

Future Trends and Strategies of Radiotherapy in Head and Neck Cancer

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Abstract: Radiotherapy or Radiation Therapy is the treatment of diseases using ionizing radiation. For therapy high-energy radiation in megavoltage range is preferred where as for diagnosis kilo voltage energy is used. The radiotherapy is based on the basic principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cell. This differential cell kill is used for the treatment of tumors.

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1. Introduction

Definition

Radiotherapy or Radiation Therapy is the treatment of diseases using ionizing radiation. For therapy high-energy radiation in megavoltage range is preferred where as for diagnosis kilo voltage energy is used.

Principles of Radiotherapy (RT)

The radiotherapy is based on the basic principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cell. This differential cell kill is used for the treatment of tumors¹.

Physical concepts in Radiation Oncology

Ionizing radiation used to treat cancers is divided into electromagnetic radiation and particle radiation. Electromagnetic radiation is the predominant therapeutic modality for radiation therapy. The electromagnetic spectrum ranges from low energy to higher energy. This includes megavoltage radiations such as gamma rays and megavoltage X-rays. Particle radiations include electrons, neutrons and protons.

X-rays and gamma rays are essentially the same type of electromagnetic radiation (photon). They differ in the ways they are produced. X-ray are produced by man made devices by introducing a target material along the pathway of fast moving electrons. Gamma rays are emitted from a radioactive isotope as part of the process of naturally occurring radioactive decay. RT with particle radiation differs from photon radiotherapy in that it involves the use of fast-moving subatomic particles to treat localized cancers. Most particles (neutrons, protons etc) deposit more energy while passing through tissues, thus causing more damage to the cells they hit. Recent advance in radiotherapy research is the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Tumor-specific antibodies against tumour antigens labeled with radioactive isotopes (radiolabeling) are injected into the body, which actively seek out the cancer cells and destroy them by the cytotoxic action of the radiation. This approach can minimize the risk of radiation damage to healthy cells.

Methods of delivery of Radiotherapy

Based on the method of delivery radiotherapy treatment is classified into teletherapy, brachytherapy and internal therapy.

Teletherapy

Radiation given using machines kept at a distance away from the patient. Based on the energy this is subdivided into:

- Superficial Therapy:** Superficial voltage machine generate X-rays 30-125 KV. This is used to treat superficial tumors like skin cancer.
- Orthovoltage Therapy (Kilovoltage):** Orthovoltage machines produce medium energy X-rays in the range of 200-300 kv. Primarily used to treat superficially situated tumors. In this situation skin dose is high and cannot be used to treat deep seated tumors.
- Megavoltage Therapy:** Megavoltage machines such as telecobalt and linear accelerators generate radiations having energy above one megavoltage. These machines are used to treat deeply situated tumors delivering lesser dose to the overlying skin.

Telecobalt Teletherapy (Co⁶⁰): In telecobalt machine radioactive isotope (Co⁶⁰) which emit gamma rays having an average energy of 1.25 MeV.

Linear Accelerator

These are the most commonly used radiotherapy machines. This does not contain a continuously emitting radioactive isotope. In this machine electrons are generated, accelerated and made to strike a target to produce high voltage X rays. The advantage of this machine is that both X rays and electrons can be utilised for treatment. Electrons are commonly used to treat superficial tumors without damaging underlying critical structures.

Brachytherapy

Radiation source is kept in close contact or with in the tumour. The commonly used isotopes are Radium ²²⁶, Cesium ¹³⁷, Iridium¹⁹² and Iodine¹²⁵. The treatment usually lasts for few days.

Brachytherapy is often divided into three types:

- a) **Intracavitary brachytherapy:** Radioactive isotopes are kept inside a body cavity, e.g. carcinoma of nasopharynx
- b) **Interstitial brachytherapy:** Radioactive isotopes are implanted into the tumor, e.g. Carcinoma tongue and buccal mucosa
- c) **Mould therapy:** Radioactive isotopes are kept in close contact with the tumor, e.g. carcinoma of hard palate and skin cancer

Interstitial and mould therapies are commonly used for the management of oral cancer. This is used as a boost following external Radiotherapy or as a single modality in early stage disease.

Internal therapy

Radioisotope is either injected or taken as a drink to treat tumors. For example: Radioactive iodine (I^{131}) in the treatment of thyroid cancer.

Phosphorus -32 in the treatment of polycythemia vera.

External Beam Radiotherapy (Teletherapy)

External radiotherapy is normally given as a series of short daily treatments, usually from Monday through Friday, in the radiotherapy department using teletherapy machine (telecobalt / linear accelerator). While taking treatment patient will be alone in the treatment room. However he will be closely monitored through a closed circuit camera. The patient can have normal social life and there won't be any radiation emitted from the patient.

Fractionation in Radiotherapy²

Fractionation is a term used to describe the manner in which daily dose of radiation is given. Fractionation of the total dose of radiation helps in minimizing normal tissue reaction. The clinical effects of fractionated radiotherapy are influenced by the ability to repair sublethal damage, reoxygenation of tumour during the course of radiation, repopulation of tumour and normal tissues between fractions and redistribution of cells into a more sensitive phase in cell cycle treatment. (The 4 R's of radiobiology).

Conventional Fractionation

Conventional fractionation is the application of daily doses of 180-200 cGy and 5 fractions per week to a total dose of 40-70 Gy depending upon the type of tumor.

Hyperfractionation

Two or more fractions per day of reduced dose (115-120 cGy) with overall treatment time similar to that of conventional fractionation. Hyperfractionation helps in increasing the total dose without increasing the late reactions.

Accelerated Fractionation

Accelerated fractionation is a means of decreasing the overall duration of treatment in an effort to reduce the repopulation of tumour cells in rapidly proliferating cancers. Repopulation (tumour –cell regeneration) occur during treatment when the overall duration of treatment is

increased. Shortening of overall treatment time can increase the tumour control in selected situation.

Accelerated Hyperfractionation

Delivering two or more fractions per day of normal dose per fraction helps in reducing overall treatment time without increasing the risk of late complication.

Concomitant-Boost Technique

A variant of accelerated fractionation is the concomitant boost technique. With this technique, treatment is delivered once daily for the first 3.5 weeks and then twice daily during the final 2 to 2.5 weeks, when tumour cells can begin to repopulate more rapidly.

Hypofractionation

Here less than four fractions per week with higher dose per fraction than conventional is planned. In selected situations this is found to be useful especially in the treatment of melanomas.

Split Course Therapy

Radiation is given in small courses with a rest period in between.

Side Effects of Radiation in Head And Neck Cancer Patients

Radiotherapy side effects are classified into acute and late.

Acute Reaction

Acute reaction occurs during and immediately after treatment upto 6 weeks. Acute effects are related to dose per treatment, total dose, volume of tissue irradiated and the site. These reactions are limited to the area irradiated and not seen outside the treatment volume. This is mainly due to the inflammation of the tissues during treatment. Symptoms include xerostomia, pain in the mouth and throat, skin reactions and falling of hair within the treatment volume may occur. The mucous membrane within the irradiated area gets inflamed leading to patchy ulceration. During therapy salivary secretion decreases and it becomes thicker and forms a coating over the tongue. This causes change in the pH of the saliva, which can lead to changes in the bacterial flora. During radiotherapy there will be alteration of taste.

These acute reactions are self limiting and usually subside in 2-3 weeks following completion of radiotherapy. There can be superadded bacterial and fungal infections. This is managed by antibiotic, antifungal and analgesics. During therapy patients are advised to take high calorie non-spicy bland food. Frequent use of soda bicarbonate and saline mouthwash is advisable. They should not use very hot and very cold food during treatment. During treatment patient should avoid application of creams and oils and rubbing of the skin with rough clothes should be avoided.

Late Reaction

This is the dose limiting toxicity and usually occurs months or years after treatment. This depends upon the dose per fraction, total dose and volume of tissue irradiated. This includes dryness of mouth, intolerance to spicy food, hair

loss and oedema of the skin with in the irradiated area. Necrosis, fistula formation, non-healing ulceration and osteonecrosis are rare. However modern radiotherapy delivery is very precise and accurate and damage to critical structures are extremely rare.

Advantages of Radiotherapy

- No tissue or functional loss
- Good cosmetic outcome compared to surgery Control of subclinical disease in the regional nodes is possible without added morbidity
- Can simultaneously treat multiple primaries.
- Better surgical salvage of radiotherapy failures than radiotherapy salvage of surgical failures.
- Rare treatment related mortality

Disadvantages of Radiotherapy

- Undesirable acute side effects such as painful mucositis, loss of taste, dryness of mouth etc.
- Potential late complications of soft tissues and bone
- Protracted treatment course
- Requires good infrastructures
- Rare possibility of development of second malignancy

Principles of Radiotherapy in Oral Cancer

The use of radiation therapy in the management of oral cancer is based on the following principles.³

- 1) Squamous cell carcinoma is generally radioresponsive and in early stage highly radiocurable.
- 2) The more differentiated the tumor the less rapid the radiation response and resolution and the higher the radiation dose required.
- 3) Exophytic and well oxygenated tumors are more radioresponsive than deeply ulcerative and infiltrative hypoxic tumors.
- 4) Squamous cell carcinoma, when limited to the mucosa are highly radio-curable.
- 5) Bone and muscle involvement by carcinoma adversely alters radioresponsiveness and subsequently decrease radiocurability.
- 6) The early small metastases can be controlled with radiation therapy alone. Advanced cervical metastatic lymph nodes are better treated with combined surgery and RT.

Indications of RT

- 1) T1-T2 lesions as single modality
- 2) T3 - T4 locally-advanced lesions

Combined surgery and radiotherapy or combination of chemoradiotherapy

Combined Surgery and Radiotherapy

Radiotherapy can be given before or after surgery. Each sequence has theoretical advantages and disadvantages.

However, the results from randomized studies favor post-operative radiotherapy.⁴⁻⁵ In practice, most surgeons also prefer to operate in an unirradiated field where frozen section control of resection margin can be obtained. In certain clinical settings, however, planned preoperative radiotherapy may be favoured. These include situations where cancer is not respectable at presentation or when a free osteomyocutaneous graft is to be used for mandibular soft tissue reconstruction. In the latter situation avoidance of irradiating the graft and delivery of a lower dose to the mandibular stump than would be necessary in postoperative setting both facilitate integration of the vascular graft.

Indications for Postoperative Radiotherapy

- Positive resected margins
- Locally-advanced primary regardless of margin
- Multiple involved nodes
- Extra capsular extension
- Perineural spread
- Vascular and lymphatic emboli

Timing of Radiation

The general guideline is to commence radiotherapy when tissues are well healed. Radiotehrapy should be started as early as possible after proper wound healing preferably within 6 weeks. The longer the interval before the commencement of radiation, the greater the opportunity for presumed clonogens to proliferate. A delay of more than 6 weeks can adversely affect the outcome.⁶

Combined Chemotherapy and Radiotherapy Treatment

Chemotherapy is generally used along with radiation in organ conservation settings, especially in locally advanced tumours to avoid surgery. Chemotherapy can be combined with radiotherapy-in various ways.⁷

Neoadjuvant /Anterior / Induction Chemotherapy

Chemotherapy is given before local treatment like radiotherapy and surgery. This has 2 percent survival benefit.

Concurrent Or Concomitant Chemotherapy

Chemotherapy is given along with RT. This has 8 percent survival benefit.

Adjuvant Chemotherapy

Chemotherapy is given after local form of treatment like radiotherapy or surgery. This has one percent survival benefit.

Table 2: Survival rates in oral cancer

Site	Stage	5-year survival rate
Lip	I-II	95
	III-IV	78
Oral tongue	I-II	67
	III-IV	20
Floor of mouth	I- II	68
	III-IV	41
Gingiva	I-II	55
	III-IV	4 4
Buccal mucosa	I-II	78
	III-IV	40

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