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Radiation therapy: Methods:Patient setup

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Running title: Various types of radiation therapy and the Procedure for the same

Clinical significance: Knowledge of the old and newly introduced methods of radiation therapy and the procedure for the same is essential for every dental professional.

ABSTRACT

Background: Treatment of recurrent head and neck cancers following decisive radiotherapy has progressed during the past 30 years. Brachytherapy, systemic therapy and chemoradiotherapy have improved the 12 month survival rate to 40-50%,but the rates of toxicity have increased.

Radiation therapy abbreviated as XRT, also called as radiotherapy or radiation oncology;is the therapeutic use of ionizing radiation as an adjunct to other methods of cancer treatment,for eradicating toxic cells. It can also be used as a palliative treatment,or used in the treatment of non-malignant diseases of the organs such as the eye, in trigeminal neuralgia, in prevention of a keloid or heterotopic ossifications, and in other conditions.

INTRODUCTION

Cancer of the head and neck is treated by: the radiation therapy, chemotherapy and surgery. The primary treatment is thesurgery and radiation therapy,or both combined; and the chemotherapy is often an adjuvant. The treatment modalities for a patient with a particular head and neck cancer is dependent on: the location of the cancer, the cancer stage or its extent.[1]Radiation therapy has played a fundamental role in organ conservation and eliminating the tumor growth in the postoperative setting ofthe locally advanced head and neck cancer.[2]

The clinical benefits of radiation therapy were understood not long after the discovery of radiographs by Roentgen, in 1895. Thereafter, many benefits of radiation therapy have been studied and it is now being recognized as an exclusive medical specialty. Radium was discovered by the Curie family in 1898 and it was Alexander Graham Bell who recommended its use, in brachytherapy, for implantation within malignant tumours. But the inability to measure the exact dose of radiation that needed to be given as a therapeutic dose was a major drawback. The standard dose was considered, as that,which resulted in a skin erythema. Early treatment did not result in much of skin damage as the intensity of radiation was minimal.

The division of the entire dosage of radiation into smaller doses, also called as fractionation, was introduced by Coutard. High energy supervoltage, and later, megavoltage dedicated radiotherapy was also introduced.Presently, the cost of the therapy is considered unaffordable by patients in the developing nation, but the investigators are hopeful that it would be made affordable by 2035.

Principles of radiation

The main target of the radiation therapy is the nuclear DNA, causing in its breakage. This breakage leads to a loss in the cell integrity by interrupting the cell cycle and resulting in the eventual death of the cell. The radiation damage is caused by indirect ionizationthrough free-radical mediatorsas a result of the radiolysis of cellular water.The cell growth, cell senescence and apoptosis which are dependent on the cell cycle are also affected by the radiation. The exact mechanism of radiation therapy is still under discussion, and the processes involved are continuously being unravelled, so that theradiation therapy can be made more operative.

The therapeutic mechanism for radiation is based on the intrinsic ability of cells to repair any damage and the ability of the radiation oncologist to take advantage of any geometric separation between malignant and benign tissues. If the cellular environment is altered it may also result in an alteration in the mechanisms of the cell damage.

It has been assumed that repeated, small doses of radiation to a single cell areless damaging than an equivalent total dose. Besides,the cell being radiosensitive, the survival of the cell may also be related to the position of the cell in the mitotic cycle, oxygen tension, and dose rate. Hence these features are apt for the 4 Rs of Radiobiology—namely, R edistribution, R epair, R eoxygenation,and Repopulation.

Physics of radiation

Electromagnetic spectrum comprises x-rays and gamma ray photons; and these dual rays can be used to explain its wave and particulate behaviour.A photon is a packet of energy that can be explained by the equation E = hv where h (Planck's constant- 6.62x 10-34 J-sec) and v (frequency of the photon).

Frequency = quotient of the speed of light (3 × 108 m/sec)/ wavelength. High-energy radiations therefore have a high frequency and a short wavelength.

When photon beam is obstructed by matter it results in the lessenedintensity of the beam.

Radioactive isotopes

Radioactive isotopes may be natural or artificial. It may decayin the long run in its energy spectrum, decay spectrum and half-life,which are its important features. Decaying occurs by (liberating positive or negative charge) internal conversion, electron capture, or a combination of these reactions. A nuclear reaction results in nuclear transformation when a chemical reaction takes place resulting in a new chemical compound.

Radiation dose or exposure is measured in units of absorbed radiation/ unit of tissue. Its unit is the Gray (Gy),and radiation dose is 1 J/kg of tissue. In the earlier days,radwas used as a measure of radiation which was equivalent to 1 cGy (0.01 Gy). The exposure and dose rate of radiation are inversely proportional to each other.

The instrument

A medical linear accelerator or cobalt-60 unit is used to deliver the radiation which is deposited sub-epithelially and is therefore, skin sparing. The deposition of the photons reduces, as the depth increases.[3] LINAC accelerates electrons, which collide with a heavy metal target and high-energy X-rays are produced.

The decision of the type of radiation therapy is dependent on the physical findings, radiographic imaging information and knowledge of the related anatomy, pathology andhistory of the tumor.Also decided would be the type of radiation therapy that needs to be given: palliative, definitive or as an adjuvant therapy with surgery and chemotherapy.[3]

Radiation therapy is used for head and neck cancer in various manners:

Definitive radiation therapy (with or without chemotherapy): This therapy signifies that the primary treatment of the cancer is radiation, which could be combined with chemotherapy, and hence called as a definitive **chemoradiation** therapy. The method may allow organ preservation, which is the prime advantage of this method. But if the method fails due to recurrence of cancer at the same site, the next step for treatment would be surgery.

Adjuvant radiation therapy (with or without chemotherapy): This method of treatment considers surgery as primary, and radiation therapy is given after the surgical removal. It has been found to prevent the recurrence of cancer. This is possibleas any cancer cell that escapes the surgical blade, is killed by the radiation. Post-operative radiation therapy is followed by chemotherapy in some cases, to further prevent the chance of cancer recurrence.

Neoadjuvant radiation therapy (with or without chemotherapy): This protocol is followed in case of clinical trials or in case of advanced stages of disease. Here the non-surgical treatment is followed by surgery. By this method the pathologists would be able to gauge the existence of remaining cancer cells and instruct the surgeon to remove it.

Palliation of symptoms: At the end stage of treatment when all methods of eliminating cancer have proved unsuccessful then radiation could be given to palliate symptoms. For eg.acancer spreading to the bones of the spine which is very painful, and where surgery is not an option, then radiation can be used to treat the tumor.

Types of radiation therapy delivery methods

Radiation can be administered by external beam radiation therapy and brachytherapy.

Standard external beam radiation therapy: This is the predominant form of radiation therapy for head and neck cancer. The ray beam could be either X-rays or gamma rays. The current method of delivering these rays is by using the intensity-modified radiation therapy (IMRT). In this method the dose is delivered through 100 thin beams of energy in a three-dimensional space. Thus the radiation oncologist is able to minimise the beams striking the normal tissue and maximize those attacking the cancerous tissue. This procedure reduces, but does not completely eradicate the side effects of radiation therapy when normal tissue is affected.

Brachytherapy: This form of radiation therapy utilises a tiny radioactive “seed” that is implanted within the tumor, and beams of photons would be shot through the skin. Needles,called as “catheters” are pierced through the skin to reach the target area. The radioactive ‘implants’or ‘catheters’can either be temporary or permanent.

Here the radiation can be continuously administered on the targeted tumorwhile sparing the normal tissue, which is better for slow-growing cancers. The main disadvantage of this procedure is that the tumor must be well defined,and cannot be used in case of the poorly marginated growths.

The implants are inserted in the operating room. The surgeon performs a tracheostomy during the placement of brachy-catheters, under general anaesthesia. The tube is removed after a few days of treatment; this is a precautionary measure in case of any major bleeding or swelling that might result in difficulty in breathing. The complication is common in case of cancers in the base of the tongue. Then, the radiation oncologistcontinues with the placement of the catheters once the patient is anaesthetised. The catheters would be inserted in such a manner that, the radiation emitted from it would face the area of interest.The next phase will be to load the catheters with a radiation source. This procedure will be performed in a private room to minimise the exposure of the other patients or the clinical staff,to the effects of radiation. Presently, for the head and neck therapy, the brachytherapy catheters are allowed to remain in place for about five to seven days to carry a considerable amount of radiation, or they can be used to boost a very detailed area for about two to three days after subjecting to the external beam radiation.

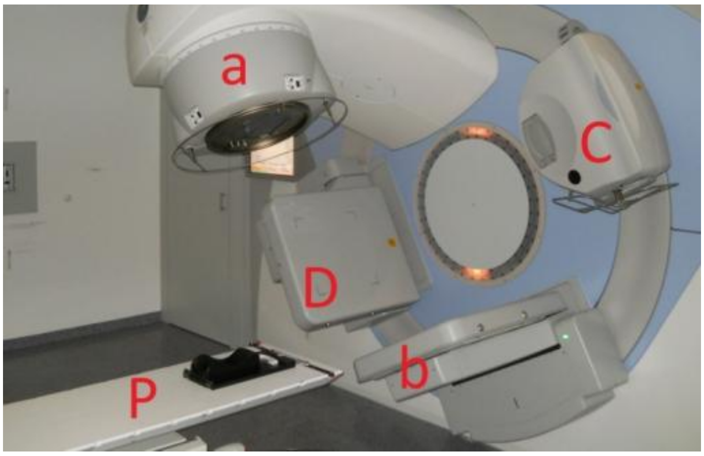
Additional types of radiation therapy include:

Three-dimensional conformal radiation therapy (3D-CRT): uses computer technology to accurately target tumors. A three-dimensional image of the tumor is made prior to the treatment and the radiation beams are programmed to "adapt" to the shape of the tumor. Since the region around the tumor is spared, higher doses of radiation can be used. This method is considered in case of tumors that are too close to vital organs, to be treated with conventional radiation therapy.[5]

Intra-operative radiation therapy (IORT): This method of radiation therapy is especially practised where the primary removal of the tumor has taken place by surgery and where the target is reached with an external beam radiation of high intensity. It is used in large cancers of the head and neck where the cancer has recurred after radiation therapy or in the case of local end stage cancers that are at a high risk of recurrence despite maximal surgery and external beam radiation.[3]

In this technique, after surgery of all obvious cancer, the radiation oncologist places an applicator in the area where microscopic cancer cells may be present. The radiation oncologist along with a team of scientists chalk out a treatment plan and use a mobile linear accelerator to direct the radiation to the site for about 30 minutes. The entire operation is performed in a CCTV set up room,to monitor the sleeping patient on the operating room table. Radiation directed intra-operatively is considered safer than directing an added dose of external beam radiation. Thisenables the retraction and shielding of the normal tissue and keeps it out of the way. Also, the radiation in IORT is much morefocally directed,especially at sites,where there is chance for residual tumor. The dosage administered, typically ranges from 10 to 20 Grays, though there is no standard quantity.[3]This cannot be considered as a standard method of treatment and studies are on-going to determine the exact role of IORT for a persistent cancer in the head and neck.[5]

Figure Courtesy: Pütz M, Wenz F - GMS Curr Top. Otorhinolaryngol Head Neck Surg (2012)



A modern linear accelerator with cone beam CT. a-b – C-D- units-irradiation source.P –couch for patient positioning with device for head fixation. a -irradiation source, b – digital image converter for checking the patient positioning with the treatment beam, C – kV-x-ray generator, D – kV-image converter to obtain CT-data

Intensity Modulated Radiation Therapy or Tomotherapy: delivers a variable intensity radiation with a rotating device. The variable intensity is obtained by the placement of “leaves” which may block or allow the passage of radiation. Like the rotation of the CT scanner, the rotating component allows for more focussed targeting of the cancer. In the conventional method of radiation therapy 5-10 beams are usually delivered from several different directions. The radiation from the Tomotherapyis deliveredfrom every point of a spiral or helix, instead of from just a few points.It directs treatment one quadrant at a time. This technology seems promising and more precise approach for the treatment of head and neck cancers, because the normal tissue is spared from radiation damage.

Radiosensitizers: Drugs that can makecancer cells more prone to damage by radiation therapy are called as radiosensitizers. They increase the normally low level of oxygen in the cancer cells, as the cancer cells with low levels of oxygen are less sensitive to radiation than cancers with elevated levels. The US Food and Drug Administration (FDA) have not yet approved the use of radiosensitizer drugs and therefore the treatment with these drugs is only available through clinical trials.

Two radiosensitizer drugs have been studied.

- ✓ A radiosensitizer called RSR 13 binds to hemoglobinthereby increasing the level of oxygen in cancers.
- ✓ RSR 13 has not yet been evaluated in humans.
- ✓ Another radiosensitizer drug, nimorazole, significantly improves the outcome of the radiotherapeutic management of cancers of the pharynx and larynx without any major side effects.

Radiation Protectors: On the other hand Radiation protectors are drugs that partially protect normal tissues from radiation treatment, during cancer cell exposure.

- ✓ Ethyol® is one of these and the only drug that has been approved by the FDA for use in patients receiving radiation therapy for cancers of the head and neck. Clinical trials have shown that Ethyol® reduces both early and late radiation-causing side effects.Treatment with Ethyol® results in fewer and less severe cases of xerostomia. [4]

Neutron beam radiation therapy: Only a few centres in the world, even in the USA, possess this type of external beam radiation. Theoretically, it is known that the higher energy neutron beams (as compared to the lower energy photon beams) have superior cell killing capability per dose, asalso in overcoming radioresistence. Hence this theory is particularly important in large tumors with areas of reduced oxygen, and in bulky slow-growing tumors. In case of the head and neck cancer, neutron beam radiation therapy is only experimental and could be thought of, to treat, only a select few persistent salivary gland cancers for eg, adenoid cystic carcinoma.

Proton beam radiation therapy: This method of external beam radiation is again rare and is only available at a few centres around the world. Here the radiation beam uses protons (in place of photons) to kill cancer cells. This procedure is more advantageous, asthe protons allow an accurate delivery of radiation as opposed to the gamma rays or the standard X-ray-based external beam radiation with IMRT. Thisthereby reduces the damage to the normal tissues, by minimising the side effects. This instrument usage is extremely expensive and more time and more study would be needed before it becomes the main treatment for head and neck cancers.

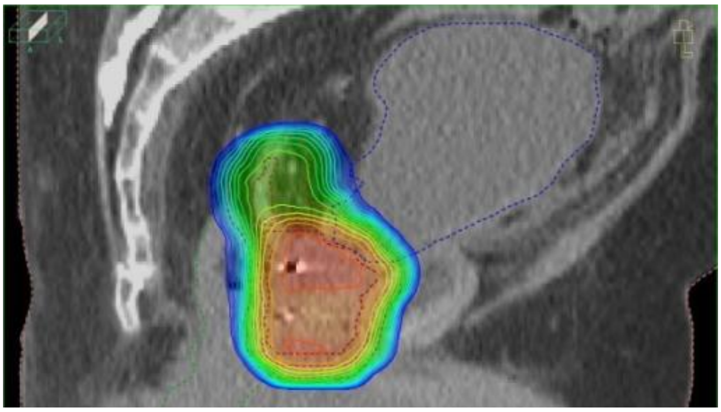


Figure courtesy: Vordermark D - BMC Cancer (2011)

Tomotherapy, an advanced type of IMRT, thatincorporates images of the patient. Radiotherapy is delivered in a sectional manner

Radiosurgery: The name is actually a misnomer and there is no surgery in the procedure. Some very tight beams of radiation arising from different directions, focuses on the target. It is known by various names, such as the Gamma Knife, Cyberknife®,and LINAC. It is mainly used for benign tumors of the brain and not commonly used in treatment for head and neck cancers.

Radioactive iodine: Mainly used in cancers and diseases related to thyroid, where iodine is consumed by the patient in its radioactive form, to reach the cancer cells and resulting in its destruction. It is NOT an external beam radiation. Thyroid cells anywhere in the body should be destroyed. Radioactive iodine does not destroy normal tissues as most normal tissues do not take up iodine. This therapy is said to have side effects such as fatigue, dry mouth and nausea; and some patients may complain of a metallic taste in the mouth.[5]

Image-guided radiotherapy (IGRT)

IGRT is the usage of a multitude of imaging techniques, such as X-rays or CT scans, alongside radiotherapy. Imaging allows us to confirm the position of the tumor in the patient and focus the radiotherapy beam more precisely.

VMAT, a new radiotherapy method, was first performed in the UK at The Royal Marsden in London. (RapidArc).[6]Here the treatment time is reduced from 15 minutes to less than five minutes, while directing a precise dose and conservingthe normal tissues. This is facilitated by controlling and altering the size, angle, speed and dose of the radiation beam all at once so that radiation is delivered to the whole treatment area at one time, rather than in small sections.

The technology uses athree-dimensional volume imaging, so that treatment can be planned to maximise the radiation dose on to the tumour and minimise the exposure of the surrounding healthy tissue.[6]

Total body irradiation (TBI): is the radiationgiven to the whole body at one time, to remove any traces of the tumor cells that may be lodged anywhere in the body or in the bone marrow; prior to a transplant. It can be used in the groundwork for bone marrow or stem cell transplants, or as part of high-dose radiation design for lymphoma and leukemia. The goal of TBI is to overpower the patient's immune system in order that the transplanted tissue is not rejected.

Accelerated whole breast radiation therapy:Here the hypofractionated radiation is delivered to the breast in fewer but larger daily doses. The treatment time is therefore reduced for the right patient, from approximately six weeks to about three weeks, and yet successfully treating the cancer.

Accelerated partial breast irradiation (APBI): as the name suggests here the radiation is given to only part of the breast. Hence the treatment period is shortened from six weeks to about a week. The surrounding normal tissues also receives reduced radiation hence is more convenient for patients.Nationwide trials are underway to determine the long-term effectiveness and safety of this technique.

Stereotactic radiosurgery (SRS): uses the same technology as the IMRT except that it is supported by additional imaging capabilities that facilitate a precise and accurate arrangement without the use of an invasive head frame. It is used to spinal cord and small brain tumors (benign and malignant) and some blood vessel abnormalities.

Stereotactic body radiation therapy (SBRT): Usesthe same principles as the SRS but main focus is on the other parts of the body. High doses of radiation are delivered with precise accuracy. It is used to treat some types of lung tumors that cannot be surgically removed. It is also highly operative on tumors in the liver and spine.

High dose rate (HDR) brachytherapy: A radiooncologist usesa combination of brachytherapy and CT scanning which is used to plan a safe and precise treatment. It is commonly used in cancers of the thyroid, head and neck, uterus, breast, cervix, and prostate.

Robotic transrectal ultrasound (TRUS): A brachytherapy guided by ultrasound and also using robotic assistance to navigate and place the implants.[7]

Planning of radiation fields

Three dimensional computer images of the anatomic data are used in planning the radiation fields. With a bird's eye view of the radiation beam, the delivery of radiation is planned suchthat the radiation field sufficiently covers the target area and avoids or reduces the dose to the healthy tissues. The beam arrangements would be placed in such a way that the target tissue is not missed. An elaborate treatment planning is spread out as a result.

The gross tumor volume (GTV) is determined at first followed by the clinical tumor volume (CTV) including the microscopic extension of the disease. On the other hand the planning treatment volume (PTV) would be decided on a day-to-day basis and may vary.

It is also essential to stabilise the position of thepatient'streatment area and this is done by making the patient wearthermoplastic masks and other devices which are regularly used in the treatment of cancer.

Fractionation

A number of methods have been used to compare various dose-fractionation schemes. These methods are dependent on the dose-response curves and the probable correlation between an acute reaction and long-term effect of the treatment.

Strandquistwas the first to study the relation between dose, time, skin reactions and cure, in treatment of skin cancers. Later, Ellis recognized that the time factor depended on the other 2 above mentioned factors. He suggested the nominal standard dose (NSD) formula: D = NSD×N0.24 ×T0.11, where D = dose, N = numberof fractions, and T = overall time. This has been modified to D1/D2 = (α/β + d2) / (α/β + d1)where D is the total dose and d is the dose per fraction.

In hyperfractionated regimens ↑higher tumor doses = long-term tissue damage (clinically acceptable). There is an unchanged or slightly increased daily dose at the same time the dose per fraction is decreased = overall treatment time remains constant.

In the accelerated fractionation schemes, the dose/ fraction is unchanged the daily dose is increased, and the total time for the treatment is reduced.

Various altered fractionation patterns have been tried and compared with the conventional treatment and clinical trials are underway. But further follow-up is essential to regulatethe overall survival benefit.Cochrane Database of Systematic Reviews has found through a study that altered fractionation (either hyper-fractionated/ accelerated fractionated) radiotherapy increasessurvival about 3.4%/ 5 years in patients with head and neck squamous cell carcinoma, with hyperfractionation providing the greatest benefit (8% absolute benefit at 5 years). Accelerated fractionation, without total dose reduction, provides a 2% absolute benefit at 5 years.[3]

The patient positioning during the radiotherapy

Before the treatment begins, the patient will have a CT or MRI scan of the affected area, so that the medical team will be able to see exactly where the tumour is.[6]Some patients may also have a positron emission tomography (PET) scan and/or magnetic resonance imaging (MRI).

A few weeks prior to starting radiation therapy, the patient undergoes a simulation session. In this session, a CT scan is taken after being injected by the contrast,into the veins, and the technician makes markings on theskin. A special mask will also be created; this is to ensure that the patient's positioning is steady each day he undergoes the treatment, and the radiation is directed as precisely as possible.[5]The mask is created in a mould room and is made from plaster, to fit the patient. It is then taken off to dry, following which, a see-through plastic mask is made to exactly fit the patient's face. [6]

The images from the CT scan will be analyzed by a radiation oncologist and a team of scientists so that the treatment can be designed; and the dosage plan is personalized for the tumor and various permutations and combinations of the treatment plan are thought of theoretically.

The exact frequency and length of time of treatment visits will be finalised by the radiation oncologist, but ideally the treatment is five days per week for nearly six weeks with each visit taking less than fifteen minutes inside the machine.[5]

Depending on the area to be treated, the therapists make a bite block which is a softened piece of plastic placed on the tongue, and which is made to harden. This will be placed in position during each treatment, to limit the swallowing. Mouth guards made by dentists will also have to be worn during the simulation and each treatment.

Skin markings (tattoos)

Skin markings are made on the patients face by using a felt marker. Then, permanent skin markings, called tattoos, are made with a drop of ink and sterile needles which feel like pin pricks. These are placed on the mask or on the patient's skin. Though the felt marks can be removed, the tattoos are permanent. Photographs of the patient are taken, with the tattoos, during the simulation which will be used to position the patient correctly on the table each day of the treatment. Radiation treatment is normally given daily, Monday through Friday, for about 7 weeks. [3]

CONCLUSION

"The novelty of the therapy today is we can deliver small spots as the radiation shoots out of the machine. It's the accumulation of these small spots that targets the tumor." The controlling of locally advanced head and neck cancers is challenging. Accelerated repopulating, tumour hypoxia during treatment and in-built radio resistance are the main offenders for the subpar tumour control. The Rs of radiotherapy, as described above, play amajor role in treatment planning, especially with regard to dose fractionation in radiotherapy.In order to offer patients an improved quality of life, all of the therapies mentioned earlier need to be further studied in order to establish the most effective agenda to present to patients before any radiotherapy has begun. It is probable that several of the above therapies would be beneficial in minimizing damage to the healthy tissues and maximizing the positive results after radiotherapy.

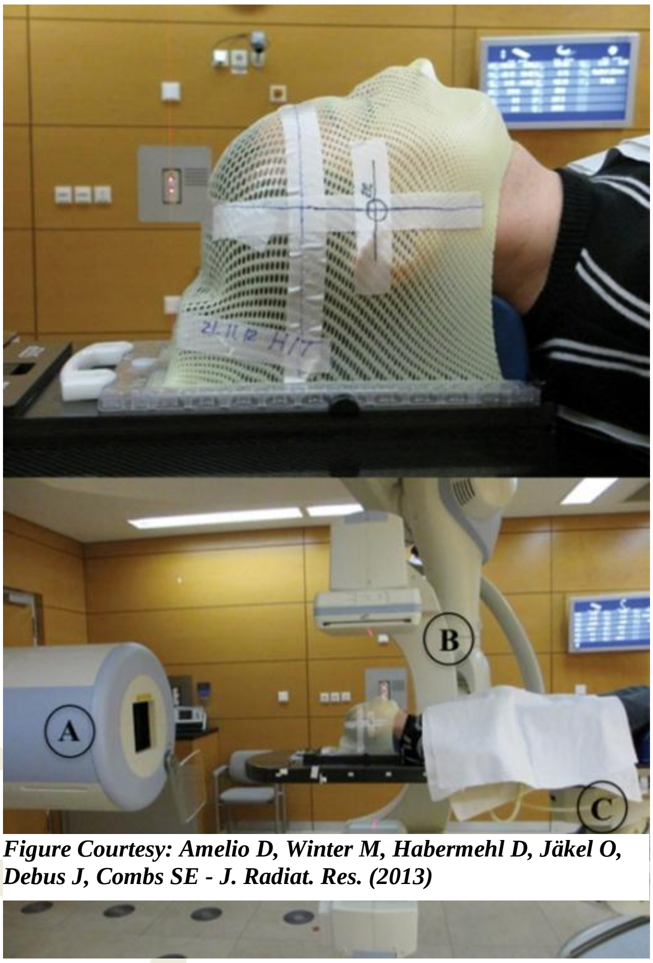


Figure Courtesy: Amelio D, Winter M, Habermehl D, Jäkel O, Debus J, Combs SE - J. Radiat. Res. (2013)

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