radical program. It can be used as palliative and symptomatic means of help to a patient.

Radical beam therapy is directed to complete treatment of a patient from a tumour and regional lymphnodes metastases by radiation doses killing cancer. Levels of cancer killing doses for various tumours are different and depend on their histologic structure, mytosis activity and degree of a differentiation of cellular elements. Tumours which can be treated radically are skin, lip, nasopharynx, larynx, breast, cervix uteri and endometrium, prostate cancer as well as seminoms, localized lymphomas, Hodgkin's disease, hypophysis adenomas. Clearly, the success can be reached at relatively early stages.

Palliative beam therapy is used for reduction of a tumour sizes and its metastases, stabilisation of tumoral growth; it is used when radiotherapy according to a radical program is impossible; and a total dose at palliative radiotherapy comprises, as a rule, 2/3 of a cancer killing dose.

Symptomatic radiotherapy is used for removal or reduction of clinical symptoms of malignant lesions, resulting in the fast death of a patient or essentially worsening of his life quality. Irradiation with symptomatic purpose is performed by vital indications in tumours of such localisations, when radiotherapy is the only method of treatment (superior vena cava compression syndrome, compression syndrome caused by a fast-growing brain tumour, sharp asphyxia by a fast-growing trachea tumour, spinal cord compression by primary and metastatic tumours). The total absorbed dose of radiation is determined individually, depending on the reached effect.

The combined treatment. This term is used, when operative treatment and radiotherapy is used in this or that sequence for special treatment of malignant tumours. Radiotherapy combined with surgical intervention can be used in the preoperative period, intra-operatively and postoperatively.

<u>Preoperative irradiation</u> is performed for improvement of conditions for radical operation and decrease in frequency of development of local relapses and the remote metastases.

Goals of preoperative beam therapy are:

1. Destruction of the most radio sensitive cells and decrease of viability of the remained tumoral elements.
2. Elimination of inflammation phenomena in a tumour and around it.
3. Stimulation and development of a connecting tissue and encapsulation of separate complexes of cancer cells.
4. Obliteration of minute vessels causing the decrease of tumour vascularization and therefore the reduction of metastasis formation.
5. Conversion of tumours in an operable status.

The basic dose not exceeding 50 Gy, with 2 Gy daily within 4 weeks shows long-term experience in carrying out of the combined treatment; it does not cause difficulties in performance of the subsequent operation and does not influencethe healing of a postoperative wound. The same can be told about other modes of fractionation according to biological effect equivalent to 50 Gy by conventional fractionation (25 Gy for 5 fractions). The dose in 40-50 Gy leads to death of 90-95 % of subclinical centres of tumoral growth. Excess of a dose in 50 Gy can increase frequency of postoperative complications, though it is desirable for enchancement of a damaging effect on tumoral cells.

Nowadays two techniques of a preoperative external irradiation are often used:

1. A daily irradiation of a primary tumour and regional zones in a dose of 2 Gy to a total dose in 50 Gy for 5 weeks of treatment.
2. Irradiation of similar volumes in a dose of 5 Gy within 5 days to a total 25 Gy.

In the first variant an operation is carried out in 2-3 weeks, and in the second – not later than 1-3 days; it is recommended only for treatment of patients with operable malignant tumours.

Postoperative radiotherapy increases the efficiency of operation by means of beam influence on implanted tumoral elements during surgical treatment (intervention). Postoperative irradiation, as well as preoperativeis directed to prevention of relapses and metastases of a malignant tumour. Its goals are:

1. "Sterilisation" of an operational field from disseminated malignant cells and their complexes during an operative intervention;
2. Destruction of the remained malignant tissues after incomplete removal of atumour and metastases.

Indications for carrying out of a postoperative irradiation are: in cases when radical operative intervention is impossible, a tumour exits the limits of that layer in which it was formed, its spread throughout the lymphatic system, organ-preserving operative treatment.

It is necessary to notice, that the postoperative irradiation is performed in conditions promoting increase of tumour cells radio resistancy (due to disorders in blood and lymph circulation). Simultaneously radio-sensitivity of normal tissues in a regeneration status increases. All this leads to reduction of a radiotherapeutic interval. However it is possible to note certain advantages of postoperative radiotherapy:

1. Volume and an irradiation technique are determined on the basis of the data received during an operation and after careful morphological studying of remote tissues.
2. Operative treatment is performed as fast as possible, after specifying the diagnostics.

Postoperative irradiation is performed if a postoperative wound if totally healed, 2-3 weeks after an operation. If malignant cells are absent in operational incisions conventional fractions in total dose of 50 Gy are used, if malignant cells are presented the irradiation dose equals to 60 Gy.

Intraoperative radiotherapy provides a unitary irradiation of an operational field or inoperable tumours during laporatomy with an electronic bunch with energy 10-15 MeV in a dose of 14-20 Gy.

Complex treatment provides combination of beam and chemotherapy and pursues the double aim: mutual enhancement of ionising radiation and chemotherapy influence on a primary tumour (additive, potentiating and synchronising effects), and creation of conditions for preventive maintenance of metastases and treatment of subclinical or revealed metastases.

Two basic variants of complex treatment are distinguished:

1. Radiotherapy is the basic method, and chemo-hormonal therapy is an additional one. This method is directed to treatment of the remote metastases with total dose not lower than 60 Gy. So, in complex treatment of a non small lung cancer irradiation doses not less than 60 Gy are used for primary tumor, and 55-60 Gy for regional lymph nodes zones.

2. Ionizing radiation is used as a prophylactic means of radiotherapy in complex treatment. In these cases a dose of an irradiation can be 30-36 Gy. It is used in treatment of Hodgkin's disease and malignant lymphomas.

The variant of conventional fractionation dose is used, as a rule.

Multimodal therapy of oncological patients provides optimal use of modern methods of surgical, beam and medicinal treatment, and also their combination to radio modifying influences.

Nowadays a beam therapy of oncological patients is carried out by use of three basic ways of ionising radiation:

1) the external beam therapy applied to patients at 95-98 %;

2) brachytherapy (intra-cavity radiation, interstitial therapy);

3) systemic (intravascular), used no more than in 0,5 % of cases.

2.4. Treatment planning

The main principle of radiotherapy is tumour treatment with the maximum protection of normal organs and tissues. For its implementation in a clinic great attention is given to working out of ways to increase the efficiency of beam influence on the basis of spatial and time distribution of ionising radiation dose and application of the means changing (modifying) tumour and organism beam reactions.

The treatment planning of radiotherapy must begin with establishing the diagnosis of malignant tumor by clinical, radiology and oblige histologic examination. After that the consultation with a radiation oncologist, a surgeon and a chemotherapist should be taken. Those actions are necessary because the treatment of malignant tumors is difficult and compound; complications are very hard.

The initial process in planning radiation therapy is to identify the target volume. In the irradiated volume the concept GTV (gross tumour volume) is applied.

<u>GTV is the big tumoral volume</u>, i.e. the tumour is defined by clinical, beam, tool methods.

<u>Clinical volume of a target (clinical target volume – CTV)</u>, is a zone in which it is necessary to liquidate macro-and microscopic displays of a malignant tumour.

CTV includes macroscopical volume of a tumour and tissues in which possibility of microscopic tumoral invasion presents.

The planned volume of a target (planning target volume – PTV) represents a zone which takes into consideration shifts of the clinical volume due to change in breath of the patient, body mobility and equipment errors.

Treated volume (TrV). This is the volume of tissue that is planned to receive a specified dose and is enclosed by the isodose surface corresponding to that dose level, e.g. 95 per cent. The shape, size and position of the treated volume in relation to the PTV should be recorded to evaluate and interpret local recurrences (in field versus marginal) and complications in normal tissues, which may be outside the PTV but within the treated volume.

Irradiated volume (IrV). This is the volume of tissue that is irradiated to a dose considered significant in terms of normal tissue tolerance, and is dependent on the treatment technique used. The size of the irradiated volume relative to the treated volume (and integral dose) may increase with increasing numbers of beams, but both volumes can be reduced by beam shaping and conformal therapy.

The planned volume of organs at risk (the-organ-at-risk – OAR) is healthy tissues and the organs getting in the field of ionising radiation influence during radiotherapy. All listed volumes (fig. 2.1) and skin contours should be represented at all slices used for planning.

For the listed structures it is necessary to calculate DVHs (dose volume histograms) – the histogram a dose-volume.

Once the target volume has been determined, an interactive process of patient simulation and dosimetry defines the treatment plan. Simulation permits accurate localization of the target volume from one or several directions; the simulator is a diagnostic-quality x-ray unit structured to mimic the treatment machine geometrically.

The position and divergence of the photon beam are identical to those of the

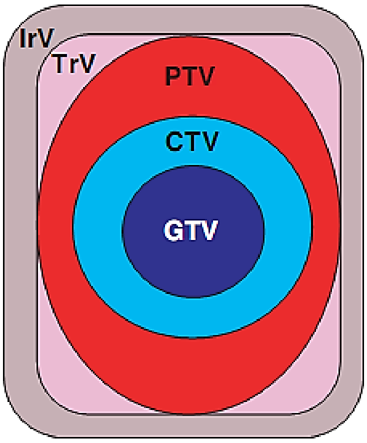

Fig. 2.1. ICRU target volume definitions showing GTV, CTV, PTV, treated and irradiated volume [112]

linear accelerator, allowing the radiation oncologist to plan accurately treatment strategies that have been identified by and may be later confirmed by computerized dosimetry. Planning seeks to maximize dose homogeneity within the target volume and permit appropriate dose limitation for critical normal structures.

Dosimetry provides a detailed analysis of the dose distribution within a given plane.

CT-based treatment planning accurately displays the dose relation based on the planned field configuration.

Radiotherapy simulator is ancillary radiation equipment. At the same time, for the account of physiological movements (basically, at breath) and the displacement of the irradiated volume connected with them, the method of visualisation working in real time is necessary: fluoroscopy. This research is carried out on the special diagnostic x-ray device − radiotherapy simulator (fig. 2.2).

There must be a mechanism of converting the concept of irradiating a certain amount of tissue into a practical plan. The specific number of radiation beams (also called radiation ports), their size, and their angles of entry into the body must be determined. The simulator is a machine that assists in the development of an actual treatment approach.

The simulator reproduces, or "simulates," the radiotherapy treatment machine (i.e., ^{60}Co or linear accelerator). The simulator contains, however, a diagnostic x-ray tube instead of a high-energy radiation source. The physician may plot the angles of the radiation beams and determine the beam size required and document each proposed "port" with a diagnostic x-ray.

This diagnostic film is used to show the tumor volume and the location of any

Fig. 2.1. A typical radiotherapy simulator. See text

appropriate lead blocks. In this way a high energy treatment plan can be developed without exposing the patient unnecessarily to radiation from cobalt or the linear accelerator.

Then the schemes of body section at "target" level are developed. Modern systems of dosimetric planning (computer systems for planning radiation therapy) perceive the information directly from magnetic carrier CT and print a map with the chosen distribution of isodoses put to it (fig. 2.3).

Isodose lines connect points to identical value of the absorbed dose. Mark relative values – in percentage of the maximum absorbed dose accepted for 100 %.

To estimate isodose curves special computer programs which consider spatial parametres of irradiated object and the dosimetric characteristic of radiation are used. To make representation about distribution of the absorbed doses in the irradiated volume, isodose curves are plotted on schemes, thus, a map of isodoses appears. In radiotherapy a dose distribution is considered acceptable if the whole tumour consists in a dose of 100-90 %, the zone of subclinical distribution of a tumour and regional lymph nodes is in limits of 80 % of an isodose, and healthy tissue – not more than 50-30 % of an isodose.

More complex field arrangements are often desirable, concentrating the high-dose volume or limiting doses to specific structures. In addition, blocks are customarily used to define the treatment volume. Customized blocks are fabricated from a lead alloy that provides precise beam definition to limit the irradiation volume to the defined anatomic region.

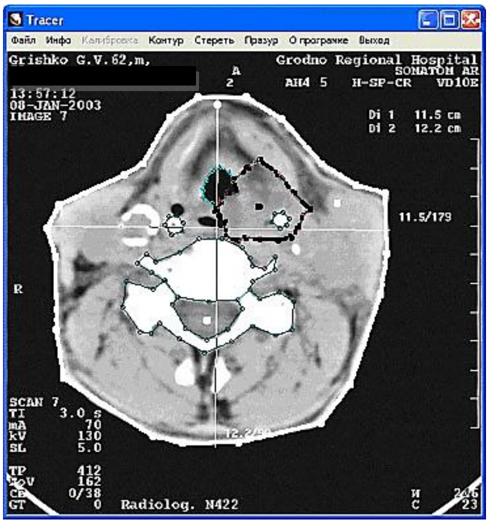

Fig. 2.3. Creation of contours on the computer tomogram for dose calculation in computer system of planning of an irradiation

With treatment volumes extending beyond one body cavity, one must use adjoining-field configurations such as mantle and para-aortic fields in Hodgkin's disease. Field junctions require exquisite attention to avoid areas of overdosage and underdosage, which may be associated with local recurrence or unnecessary toxicity.

Optimization of treatment techniques. Since the beginning of radiation therapy a very extensive number of methods, beam modalities and irradiation techniques have been developed. Beside the choice of radiation modality there is a large number of degrees of freedom that can be used for treatment optimization including: beam energy, beam directions, beam collimation, beam profiles and the irradiation technique in general as determined by the type of equipment used.

Radiation modality. The basis of means of modern radiotherapy is made by gamma therapeutic devices and linear accelerators (fig. 2.4. and 2.5). And, both photon, and electronic radiation in the latter case can be used.

External gamma therapy. Gamma radiation (^{60}Co) creates a dose on the skin surface, 70 % equal approximately maximum which arises on depth of 5-6 mm. In process of energy decrease at the further passage of radiation to tissues on depth of 10 sm there pass 50 % an isodose. Peripheral departments of a bunch of gamma beams bear not enough energy for reception of steady medical effect, therefore in practice it is accepted to enter volume of tissues subject to an irradiation in the central parts of a bunch limited of 50 % to an isodose.

Therapy by x-ray radiation of accelerators. Basically linear accelerators which

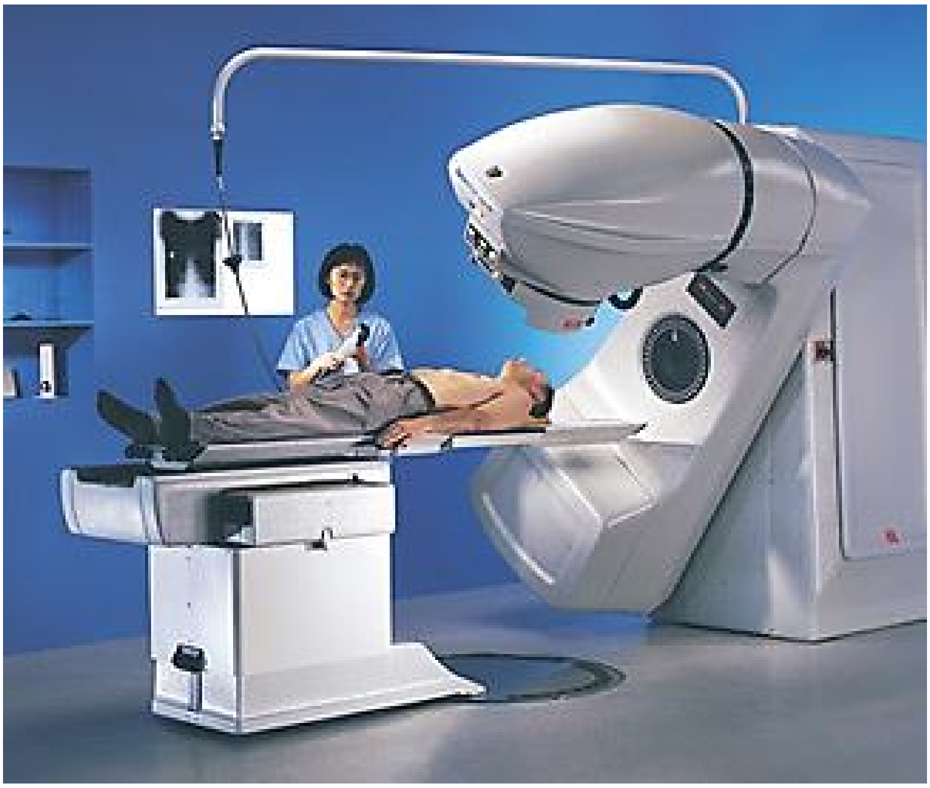

Fig. 2.4. Cobalt telegammatherapy (apparatus Teratron)

generate x-ray radiation with energy from 4 to 42 MэВ are used. With increase of energy of radiation getting ability of beams and, accordingly, a relative deep dose considerably increases. The skin dose at use of brake radiation with energy 4-42 MэВ

Fig. 2.5. The linear accelerator – the basic device for modern radiotherapy

makes from 20 to 30 % maximum, i.e. it is essential it is less, than at gamma therapy, and the zone of dose maximum moves on depth of 1 sm at energy 4 MэВ and 4-5 sm - at 25-42 MэВ. On depth of 10 sm the dose makes 60-90 % of the maximum. The important characteristic of this radiation is almost full absence of absent-minded radiation. All diameter of a bunch bears almost identical energy. In practice it means possibility of application of narrower bunches (than at gamma radiation), reduction of an irradiation of the tissues next to a tumour and, accordingly, to reduction of an integrated dose.

Electron beam therapy. High energy of electrons is in regular intervals absorbed by tissues on all way of these particles. Electron beams have a finite range, after which dose falls off rapidly. Therefore they spare deeper healthy tissue.

The dosimetric characteristic electrons with high energy in expediency of their application at an arrangement of the pathological centre not more deeply 5-7 sm. Electrons with high energy (fast electrons) and x-ray with high energy receive on linear accelerators.

Proton beam therapy. During the last decades heavy charged particle therapy with neutrons, protons and heavy ions have been used more extensively too. High-energy cyclotrons produce energetic charged particles of potential value in radiation therapy (fig. 2.6). Protons, for example, yield a discrete volume of increased dose at a depth that varies with the energy of the incident proton beam. The dose distribution is characterized by a Bragg peak resulting from relatively dense nuclear reactions as the particle loses velocity (fig. 2.7). Therapeutically useful proton energies (e.g., 160

MeV) have an RBE only slightly higher than that of photons. Other particles (e.g., high-energy carbon, neon, or argon ions) have a similar dose distribution. In addition, the liner energy transfer (LET) of the latter particles is increased in the region of peak physical dosage, resulting in an even greater biological dose differential at the depth of the Bragg peak. Protons have produced intriguing results in focal intraocular tumors such as choroidal melanoma and in pituitary adenomas.

A further reason for leaving out the heavy high liner energy transfer (LET) particles are that they are not universally applicable. Due to their high ion density the damage to the genome is more severe and generally not repairable.

Since the more efficient repair capacity of the normal tissues is one of the cornerstones of radiation therapy, high LET radiations are not really suitable for treating often extensive microscopic disease.

2.5. External radiotheraphy

Nowadays all methods of external radiotheraphy can be conditionally divided into: conventional irradiation, conformal irradiation and intensity-modulated radiation therapy (IMRT), corrected under images (image guided radiation therapy – IGRT).

Fig. 2.6. The cyclic accelerator for beam therapy by protons high energy

Conventional radiotherapy is based on use of rather simple techniques of irradiation of patients (formation of fields of irradiation by means of diaphragms with unchangeable degree of ionising radiation absorption, standard lead blocks and wedge-shaped filters).

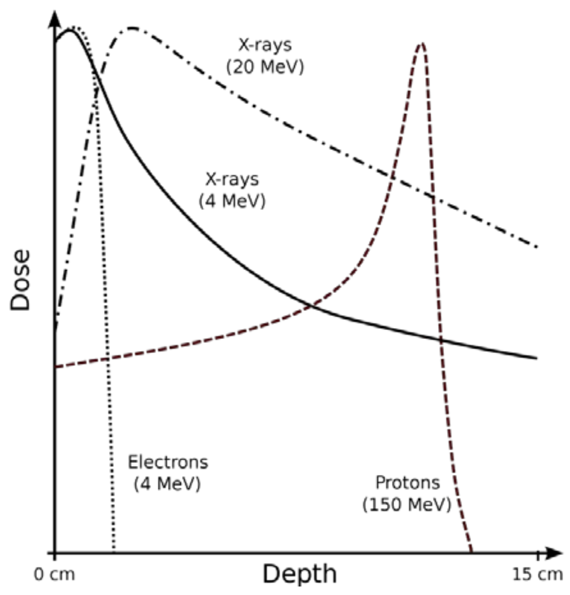

Fig. 2.7. Histograms doses distribution of various types of ionizing radiation in the human body during radiotherapy. Note the rapid falloff for 4 MeV electron compared to X rays and presence of the Bragg peak in proton radiation [100]

The choice of the centre and field borders in conventional radiotherapy is carried out on the basis of the projective image received under the set corner. For conventional radiotherapy application of two-dimensional planning with use for positioning of the irradiated volume radiography or computer tomography and a x-ray simulator of an irradiation also is characteristic. For dosimetric maintenance water phantoms and the tissue equivalent phantoms are used. Traditional radiotherapy is used till now in clinical practice.

Conformal therapy. Conformal radiotherapy was a following stage of radiotherapy development. In conformal radiotherapy three-dimensional planning of irradiation is necessarily used. The devices which contain radiotherapy simulator of an irradiation and computer tomography are called a simulator-CT that allows using more exact preparation of the patient for radiotherapy including fields of an irradiation of a compound configuration.

More modern means of definition of the irradiated volume are presented by a CT-simulator, which includes the spiral x-ray computer tomograph providing the three-dimensional image of a tumour and surrounding healthy tissues. At conformal radiotherapy for creation of more exact dose distributions in the irradiated volume various variants of figured blocks are applied.

One of versions of conformal radiotherapy is a gamma knife technology (Lexell Gamma Knife). There are 201 sources of ionising radiation in a gamma knife (^{60}Co with a radioactivity 30 Cu; 1,1 TBq everyone), each placed in a circular array in a heavily shielded assembly (fig. 2.8).The gamma knife used to treat brain tumors by administering high-intensity radiation therapy in a manner that concentrates the radiation over a small volume. The device directs gamma radiation through target points in the patient's brain. The patient wears a specialized helmet that is surgically fixed to the skull, so that the brain tumor remains stationary at the target point of the gamma rays. An ablative dose of radiation is directed to a tumor in one treatment session, while surrounding brain tissues are relatively spared. Radiosurgery uses high doses of radiation to kill cancer cells and shrink tumors, delivered precisely to avoid damaging healthy brain tissue.

Gamma knife radiosurgery is able to focus accurately many beams of high-intensity gamma radiation to converge on one or more tumors. Each individual beam is of relatively low intensity, so the radiation has little effect on intervening brain tissue and is concentrated only on the tumor itself.

Gamma knife radiosurgery has proven its effectiveness in patients with benign or malignant brain tumors up to 4 centimeters in size, vascular malformations such as

Fig. 2.8. A typical gamma-knife machine

an arteriovenous malformation, pain or other functional problems. For treatment of trigeminal neuralgia, the procedure may be used repeatedly on patients. The risks of gamma knife radiosurgery treatment are very low, and complications are related to the condition being treated. Dose distribution generated by sources, is close to the spherical. Radiation from all sources gathers and operates like a noninvasive surgical knife (the dose is unitary brought to the pathological centre till 60-70 Gy, sufficient for destruction of a tumour or obliteration of vascular malformations). Diameter of isodose spheres is defined by secondary replaceable colimatory in a helmet made of tungsten. Similarly surgery operations, treatment procedure is spent unitary, however thus there are no cuts of a skin and there is no necessity to spend cranial trepanation. Radio surgery is considered to be the most significant achievement in neurosurgery development for last 20 years. Thanks to reliability, accuracy and efficiency the gamma knife is considered to be «a golden standard» in radio surgery.

A following step to development of beam therapy was *intensity-modulated radiation therapy (IMRT)*. Additional formation of a bunch is reached by use of multi-leaf collimator (fig.2.9). It has the mobile leafs which blocking a certain part of a radiating bunch. Usually multi-leaf collimators have from 20 to 80 and more leafs located steams. Computer management of position of leafs gives the possibility to generate a field of the necessary form.

Establishing leafs in a demanded position, receive a field most corresponding to the form of a tumour. Field adjustment becomes by means of changes in the computer file containing installations for leafs. For recognition of position of a leaf the video optical system uses the same light source, as for positioning of the patient. The return reflector is mounted near to the end of each leaf. Video signal is digitized and the image showing positions of reflectors is formed.

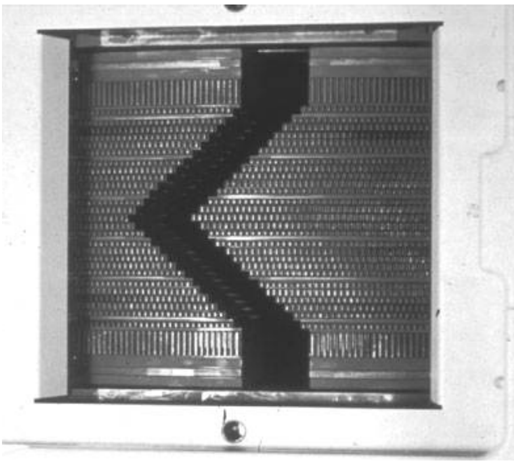

Fig. 2.9. Multi-leaf collimator

The basic tenet of intensity modulated radiotherapy is that the treatment beams have a non-uniform beam intensity across their profile. Conformal radiotherapy aims to reduce normal tissue dose by shaping the beams to the projection of the tumour, but IMRT goes a step further, enabling much more complex 3D dose distributions to be created by the use of intensity modulated beams. At IMRT continuous adjustment of the form of a therapeutic radiating field in a projection of the planned volume of a target during an irradiation session takes place.

Use IMRT in clinic demands absolutely obligatory maintenance of following conditions:

– presence of the correct image of a primary tumour and the structures surrounding it, received by radiological methods of diagnostics;

– because of possible physiological movement targets (tumour) and organs at risk rigid immobilization of a patient on a medical table of the radiotherapeutic device is necessary.

At IMRT more rigid immobilization, than at conventional radiotherapy is used. Usually there is a special lath made of carbonic fibres on a table which, in combination with thermoplastic materials, gives the chance to save the same position of the patient during all time of radiotheraphy session (fig. 2.10).

In planning of IMRT enough rigidness should be provided according to the recommendations made in reports №50 and №62 ICRU (International Comission Radiation Units and Measurement). Dose distribution should completely correspond to following criteria:

<5 % from OAR receive <60 % from a planned dose;

> 95 % PTV receive> 95 % from a planned dose;

<10 % PTV receive> 120 % from a planned dose.

IMRT provides more selective beam influence on a tumour in comparison with conventional and conformal radiotherapy.

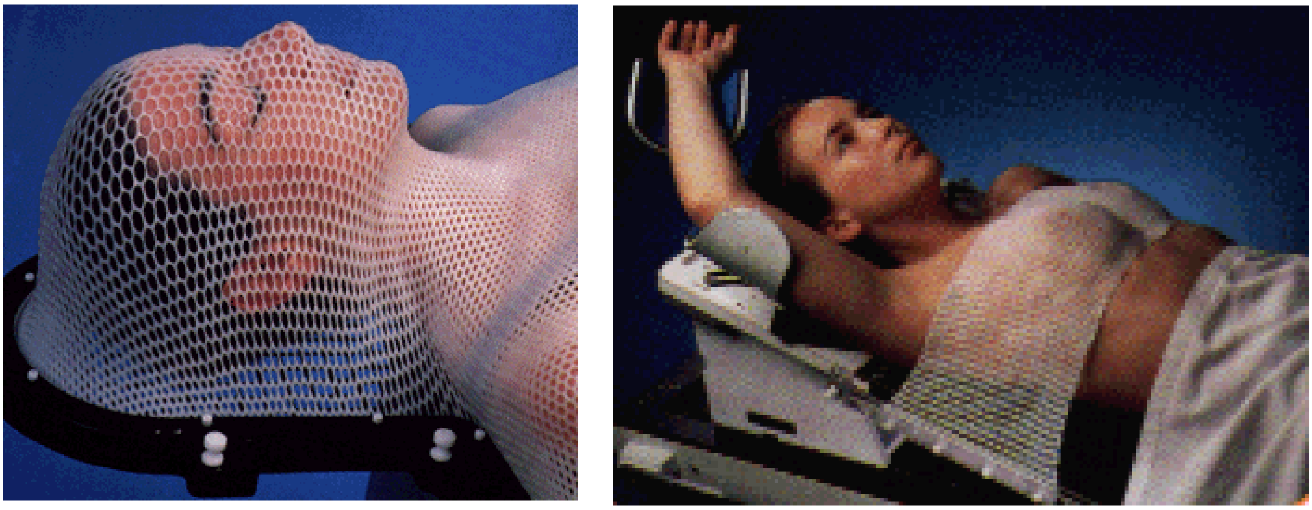

Fig. 2.10. Immobilization devices. The fixing device from special plastic for a head and chest

Nowadays the methods of overcoming the problems connected with moving of tumours and organs are rapidly developing. Body parts move both in sessions of radiotherapy, and between them owing to breath, digestion and small differences in position of the patient during each session of radiotherapy. Such moving can lead to reception of an excessive dose of radiation by the normal tissues surrounding a tumour, and wrong treatment of the tumour.

The radiotherapy corrected under images (image guided radiation therapy – IGRT), provides reception of images of the tumour and surrounding of healthy tissues directly ahead of a session of radiotherapy and during it. These images are used for definition of moving of a tumour and healthy tissues and correction of a direction of a therapeutic bunch of radiation according to the above-stated moving. According to system of respiratory "shutter" which switches on and disconnects a therapeutic bunch of radiation synchronously with breath, it is possible to limit treatment by a part of a respiratory cycle, when the tumour is in the field of a therapeutic bunch and by that to limit the planned volume of an irradiation. It gives the chance to increase the absorbed dose in a tumour and to reduce a dose falling to healthy tissues surrounding it. At this technology cone or fan beams of therapeutic radiation can be used.

The fan bunch of radiation is used in the most modern methods of beam therapy – tomotherapy. Tomotherapy represents the innovative radiotherapeutic method, allowing to realise intensively modulated radiotherapy (IMRT) and radiotherapy with image correction (IGRT). The method is based on a level-by-level irradiation by a fan bunch of photons with modulation of intensity and realised by means of the installation combining in functionality linear accelerator and a spiral computed tomography.

Installation for tomotherapy represents the ring console in which subsystems of the linear accelerator and detectors for a computer tomography (fig. 2.11) are mounted.

Idea is to use a fan beam modulating collimator for "spiral irradiation" much in the same way as used as spiral computed tomography. The patient is then being moved through a continuously rotating modulated fan beam. Installation for tomotherapy represents the ring console in which subsystems of the linear accelerator and detectors for a computer tomography are mounted. Tomotherapy uses the x-ray with high (MeV) energy, which collimates in a fan bunch with a help of similar fissura multi-leaf collimator.

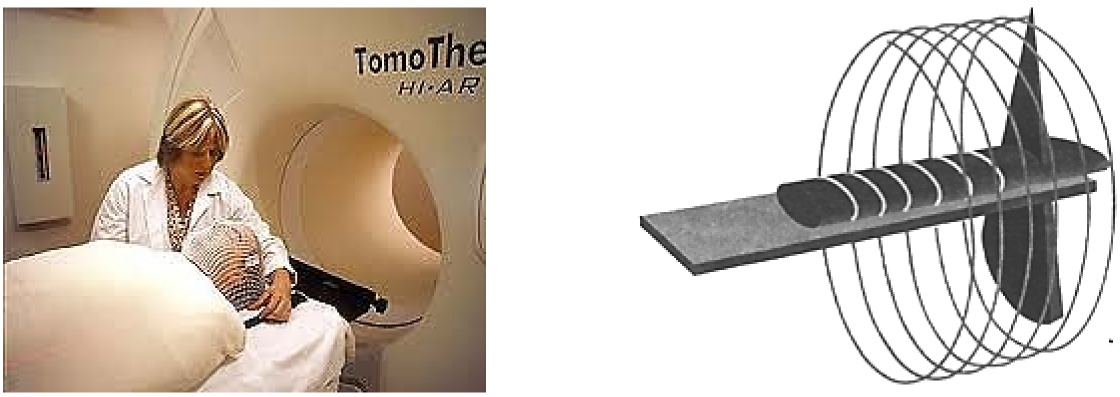

Fig. 2.11. Preparation for a session of tomotherapy; on the right: the schematic image of a principle of a spiral irradiation

Thus this radiation is used for diagnosing and receiving computer-tomography images as well as with therapeutic porpuses.Tomotherapy provides the closed cycle for planning, simulations, leading of the medical absorbed dose and verification of radiotherapy within the limits of one separate device. One of its most important advantages is considerable simplification of conformal therapy in comparison with cone bunches therapy without deterioration of possibilities of formation dose fields. Key component of tomotherapy is four-dimensional representation of a target and surrounding tissues where the fourth dimension is time coordinate which should be considered in a context of change of the specified structures during a medical course. It is considered important, that the computer tomography on megavolt photons represents the information in numbers of Hounsfield, which is necessary for dose calculation. According to these data the analysis of the medical plan is carried out.

Technologies IMRT and IGRT essentially improve results of radiotherapy as give the chance leading considerably more radiation doses, than at conventional treatment.

Variant of IGRT is a KyberKnife system in which the special compact linear accelerators are established on the robotised hand supervised by the computer (fig. 2.12). In this technology there is a superfast computer system of irradiation planning in which basis lies the comparison of three-dimensional reconstruction of CT, MRI and PET images. The images of monitoring system define a site of a tumour and corrects a direction of a bunch of photons. By means of the robotised hand of a kiber-knife it is possible to direct irradiation in the centres of the complicated form with the modulation of intensity. The course of radiotherapy thus consists of one or several fractions. Unlike a gamma knife, a kiber-knife system does not use invasion immobilization and it is possible to direct beam treatment to tumours of backbone channel. The same can be reached at application multi-leaf collimator with steriotaxis prefixes on modern linear accelerators.

Fig.2.12. Kiber-knife machine

2.6. Brachytherapy

A contact irradiation is also named brachytherapy (from Greek «brachys», short). In contact irradiation the basic advantage of radiotherapy is the sharp gradient of a dose in process of removing from a source of radiation that allows to spare normal tissues at an adequate irradiation of a tumour. The dose distribution in brachytherapy is governed largely by the inverse square law. By geometric planning, one can achieve a dose distribution encompassing the desired target volume with far less irradiation of surrounding normal tissues than can be achieved with external-beam irradiation. To assure relative dose homogeneous within the target volume, brachytherapy applications are used primarily for tumors less than 5 cm in the largest diameter.

Nowadays closed and opened radionuclides are applied. Intracavitary and interstitial irradiation (the radiation source is in tissue of a body of the patient) are carried out, consistently entering endo - or intrastat in a cavity or tissue, and then a radiation source on command from a control panel from protected room for radiation action of a premise arrives in endo - or intrastat. During this irradiation procedure the personnel do not present in the room.

The dose rate of brachytherapy refers to the level or 'intensity' with which the radiation is delivered to the surrounding medium and is expressed in Grays per hour (Gy/h).

Low-dose rate (LDR) brachytherapy involves implanting radiation sources that emit radiation at a rate of up to 2 $Gy{\cdot}h^{-1}$. LDR brachytherapy is commonly used for cancers of the oral cavity, oropharynx, sarcomas and prostate cancer.

Medium-dose rate (MDR) brachytherapy is characterized by a medium rate of dose delivery, ranging between 2 $Gy{\cdot}h^{-1}$ to 12 $Gy{\cdot}h^{-1}$.

High-dose rate (HDR) brachytherapy is when the rate of dose delivery exceeds 12 $Gy{\cdot}h^{-1}$. The most common applications of HDR brachytherapy are in tumours of the cervix, esophagus, lungs, breasts and prostate. Most HDR treatments are performed on an outpatient basis, but this is dependent on the treatment site.

Pulsed-dose rate (PDR) brachytherapy involves short pulses of radiation, typically once an hour, to simulate the overall rate and effectiveness of LDR treatment. Typical tumour sites treated by PDR brachytherapy are gynaecological and head and neck cancers.

The principal types of brachytherapy include intracavitary applications (within body cavities such as the vagina or nasopharynx), interstitial implants (directly into a tissue), and mold applications (adjacent to tumor sites such as skin or eye). Brachytherapy has been used in adults most often for cancers of the female genital tract, upper aerodigestive tract, breast, soft tissues, prostate cancer (fig. 2.13). Pediatric applications have been described more recently, primarily for retinoblastoma and soft-tissue tumors.

The closed source of radiation (the closed radioactive preparation) is the radioactive substance which is concluded in such cover or insuch physical status which prevents distribution of substance into environment. Being the closed sources they most oftenuse needles and tubules with ^{137}Cs (energy of gamma radiation 0,66 MeV, a half-life period of 30 years) and preparations ^{60}Co (energy of gamma radiation 1,17 and 1,33 MeV, a half-life period 5,26 years). Last years ^{192}Ir (energy of gamma radiation 0,30-0,61 MeV, a half-life period 74,4 days) is widely used as it

Fig. 2.13. Implantation needles for interstitial high-dose-rate brachytherapy with ^{192}Ir prostate cancer

possesses a high specific radio-activity, that allows to apply sources of the small sizes.

The preference is given to intracavitary, and to interstitial irradiation with high capacity of a dose. Treatment occupies some minutes and is applied both in the independent plan, and in a combination with remote irradiation.

Current practice most commonly uses ^{192}Ir, an artificially produced radionuclide imbedded in wire or seeds that can be after loaded into hollow silastic tubes. Interstitial placement of the tubes is performed by direct positioning or by stereotactic localization using computed tomographic (CT) guidance. The geometry of the implant can be planned before insertion, confirmed by radiographs during the procedure, and altered if necessary; when it is satisfactory, the tubes are loaded with the radioactive sources. This sequence allows greater accuracy while limiting exposure of medical personnel. The implant remains in place for a calculated period of time, typically about 20-30 minutes, and is subsequently remove. Brachytherapy experience has been well documented in cancer of uterus, rectum, mouth cavity. Recent series document successful applications of both intracavitary and interstitial brachytherapy in soft-tissue sarcomas. Constant implants, basically iodine seeds (^{125}I), are applied first of all for treatment of early forms of prostate cancer as alternative of surgery treatment.

Interstitial radiotherapy is surgical procedure, therefore it should be lead up with observance of the general surgical rules.

System radiotherapy is carried out with radioactive iodine (^{131}I), radioactive strontium (^{89}Sr) and is based on metabolic features of tissues. It gets to the pathological centres (metastasises) and realizes radio therapeutic action.

Lowvoltage x-rays radiotherapy. The basic features lowvoltage x-rays radiotherapy are: radiation is generated at voltage no more than 100 kV, a small skin-source length (to 7,5 sm), small fields of an irradiation (to 25 sm^2). Spectral distribution of x-ray radiation can be changed with the filters made of aluminium, and also in skin-source length size. Aluminium filters look like plates of various thicknesses and serve for selection of necessary qualitative structure of a beam of radiation at the expense of a long-wave spectrum filtration (fig. 2.14).

In lowvoltage x-ray radiotherapy 50 % of isodose lines are on depth up to 1 sm. In lowvoltage x-ray radiotherapy intensity of radiation and, accordingly, a dose sharply reduces at furthers distances from skin. Nowadays lowvoltage x-ray radiotherapy is widely used as an independent method of treatment of malignant tumours of skin and, less often, as a component cancer treatment of oral cavity, a rectum.

Contra-indications for lowvoltage x-ray radiotherapy:

1. Deep skin lesions (cancer in scars after burns, lupuses, syphilis, relapse of skin cancer after beam therapy).
2. Lesion is deeper than 12 mm; external methods of irradiation are more preferable.

Fig. 2.14. Lowvoltage x-rays apparatus (40-100 kV)

2.7. Structure of a radiotherapy course

The prebeam period. During the prebeam period preparation to treatment is carried out. It should begin with psychological preparation.

Necessity of radiation influence is explained to a patient, its efficiency specifies possible changes in the state of health and some radiation reactions as well asa diet peculiarities.

The next important phase is clinical topometry. The prebeam period ends with finalization of a medical plan. The beam plan is a set of documents of the radio biological and dosimetric planning, including a map of dose distributions in a patient’s body and the radiographies made through entrance fields and proving the correct direction of a radiation bunch to the centre.

From a mathematical point of view classical radiation therapy planning has been treated as a forward process as it tries to answer the question: how will the absorbed dose in the target volume and surrounding normal tissues be distributed for a given target volume, associated patient geometry and suggested configuration of the incident beams? Classical radiation therapy optimization is therefore generally a trial and error process, where gradually improved dose plans can be found by trying out an increasing number of beam configurations.

However, in mathematical terminology radiation therapy planning is fundamentally an inverse problem. This is so, because what we really want to find, is the optimum combination of incident beams for a given target volume. More exactly, the planning process should answer the question: which configuration and shape of the incident beams is best for controlling the tumor growth with minimal damage to normal tissues? At least under the assumption that the desired dose to the target volume or the geometrical and radiobiological properties of the tumor and normal tissues of the patient are known, it should be possible to find the optimal irradiation technique (fig. 2.16).

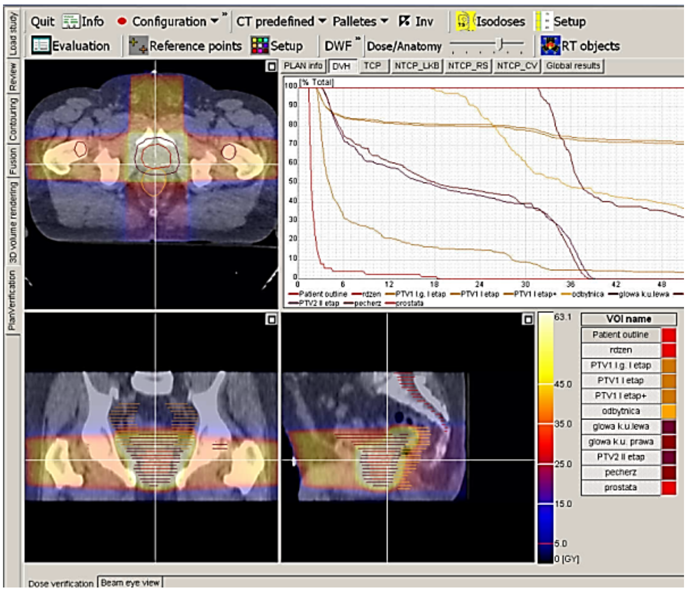

Fig. 2.16. Example screen of 3 dimentional dose distribution in computer planning system of irradiation.

The question mark indicates the principal quantity calculated, the isodose distribution in the patient and the optimal incident beam profiles. Obviously the absorbed dose distribution in the patient is also obtained by the inverse calculation either by an ordinary forward calculation or by the inversion method itself.

So, to make a treatment program for each patient it is necessary to define sequentially:

1. The treatment purpose.
2. To solve a question on a single and total dose.
3. To choose a method of irradiation and ionising radiation source.

4. To define conditions of irradiation: number and sizes of fields, a direction of the central bunches of beams.

The beam period. The beam period is the period of performing irradiation under constant medical supervision over the patient. For irradiation of each field a patient should take comforable position. It is crucially important to immobilize patients. In the course of irradiation the doctor or the nurse observes the patient using a TV screen. Intercoms provide communication of the doctor and the patient. Upon termination of irradiation the patient is recommended to have a two-hour-rest on fresh air or in a chamber with good ventilation. Data on each irradiation session are registered in a protocol.

The post beam period. In the postbeam period, even in absence of clinically defined signs of a radiation injury, there is a decrease in tolerance of the irradiated healthy tissues to additional injuring influences. Therefore patients are recommended to avoid physical and chemical traumas of irradiated zones. Intensive ultra-violet irradiation, general thermal, physiotherapeutic procedures are absolutely counter-indicated to oncological patients, irrespective of term and irradiation area. In the postbeam period rehabilitation actions are of great value.