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Head and Neck Cancer (HNC), Adaptive Radiotherapy, Proton Radiotherapy and Radiation Toxicity: Cellular and Cancer Response to Radiation

Sabreen Abbas Marzooq [1], Mohammed Hamed Sadaa [2], Amena Thamer Ahmed [3], Mustafa Khamees Fahad [4]

[1]University of Karbala, College of Science, Department of Biology, Iraq

[2]University of Technology, Department of Applied Sciences, Biotechnology, Iraq

[3]University of technology, Applied Sciences , Biotechnology, Iraq

[4]University of Anbar, College of applied science, Department of Biophysics, Iraq

Abstract: At more than half a million cases reported yearly, head and neck cancer (HNC) is one of the most prevalent types. Ninety percent of the cases are oral, pharyngeal, and laryngeal squamous cell carcinomas (SCC). Over the last few decades, radiation, surgical resection, or both have been applied.1,2 In the United States, the surveillance, epidemiology, and end results data indicated that radiotherapy is often one of the main cancer therapies. For cancer patients, radiotherapy enhances their clinical, form, and functional results. Nowadays, radiotherapy will help about 75% of head and neck cancer (SCC) patients, either as a main or adjunctive treatment following surgical resection. Early on in the course of cancer, radiation can take the role of surgical resection. Patients with advanced local cancer can get concurrent treatment with chemotherapy or with surgical removal followed by adjuvant radiation. One of the radiation techniques utilised in the operation is to preserve the organs, such as chemoradiotherapy to prevent laryngectomy. This paper aimed to summarise the evolution of radiation therapy for head and neck cancer with various caused toxicity and their management. Late in the 19th century, ionised radiation was first used to treat cancer. On November 30, 1895, Roentgen made the discovery of the x-ray, which launched the fields of radiology and radiation oncology. Following that, in 1896 Grubbe became the first to use a sheet as a protective covering, to use x-rays therapeutically, to suffer from x-ray dermatitis, and to assert that radiation might cure cancer patients. Glver Lyon proposed the possibility of bactericidal effects of the radiation that same year. But before the development of antibiotics, steroids, and chemotherapeutic drugs, radiation was used to help the resolution of inflammation for both bacterial and non-bacterial infections. In 1902, after multiple field tests, it was determined that the radiation had no bactericidal effects.

Keywords: Head and neck cancer (HNC), Adaptive Radiotherapy, Proton Radiotherapy, Radiation Toxicity

Corresponding Author: Sabreen Abbas Marzooq†, University of Karbala, College of Science, Department of Biology, Iraq

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Introduction

Mostly, brachytherapy and intensity-modulated radiation (IMRT) are used to treat head and neck cancer. The advanced version of three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy allows the radiation intensity at the sharply conformal target to be adjusted without endangering the nearby healthy tissues. Intracavitary (implant placed in a cavity) and interstitial radiation (implant placed in or near a cavity, other

than a bodily cavity) are the two forms of brachytherapy [1]. Early on in head and neck cancer, a dosage of 56–70 Gy is recommended. Two Gy per cent can be given every day for six weeks. The dosage ranges between 56 and 66 Gy depending on the kind of radiation. The adverse effects are discomfort, hair loss, teeth decay, and difficulty swallowing. A delayed complication results in xerostomia, which is a bad dental state, bad oral hygiene, changed taste sense, nutritional deficit, bad sleep quality, and speech impairment. Xerostomia is the consequence of a 35 Gy treatment that permanently destroys salivary gland function.

Radiation doses to surrounding healthy tissues should be minimised while a tumour target receives a homogenous dose [2]. Thus, the greatest number of clonogenic cancer cells can be eliminated with the lowest possible risk of damage to healthy tissue [3]. While conventional external beam radiotherapy with a limited number of rectangular or simply shaped beams partially accomplishes this, for many cancer sites it exposes excessively vast amounts of normal tissue [4]. Conformal radiation seeks to reduce the amount of normal tissue exposed by forming the dose distribution to closely match the geometry of the tumour, hence lowering the dose to nearby healthy tissues [5]. Higher levels of target localization made possible by sufficient immobilisation of the target and enhanced three-dimensional (3D) imaging allow the usage of smaller margins around the target [6]. Multiple beams directed from each beam's eye view (BEV) according to the shape of the target are part of three-dimensional conformal radiotherapy (3DCRT). Dosimetric techniques enable a treatment planning computer to compute 3D dose distributions. Studies on radiotherapy planning have shown that, as compared to conventional radiotherapy, 3DCRT lowers the volume of normal tissue inside the high dosage volume. Patients with prostate cancer receiving 3DCRT have shown a clinically significant decrease in late radiation side effects as compared to conventional radiotherapy in randomised clinical studies [10], and in non-randomized comparisons at different tumour locations. For 3DCRT, a further difficulty is dose escalation within reasonable rates of normal tissue problems. Prostate cancer non-randomized clinical trials have indicated that dosage escalation with 3DCRT enhances tumour control; multiple randomised clinical trials are currently in progress [7]. Delivery of dose distributions with concave isodose forms is made possible by intensity modulated radiotherapy (IMRT). It has been proposed that 30% of cancers have a concavity in the planned target volume (PTV) where IMRT may be used to save vital normal tissue irradiation.

Neck and head cancer

IMRT clinical uses

Multiple intensity modulated beams are combined in IMRT, a type of conformal therapy. Highly conformal, the resulting isodoses can, for the first time, produce a concave distribution. In many clinical cases after radiation, radiosensitive normal tissues are found inside a concavity encircling the PTV. Treatment of patients with thyroid, pharyngeal, or laryngeal cancers is a suitable example. A horseshoe-shaped PTV with the spinal cord within the concavity is produced when the clinical target volume (CTV) consists of a midline target and bilateral cervical lymph nodes [8]. It is difficult to use traditional external beam radiotherapy to homogeneously irradiate these PTVs to severe doses (50–66 Gy). Electron beams are normally matched with parallel-opposed photon portals. This method not only underdoses the posterior cervical lymph nodes near the spinal cord but also causes dose inhomogeneity at the photon-electron matchline [9]. With IMRT, this shape of PTV can be treated uniformly without the need for electrons. Tumour dose escalation is possible and the dose reaching the spinal cord can be maintained well inside tolerance [10]. Planning studies for cancers of the maxillary antrum, nasopharynx, lung and prostate have also shown significant normal tissue sparing using IMRT. Delivered complex dosage distributions can avoid several radiosensitive normal tissues near a tumour. Large parallel-opposed lateral portals are utilised, for instance, to treat nasopharyngeal cancer, including both macroscopic disease and locations of occult metastases. With this method, the brainstem, spinal cord, and parotid glands are invariably included in the irradiation volume even if they are not necessary to be included in the target volume.

Malignancies of the head and neck

Patients receiving radiation for head and neck cancers at the University of Michigan had salivary gland tissue spared by IMRT. PTV comprised the subdigastric node as well as the main tumour and the cervical nodes on each side. Judged to be at extremely low risk of containing concealed metastases, the submandibular salivary glands and the contralateral parapharyngeal area were spared [11,12]. Patients received treatment with a forward-planned "step and

shoot" IMRT approach (see below) that employed low weighted electron fields and several non-coplanar photon beams. Beam directions that eluded the parotid gland were chosen using a BEV facility [13]. Salivary flow, stimulated and unstimulated, was measured from each parotid gland before and after radiation, and then again after three, six, and twelve months. IMRT increased the minimal dose in 15 individuals receiving this parotid-sparing treatment. IMRT reduced dose inhomogeneity to the lymph node and main tumour areas more than conventional three-field conformal designs. The standard plan's radiation dose to the contralateral parotid gland was 93%; IMRT's was 32%. Although unlikely to be clinically significant, smaller, statistically significant reductions in dosage to the spinal cord, contralateral submandibular gland, and oral cavity were also seen. The mean stimulated salivary flow from the contralateral parotid gland one to three months after radiation was 60% (SD 49%) of pre-treatment values [14].

With a longer follow-up of 11 of these patients, it was found that, after a year, treated parotid glands got 57.5 Gy, whereas sparing parotid glands, which received a mean dose of 19.9 Gy, regained 63% of their pre-treatment stimulated salivary flow rates [15, 16]. To create dose-response curves for parotid gland function, an examination of 88 patients receiving parotid-sparing IMRT permitted correlation of radiation dose with salivary flow measurements. Both stimulated (26 Gy) and unstimulated (24 Gy) saliva flow rates were found to have a mean dosage threshold, below which glands receiving radiation exhibited significant preservation of saliva flow, which may continue to improve over time. Most glands that received mean dosages above the threshold, on the other hand, generated little saliva and did not recover over time (A Eisbruch, personal communication).

Three patients with recurring or second primary tumours of the nasopharynx, oropharynx, and hypopharynx treated with IMRT recently published their outcomes from the University of Gent. All of the patients had incurable disease and had undergone radical radiation (tumour dose 66±70 Gy, spinal cord dose 44± 45 Gy). The cancer was retreated using an IMRT approach (minimum target dosage 48±65 Gy) with a concave dose distribution to avoid the brainstem and spinal cord (maximum spinal cord dose 21±34 Gy, maximum brainstem dose 67 Gy) [17]. While one patient stayed in partial remission seven months following treatment, the other two patients experienced complete remission but relapsed within a year of radiotherapy. Though there was little time for follow-up, no patient developed myelopathy. The same author has described a method of irradiating neck tumours that reach the upper mediastinum using IMRT. With this method, maximal spinal cord dose is limited to 50 Gy and target dose escalation up to 70±80 Gy has been used to treat thyroid, laryngeal, and pharyngeal tumours [18].

Though some of the gross tumour volume (GTV) received 90 Gy, 96% of the primary tumour PTV for a patient with nasopharyngeal cancer reached the target dose of 72 Gy. Although the lymph node chains were supposed to receive a goal dose of 54 Gy, 12% of this PTV received a minimum dose of 26.5 Gy. With 99% and 98%, respectively, receiving 45 Gy, parotid and spinal cord sparing was attained. Similarly, although target dose imhomogeneity was significant, mean target doses were reached and normal tissue structure sparing was successful for tumours of the larynx and ethmoid sinus. However, in calculating the acceptable tolerance of such dose inhomogeneities, the exact position of lower dose zones, and impacts, for example, of patient mobility as well as the precision of the planning algorithm need to be considered in comparison to typical procedures [19]. Published recently is the first clinical report of 28 patients treated with the multivane intensity modulating collimator (MIMiC) tomotherapy device (NOMOS Corporation, Sewickley, PA) for a variety of head and neck malignancies [20]. After prior conventional radiation, ten patients received treatment for tumour recurrence; in eighteen individuals, IMRT was the mainstay of therapy. Although half of their patients are today immobilised in a normal thermoplastic mask [21], patients were first immobilised using an intrusive ®xation device (Talon, NOMOS Corporation, Sewickley, PA) that fastened to screws implanted in the inner table of the skull vertex.

Treatment delivery confirmation

With IMRT in particular, where any changes in the patient's position can impact the irradiation field, image-guided radiotherapy is crucial before radiation delivery. Thus, images can be obtained by cone beam CT, for instance [22, 23], to evaluate the bony landmarks and compare it with the initial planning scan, by placing the patient in the radiation field and using an immobilisation custom fitted thermoplastic mask to limit the motion of his shoulder, jaw, and head. The patient can be positioned in the intended radiation field as long as it is the same position for every treatment dose.

Adaptive Radiation Therapy

After a course of radiation, it is often the case that the tumour and the surrounding healthy tissues change. Every day the tumour and lymph nodes decline by three percent of their volume, and during therapy, the tumor's size, shape, and position change. The outcomes of the patients also change as weight and muscle mass are lost [23, 24]. For instance, the medial site of the parotid gland shifts into a stronger radiation environment. Adaptive radiation therapy, or re-planning of the radiation dose to account for changes in anatomy and target volume, thereby yields better treatment efficacy and quality of life than non-adaptive radiation therapy.

Oncology of Protons

Because the beam energy can be targeted at a precise depth and a reduction in dose results, proton beam therapy was first utilised in radiotherapy to treat cancer that is near to important anatomical structures. It is not, therefore, the same as external photon (x-ray) radiotherapy in that, while the radiation dose increases to the tumour area, it can maintain the same radiation dose for the normal surrounding tissues. Furthermore, it can give the surrounding structure a lower radiation dose while the tumour receives the same amount.

Radiation reaction of cells and cancer

Ionising the oxygen, high-voltage x-rays cause free oxygen radicals and the death of cancer. Consequently, this high-voltage x-ray may harm the DNA, the genetic material of the cells, which prevents division and growth.

The reaction to radiation is enhanced when oxygen is present.

Typically hypoxic, cancer cells are also rather resistant to radiation treatment. Radiation sensitizers can enhance the reaction to radiation.40 Radiosensitizers include the chemotherapy drug cisplatin (cisdiaminedichloroplatinum, CDDP) [26, 27]. Concurrent radiation and cisplatin are often utilised to preserve the larynx and regulate locoregionally. For those with locoregional advanced SCC of the head and neck, Bonner et al. found that chemoradiotherapy improved 5-year overall survival substantially more than radiation alone.

Environmental Toxicology

Apart from its ability to suppress cancer, radiation therapy can also harm the healthy tissues that are close to the radiation source. Adverse occurrences or consequences following radiation, which might be any temporary or permanent changes in the normal tissues, are referred to as toxicity after radiotherapy [28, 29]. When it happens within 90 days of therapy, it is regarded as acute toxicity; when it develops after 90 days of radiation, it is regarded as late toxicity. It is discovered that when chemotherapy is given alongside radiotherapy, the toxicity is increased. According to Cooper et al., 77% of patients receiving chemoradiotherapy experienced acute toxicity of grade 3 or above, compared to 34% of patients receiving radiation alone.

Toxicity of Radiation

Apart from its ability to combat cancer, radiation therapy can also harm the healthy tissues that are close to the radiation source. Adverse occurrences or consequences following radiation, which might be any temporary or permanent changes in the normal tissues, are referred to as toxicities after radiotherapy [28, 29]. When it happens within ninety days of treatment, it is regarded as acute toxicity; when it develops after ninety days of radiation, it is regarded as late toxicity. Radiation coupled with chemotherapy has been shown to have a higher toxicity. According to Cooper et al., 77% of patients receiving chemotherapy had acute toxicity of grade 3 or above, compared to 34% of patients receiving radiation alone.

Conclusions

The advantages of IMRT are probably going to be highest for patients with concave tumour targets and where clinically significant normal tissue avoidance is concerned. This is why it has been proposed that 30% of present radiation patients would benefit significantly from an IMRT treatment. Complex, time-consuming to plan and administer, IMRT may not be as beneficial to some patients as more straightforward traditional methods. In a health service with few resources, it is crucial to assess the possible advantages of any new method, to project the number of patients who would benefit, and to look into the magnitude of such advantages. The greatest chance to do this is

provided by radiotherapy planning studies. The possible benefits of IMRT introduction might be calculated by comparing the present radiotherapy approach with an IMRT technique for a specific tumour site. Planning studies have the benefit of being comparatively quick to carry out and allowing the "control group" to be made out of data from previously treated patients. One may compare many competing treatment modalities and use objective end points (like radiation dose to a specific organ). The planning study's findings need to be carefully interpreted, but they could point up tumour locations that are appropriate for more clinical research.

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