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Advanced Radiation Therapy for Head and Neck Cancer: A New Standard of Practice

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1. Introduction

Radiation therapy plays an important role in head and neck cancer management, including in the definitive nonsurgical setting, in postoperative patients with high-risk features and in recurrent setting. Because head and neck cancer can be very aggressive with a high tendency to recur locally, it is important to adequately irradiate all local-regional cancer cells (both gross disease and microscopic disease) to doses sufficient for tumor control. At the same time, many of the normal tissues in the head and neck area are very sensitive to radiation; such anatomic structures as the salivary glands, larynx, and constrictor muscles can be particularly damaged by treatment resulting in long-term sequelae.

The radiation oncologist was placed in the difficult situation of attempting to provide high doses of radiation to tumor and target volumes and minimal doses of radiation to normal structures. New technologies along with increased clinical familiarity and experience with these technologies have allowed the practice of radiotherapy to increase the distance between tumor dose and normal tissue dose, which in turn improves the ratio of cancer cure to treatment morbidity. The evolution in radiation therapy techniques over the last 30 years began from 2 dimensional (2D) radiation therapy using coplanar beams, usually in single or opposing pairs: e.g., right and left lateral or anterior field in head-and-neck cancer (Figure 1).

During the late 1980s, advancements in imaging and computer technology introduced the new methods to identify the targets on CT scans and display the radiation beams in three dimensions relative to the anatomy. In addition, radiation therapy by modern computer planning and multileaf collimators became available. The result was the introduction of Three Dimensional Conformal Radiotherapy (3D-CRT), which allowed better precision of irradiation delivery to image-based targets and some improvements in the sparing of noninvolved critical tissue. Another step forward was the development of Intensity Modulated Radiation Therapy (IMRT), which facilitated a higher degree of dose conformality and offered opportunities for additional clinical gains. More recently, Imaging-Guided Radiotherapy (IGRT) has emerged, making the better precision of patient setup with the ability for tracking of tumor regression and anatomical changes in the surrounding tissue during the whole course of radiation therapy. The other different techniques have evolved in head and neck cancer treatment. Stereotactic irradiation, gamma knife unit or linear

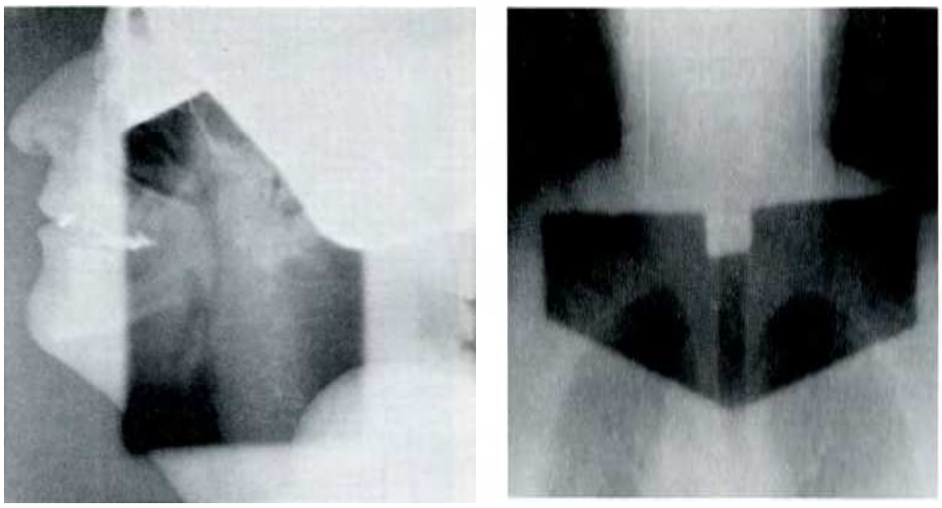


Fig. 1. Example of radiotherapy field using conventional – 2D radiation therapy, usually in single or opposing pairs: e.g., right and left lateral or anterior field in head-and-neck cancer

accelerator (LINAC)-based, is one method used in radiation therapy treatment. The radiation delivered has a sharp dose fall-off between the target and the surrounding normal tissue, thus allowing very precise delivery of radiation beam to the tumor while sparing and minimizing the radiation dose delivered to the surrounding organs. Lastly, other technical approaches such as proton beam radiotherapy or the CyberKnife are also used in this setting.

2. Intensity Modulated Radiation Therapy (IMRT)

IMRT is a form of 3D-CRT that implies the use of multiple radiation fields whose intensity varies across the field, depending on the thickness of the target and the existence of critical organs or critical noninvolved tissue. IMRT allows a relatively uniform dose in an irregularly shaped target while avoiding a high dose to the surrounding structures. The major differences between IMRT and more traditional radiotherapy techniques are the introduction of computer-controlled multileaf collimators, and the computer planning software (inverse planning) that allow for the intensity modulation of the various radiotherapy beamlets. Due to the relative ease of implementation of this technology (eg, compared with proton beam irradiation) and the obvious theoretic benefits, IMRT has quickly become standard for many cancers, including head and neck.

2.1 Imaging for treatment planning

Most of the case, the simulation contrast-enhanced CT is the only imaging modality required for the delineation of the targets. Magnetic resonance imaging (MRI) is a necessary adjunct to CT because it provides better detail of tumor extension and surround normal organ such as the tumors located close to the base of skull and the parapharyngeal and retropharyngeal spaces (Som,1997; Schechter et al., 2001) (Figure 2) Another potential imaging modality for this purpose is fluorodeoxyglucose-positron emission tomography (FDG-PET). However, in a series of HNCs in which CT, MRI, and FDG-PET were obtained, and surgery was then performed to validate the primary tumor extent and lymph node

involvement, a rather limited benefit of FDG-PET over CT and MRI was found. (Schechter et al., 2001). PET-derived gross tumor volumes were smaller than those derived from CT and MRI, and surgical specimens were even smaller. However, when examined in detail, despite overestimation in most dimensions, all three imaging modalities actually underestimated the mucosal extent of disease (Schechter et al., 2001). Therefore, physical examination and laryngoscopy findings should be part of the definition in addition to image modalities such as CT and PET.

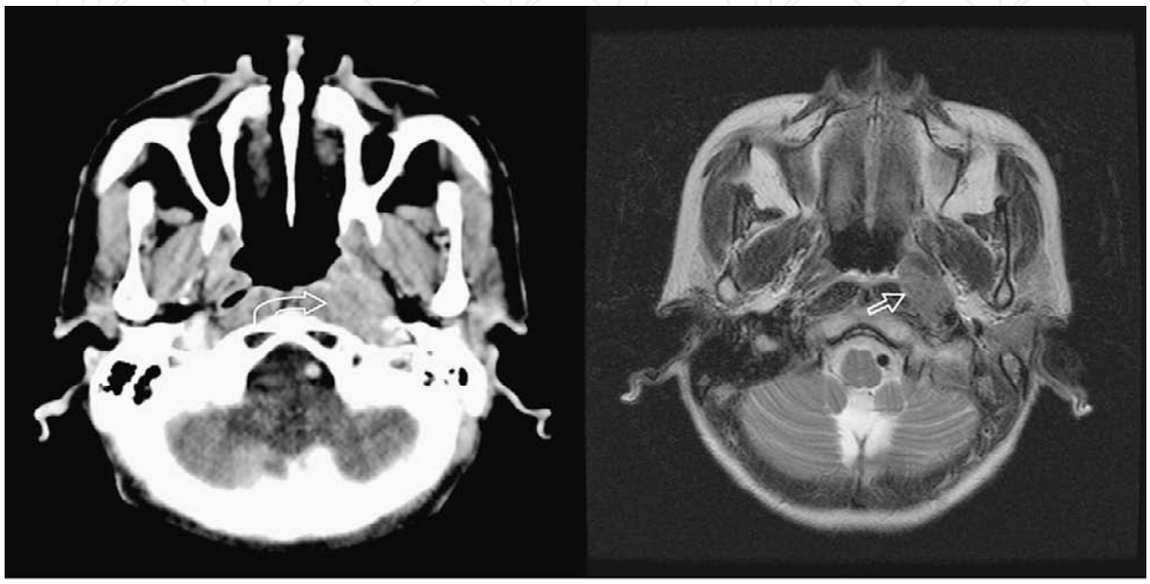


Fig. 2. CT (left) and MRI (right) scan of nasopharyngeal cancer . MRI provides information in prevertebral muscle invasion better than CT scan (arrow)

2.2 Delineating tumor and target volume

ICRU 50 defines five volumes of interest related to treatment. The following definition are illustrated in Figure 3.

2.2.1 Gross tumor volume (GTV): The GTV is the volume that contains the gross palpable or visible extent and location of malignant growth. The GTV may be identified on physical examination, a radiograph, or sectional images.

2.2.2 Clinical target volume (CTV): The CTV is the volume that contains the GTV and any suspected microscopic disease. The CTV is the volume that must receive the prescribed dose to effect cure or palliation.

2.2.3 Planning Target Volume (PTV): The PTV is a volume that contains the GTV and CTV and that is defined to account for the irradiation geometry and all uncertainties in treatment, such as organ and patient motions and set-up errors. The PTV is a volume that, when covered by the prescription dose, will ensure the delivery of the prescription dose to the CTV. The PTV includes a margin for motion and set-up error but not for microscopic disease. The PTV is a function of treatment geometry, because the number of beams and their orientations may impose limitations on the PTV's shape or scope.

2.2.4 Treated volume (TV): The TV is the volume enclosed by a selected (prescribed) isodose surface and is a function of the treatment geometry required for planning the PTV. For an acceptable plan, the TV is greater than the PTV, although an ideal TV/PTV ratio would be 1.0, indicating perfect conformation (assuming the locations of the volumes were identical).

2.2.5 Irradiated volume (IV): The IV is a volume that receives a significant dose; significance is determined by morbidity or other measures.

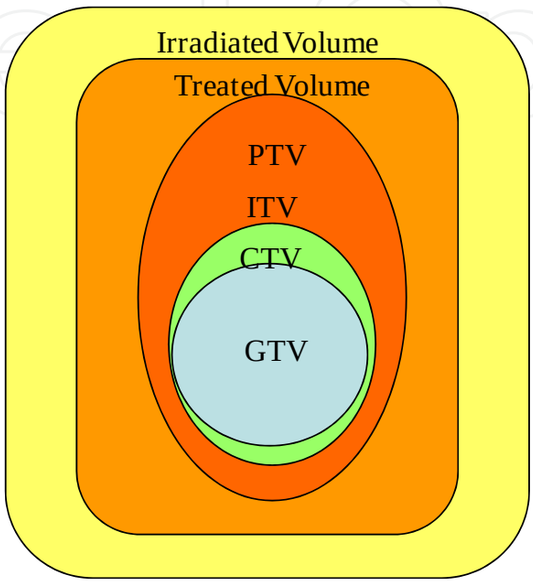
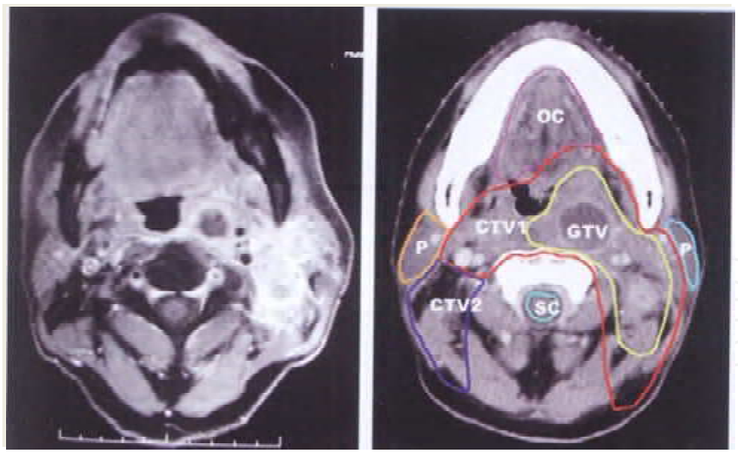


Fig. 3. The Internatinal Commission on Radiation Units and Measurement Report 50 (ICRU 50) defines five volmes of interest related to treatment.

In the routine practice, once the GTVs and CTVs are outlined on the axial CT scans, a expansion of CTV is performed to obtain the PTVs that accommodate setup uncertainties. Typically the magnitude of the margin is 3 to 5 mm, which means that an extra 5-mm ring of normal tissue around the target receives full dose. In a region with critical targets and organs at risk is close to the tumor, reducing this margin can potentially reduce treatment-related toxicity. An example of the delineation of the targets and noninvolved structures in a case of nasopharyngeal cancer is provided in Figure 4.

2.3 Dose prescription

The delivery of a single IMRT plan throughout the course of treatment provides better dose conformality than the use of several consecutive plans common in conventional radiotherapy, which consist of initial fields encompassing all targets followed with a boost to the gross tumor. Generally, when a single plan is prescribed, the PTV of gross tumor receives both a higher dose per fraction and total dose than the PTVs of the subclinical disease. Therefore, with a standard IMRT plan, the GTV would receive 70 Gy over 35 fractions , and the PTV of subclinical disease would receive lower fraction doses, usually 63 Gy to the high-risk and 56 to 59Gy to lesser-risk elective targets, over 35 fractions (1.8 Gy and 1.6-1.7 Gy) . Figure 5 shows isodose distribution in oropharygeal cancer compared between 3D-CRT and IMRT technique.



P represents the parotid gland; *red* represents CTV1 (high risk area) ; *purple* represent CTV 2 (low risk area) ; *yellow* represents GTV.

Fig. 4. Delineation of the targets and noninvolved structures in a case of nasopharyngeal cancer.

Radiation Therapy Oncology Group protocol H-0022 specified the prescription dose as the dose that encompasses at least 95% of the PTV. No more than 20% of the PTV can receive more than 110%, and no more than 1% of the PTV can receive less than 93%, of the prescribed dose.

Dose constraints regarding critical organs are usually stated in terms of the maximal dose. Commonly applied constraints in the head and neck are maximal doses of 45 Gy to the spinal cord, 54 Gy to the brainstem, 70Gy to the mandible, 50 to 55Gy to the optic pathway and maintain the mean dose to the contralateral parotids less than 26 Gy.

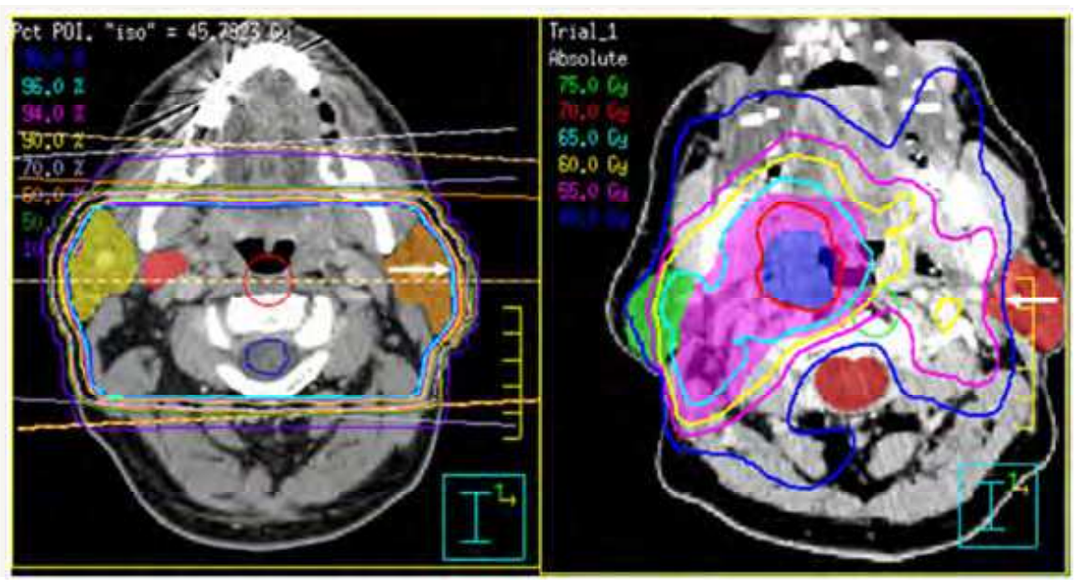


Fig. 5. Isodose distributions contrasting conventional (left) and IMRT (right) H&N treatment plans. Significant reduction of dose to the left parotid gland is achieved with the IMRT plan.

2.4 Clinical results in head and neck cancer treated with IMRT

In general the main intent in IMRT planning is preservation of function. One of the main issues is reducing xerostomia. Other potential functional gains from IMRT compared with conventional RT include reduced long-term dysphagia. Sparing of pharyngeal constrictors and the glottic and supraglottic larynx may be beneficial in this regard. (Eisbruch et al., 2004) . Most studies comparing IMRT with conventional treatments are retrospective and therefore have a potential selection bias. The only one randomized study from England (PARSPORT trial) (Christopher et al., 2011) was compared IMRT and conventional radiation in term of the incidence of xerostomia in head and neck cancer patient. At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT (29%) than with conventional radiotherapy (83%) (p<0.0001). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry- mouth-specific and global quality of life scores. Until now, it still has no standard criteria to select which patients were more suitable for IMRT treatment. Many different selection factors were used to each institute. Generally, in patients who have poor performance status, cannot tolerate lengthy treatment, to be too sick to benefit from complex therapy, requiring urgent start of therapy, more simple, conventional treatment may be selected. Therefore the comparison of IMRT with conventional RT in such situations would be very difficult. We summarized the clinical result of IMRT in head and neck cancer as describe below.

2.5.1 Nasopharynx

The use of IMRT for the nasopharynx represents opportunities to spare many critical noninvolved structures and to improve tumor coverage, as detailed previously. These improvements have been demonstrated in several treatment planning exercises in nasopharyngeal and oropharyngeal tumors, in which IMRT plans were compared with "standard 3D" plans in the same patients.(De et al., 1999; Yao et al.,2005). The available level I evidence (two randomized prospective trials) to document the efficacy of IMRT involves nasopharyngeal cancer (NPC). Similar in design, each trial randomized patients between conventional radiation and IMRT along with concurrent chemotherapy(Pow et al., 2006; Kam et al., 2007). The results were that salivary gland (parotid) function was significantly and dramatically improved in both studies. Regarding to Pow and coworkers study (Pow et al., 2006), they found an improvement in stimulated saliva flow with IMRT and also found that patients treated with IMRT had an improvement in patient-reported quality of life scores. Similarly, Kam and coworkers (Kam et al., 2007) found a reduction in observer-rated xerostomia from 82.1% with conventional radiotherapy to 39.3% with IMRT along with improvements in measured parotid flow rates. The primary end point for both studies was parotid function; neither trial was powered or intended to examine the role of IMRT in disease control or overall survival. Although there is no level I evidence proving that IMRT is equal to or superior to conventional radiation therapy in terms of disease control, several large retrospective series have been reported. A large clinical series of IMRT of nasopharyngeal cancer has been reported by investigators at the University of California in San Francisco (Sultanem et al., 2000). They reported in 67 patients treated in the years 1995 to 2000. This regimen yielded excellent locoregional tumor control: The rate was 97% at median follow-up of 31 months, with reasonable rates of acute toxicity. Another large

clinical series from the memorial Sloan-Kettering (Wolden et al., 2006) reported on 74 patients with newly diagnosed, nonmetastatic nasopharyngeal cancer were treated with IMRT. Most of the patients received concurrent and adjuvant platinum-based chemotherapy. At the median follow-up of 35 months, the 3-year actuarial rate of local control is 91%, and regional control is 93%; freedom from distant metastases, progression-free survival, and overall survival at 3 years are 78%, 67%, and 83%, respectively. There was 100% local control for Stage T1/T2 disease, compared to 83% for T3/T4 disease (p = 0.01). There is a trend for improved local control with IMRT when compared to local control of 79% for 35 patients treated before 1998 with three-dimensional planning and chemotherapy (P= 0.11). Rates of severe (Grade 3-4) ototoxicity and xerostomia are low with IMRT as a result of normal-tissue protection.

2.5.2 Paranasal sinuses

The proximity of the optic apparatus is the main obstacle to adequate irradiation of tumors in the locally advanced paranasal sinuses. In these cases, IMRT can provide adequate target coverage while sparing the optic pathways. The clinical series of IMRT in paranasal sinus cancer has been reported from the UCSF (Daly et al., 2007). In this study, 36 patients with malignancies of the sinonasal region were treated with IMRT. The 2-year and 5-year estimates of local control were 62% and 58%, respectively. One patient developed isolated distant metastasis, and none developed isolated regional failure. The 5-year rates of disease-free and overall survival were 55% and 45%, respectively. The incidence of ocular toxicity was minimal with no patients reporting decreased vision. The another study from University Hospitals Leuven in Belgium (Dirix et al., 2010) was compared the results of IMRT and convention radiotherapy for paranasal sinus cancer. From this study, 40 patients with cancer of the paranasal sinuses (n = 34) or nasal cavity (n = 6) received postoperative IMRT to a dose of 60 Gy or 66 Gy. Treatment outcome and toxicity were retrospectively compared with that of a previous patient group (n = 41) who were also postoperatively treated to the same doses but with three-dimensional conformal radiotherapy. Two-year local control, overall survival, and disease-free survival were 76%, 89%, and 72%, respectively. Compared to the three-dimensional conformal radiotherapy treatment, IMRT resulted in significantly improved disease-free survival (60% vs. 72%; p = 0.02). The use of IMRT significantly reduced the incidence of acute as well as late side effects, especially regarding skin toxicity, mucositis, xerostomia, and dry-eye syndrome. The largest clinical series of IMRT for paranasal sinuses was reported from Ghent University Hospital in Belgium (Madani et al., 2008). In this study, 84 patients with sinonasal tumors were treated with IMRT. The median follow-up of living patients was 40 months. The 5-year local control, overall survival, disease-specific survival, disease-free survival, and freedom from distant metastasis rate was 70.7%, 58.5%, 67%, 59.3%, and 82.2%, respectively. No difference was found in local control and survival between patients with primary or recurrent tumors. On multivariate analysis, invasion of the cribriform plate was significantly associated with lower local control (p = 0.0001) and overall survival (p = 0.0001). One patient developed Grade 3 radiation-induced retinopathy and neovascular glaucoma. Nonocular late radiation-induced toxicity comprised complete lacrimal duct stenosis in 1 patient and brain necrosis in 3 patients. Osteoradionecrosis of the maxilla and brain necrosis were detected in 1 of the 5 reirradiated patients.

2.5.3 Oropharynx

In general, all series investigating IMRT for oropharyngeal cancer have reported outstanding locoregional control rates. (Clavel et al., 2011; Setton et all, 2010; Lok et al., 2011). These series reported 2-year locoregional tumor control rates of 90% to 98% for patient populations who mainly had stage III or IV tumors. Clavel et al ((Clavel et al., 2011) was compared the toxicity and efficacy of IMRT vs. conventional radiotherapy (CRT) in patients treated with concomitant carboplatin and 5-fluorouracil for locally advanced oropharyngeal cancer. From this study, 249 patients were treated with definitive chemoradiation. One hundred patients had 70 Gy in 33 fractions using IMRT, and 149 received CRT at 70 Gy in 35 fractions. Median follow-up was 42 months. Three-year actuarial rates for locoregional control, disease-free survival, and overall survival were 95.1% vs. 84.4% ($P = 0.005$), 85.3% vs. 69.3% ($p = 0.001$), and 92.1% vs. 75.2% ($p < 0.001$) for IMRT and CRT, respectively. IMRT was associated with less acute dermatitis and less xerostomia. This study suggests that IMRT is associated with favorable locoregional control and survival rates with less xerostomia and acute dermatitis than CRT when both are given concurrently with chemotherapy. The largest series of OPC treated with IMRT was reported from the Memorial Sloan-Kettering Cancer (Setton et al., 2010). In this study, 442 patients with histologically confirmed OPC underwent IMRT. Most of the patients (91%) received chemotherapy. Median follow-up was 36.8 months. The 3-year cumulative incidence of local failure, regional failure, and distant metastasis was 5.4%, 5.6%, and 12.5%, respectively. The 3-year OS rate was 84.9%. The incidence of late dysphagia and late xerostomia ≥Grade 2 was 11% and 29%, respectively. The further study from MSKCC was reported (Lok et al., 2011). In this update study, the 2-year cumulative incidence of LF, RF and DF was 6.1%, 5.2%, and 12.2%, respectively. The 2-year OS rate was 88.6%. In their cohort study, Gross tumor volume was found to be associated with overall survival, local failure, and distant metastatic failure.

2.5.4 Larynx and hypopharynx

IMRT can improve target dose homogeneity for laryngeal and hypopharyngeal SCC while reducing the dose to the normal tissues at risk (Daly et al., 2011; Studer et al., 2010; Huang et al., 2010). Clinical data on IMRT for laryngeal and hypopharyngeal SCC are scarce, however, and include limited numbers of patients within large heterogeneous series of multiple HN tumor sites (Sultanem et al., 2000; Huang et al., 2010). In general, Hypopharyngeal tumors, which fare worse than laryngeal tumors, warrant investigation of more aggressive treatment. For example, at Stanford university (Daly et al., 2011), 42 patients with squamous cell carcinoma of the hypopharynx (n = 23) and larynx (n = 19) underwent IMRT .Three local failures occurred within the high-dose region and 3 occurred in regional nodes. Seven patients developed distant metastasis as the initial failure. Three-year actuarial estimates of locoregional control, freedom from distant metastasis, and overall survival rates were, respectively, 80%, 72%, and 46%.The largest series was reported from Studer et al (Studer et al., 2010). In this study, 65 hypopharyngeal, 31 supraglottic, and 27 locoregionally advanced glottic tumor patients underwent definitive IMRT (with simultaneous chemotherapy in 86%). The 2-year local, nodal, and locoregional control rates for the entire cohort were 82%, 90%, and 77%, respectively; the disease-free and overall survival rates were 75% and 83%, respectively. The ultimate 2-year LRC rate, including salvage surgery, was 86%.

Although the benefits of IMRT warrant its widespread use, there are some disadvantages to this technology such as the planning process and treatment delivery for IMRT is much more consume a higher time and cost than traditional radiotherapy planning. This prolonged treatment planning time can occasionally delay treatment initiation, which has been shown to be detrimental in the setting of head and neck cancer. (Ang et al., 2001). In addition to IMRT is a relatively new technology, the physician or dosimetrist might need very high conformal dose distribution and spare normal tissue as much as possible. But too tight of dose constraint on normal organs can result in inadequate treatment of the cancer. A recent report (Cannon & Lee, 2008) describes three cases in which patients had a recurrence near the parotid gland, which was spared using IMRT technology. It is possible that these recurrences may have been avoided with conventional radiotherapy that did not attempt to reduce the radiation dose to the parotid glands. Finally, some of the long-term effects of IMRT are unknown. The increased of number of beam and radiation output from IMRT results in an increased the other normal structure and total body dose of irradiation to the patient. Some studies (Rosenthal et al., 2008; Lee et al., 2002) describe the increased dose to several normal structures, such as brainstem, cochlea, scalp, mucous membrane and skin. For increasing in total body radiation dose, this is unavoidable because of radiation that leaks out from the linear accelerator head during long treatment times. In addition to this increased scatter radiation, IMRT exposes a larger volume of normal tissue to low-dose radiation in an effort to avoid high doses of radiation to one or more critical structures. The combined effects of increased scatter and low-dose radiation have a theoretic risk of increased secondary malignancies.

3. Image-Guided Radiotherapy

Image-guided radiotherapy (IGRT) is a broad term of radiation therapy technique that is incorporation of multidimensional imaging modalities into the planning and implementation of radiotherapy. The aim of IGRT was for minimizing setup uncertainties, enable to reduce the PTV margins, and assessing anatomic changes in tumor and critical tissue during the whole course of therapy. Imaging has always been used in the design of radiotherapy fields, previously in the form of fluoroscopy, two-dimensional planning films, and more recently the routine use of CT simulation. With the much improvements in diagnostic radiology, three-dimensional imaging, such as positron emission tomography (PET) and MRI, are now readily available as is the ability to obtain daily CT scans and four-dimensional imaging (with time as the fourth dimension) that allows even greater precision and accuracy for radiotherapy treatments. IGRT can be divided into three separate areas. The first is the use of IGRT in treatment planning including the integration of diagnostic radiology information into treatment field design before the patient starts treatment. Second is the use of various technologies (eg, Linac-mounted cone-beam CT [CBCT] scan devices) for improved treatment precision and correction of daily set-up variables. The third form of IGRT combines the first two and uses available technology to replan and adjust the radiotherapy throughout the course of treatment (adaptive radiotherapy).

3.1 Use of diagnostic radiology

One form of IGRT is in using diagnostic technology to better define treatment volumes. 18-Flurodeoxyglucose (FDG) PET scans, especially with incorporation of a diagnostic CT scan

(PET-CT scans) and Magnetic Resonance Imaging (MRI) are increasingly used in radiotherapy planning. FDG-PET scans use a radioactive glucose that is specific uptake at a higher rate by tumor and involved lymph nodes than by normal tissues. The difference in uptake rate between tumor cell and normal tissue allow the clinician easily define which is tumor or normal structures. PET scans can also help discover tumors areas that appear normal on CT scan but have significantly increased metabolic activity (and likely contain malignancy) as shown in Figure 6. Clinical experience is growing regarding the ability of PET scans better to define gross disease and nodal volumes.(Heron et al., 2004; Scarfone et al., 2004; Nishioka et al., 2002; Koshy et al., 2005; Wang et al., 2006; Vernon et al., 2006). For example, Heron and coworkers (Heron et al., 2004) reported on the use of integrated PET-CT radiotherapy planning versus conventional CT planning and found that the CT-based planning overestimated the tumor volume by 150% compared with PET-CT–based planning.

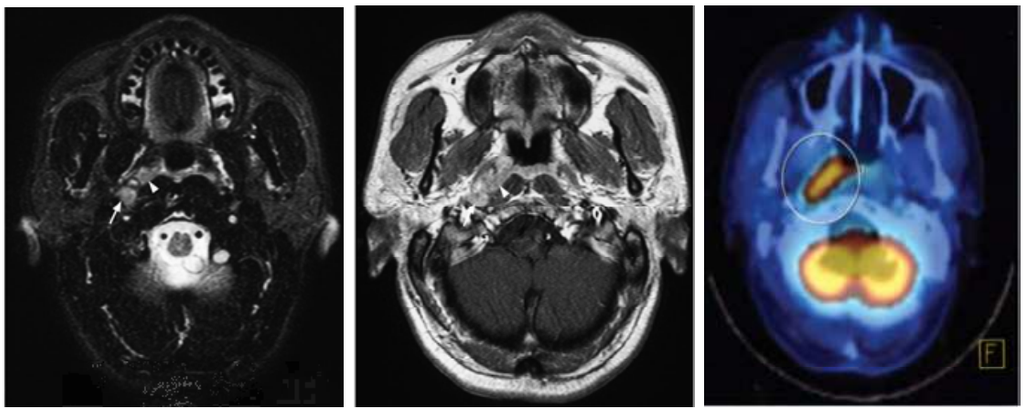


Fig. 6. CT scan (left, middle) and PET scans (right). PET scans can discover tumors areas that appear normal on CT scan but have significantly increased metabolic activity

3.2 Technologies for improved treatment precision and correction of daily set-up variables

Several target localization technologies can be used for monitor the patient's position during treatment delivery. For example, surface markers and optimal tracking, megavoltage Electronic Portal Imaging (EPIDs), implanted radioplaque markers, kilovoltage imaging, ultrasound and in-room CT systems. There is an emerging shift from localization inferred from surface marks or radiographs, to the more direct use of implantable markers and soft tissue localized via volumetric imaging in the treatment room. The classic method for patient set-up is to immobilize the patient using a face mask. Markings are made on this mask and before the daily radiotherapy treatments; radiation therapy technologists use the mask marks to position the patient. The positioning is typically confirmed by taking a two-dimensional radiograph (portal film) before the first radiation treatment and then periodically (different institutions have different policies on how often these verification films are taken; once per week is a commonly accepted standard). If the verification films show an obvious displacement, the patient is repositioned before treatment. These two-dimensional verification films are capable of detecting most large errors (>5–10 mm), but have limitations because they only use two dimensions and can lead to missing potential

set-up inaccuracy. They are also highly dependent on bony rather than soft tissue and tumor geometry. The method to reduce daily set-up error that may not be noticed on traditional two-dimensional verification films is the use of CT imaging in the treatment room. The common system is cone beam CT (CBCT) (Figure 7). A CBCT scan is essentially a CT scanner built into the linear accelerator. The CBCT is used to obtain a CT scan of the patient in the anatomic area of interest (eg, the head and neck region) after the patient has been positioned on the treatment table. After the CBCT has been taken, a computer algorithm aligns the CBCT to the initial planning CT scan and adjustments, if required, can be made before the start of treatment. Several authors have reported on the use of CBCT in head and neck radiotherapy (Hong et al., 2005; Li et al., 2008). Hong and coworkers (Hong et al., 2005) analyzed the magnitude of difference between two- and three-dimensional patient set-ups, finding that substantial set-up errors could be discovered when all six degrees of freedom were registered. This set-up error was then used to calculate dosimetric consequences of not correcting these errors, finding that the planning tumor volume could be underdosed by as much as 20% to 30%. Others (Sharpe et al., 2005; vakilha et al., 2007) have found reductions in the parotid and spinal cord dose with the use of daily imaging for position verification. CBCTs have the potential to increase set-up accuracy, and this could allow reduction in the tumor margins that would increase the distance from the high-dose radiation areas to the normal structures. Even small changes in margin can have significant effects on normal tissue doses and outcomes. The increasing of radiation dose to the patient associated with CBCT might be concern regarding to the complication especially in the risk of secondary malignancy. Most CBCT systems add the extra patient-received radiation dose about 3 cGy (Islam et al., 2006; Sykes et al., 2005), whereas the typical daily radiation treatment dose is 180 to 200 cGy. The daily CBCT represents 1% to 1.5% of the daily radiation dose. It should be mentioned, however, that unlike the daily radiation dose, the dose from the CBCT involves significantly more normal tissue and has higher skin dose.

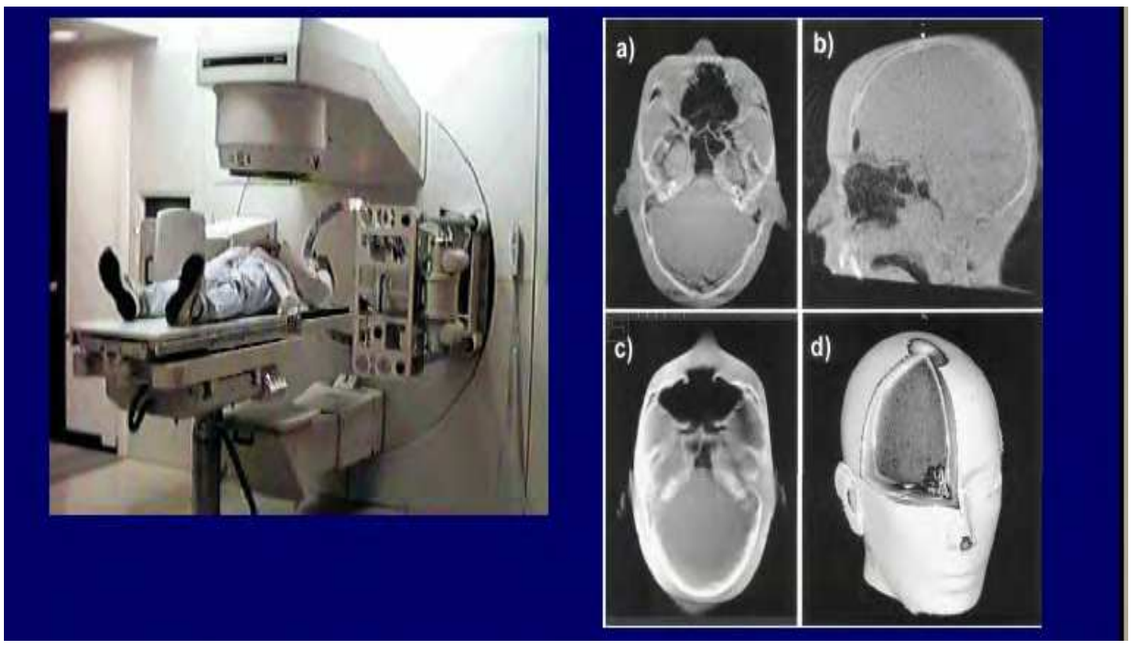


Fig. 7. Cone beam imaging at Linac unit can provide daily set up

3.3 Technology to replan and adjust the radiotherapy throughout the course of treatment (adaptive radiotherapy)

With advancement of IGRT and available volumetric information, it has become evident that a single pretreatment planning CT cannot represent the patient's anatomy for the entire treatment course, particularly for head and neck cancer patients. The patient anatomy changes from day to day (interfractional organ motion) and even during the dose delivery process (intrafractional organ motion) due to patient setup inaccuracy and voluntary or involuntary physiologic processes of the patient. For example, organ motion happens involuntarily for structures that are part of or adjacent to the digestive or urinary systems, Changes in the patient's condition, such as weight gain or loss and rapid changes in the tumor volumes due to the treatment response, can also affect the relative position of the clinical target volume. An alternative way that IGRT can be used is in replanning radiotherapy or adaptive radiotherapy. Repeating a CT-simulation scan at one or more time points during the course of therapy, a second treatment plan, using the patient's altered anatomy, can be used to increase the accuracy of the radiotherapy. Realization of the anatomic changes and subsequent radiotherapy replanning can result in improved dose to both tumor and normal structures. Several authors(Hansen et al., 2006; Dogan, 2007; Han et al., 2008) found that without replanning, tumor coverage and dosimetry decreases (despite the typical decrease in tumor volume size during therapy), whereas at the same time spinal cord dose is increased by up to 10%.

4. Proton therapy

Interest in the use of charged particle radiation has been primarily stimulated by the superior dose distributions that can be achieved with these particles compared with those produced by standard photon. Charged particles deposit energy in tissue through multiple interaction of energy is also transferred to tissue through collisions with the nuclei of atoms the energy loss per unit path length is relatively small and constant until near the end of the range, where the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose. This portion of the particle track, where energy is rapidly lost over a short distance, is known as the Bragg peak (Figure 8). The proton dose distribution is still characterized by a lower dose region in normal tissue proximal to the tumor, a uniform high-dose region in the tumor, and zero dose beyond the tumor.

With the use of inverse planning, intensity-modulated proton therapy (IMPT) can further improve the therapeutic index of radiotherapy. Several groups have published treatment planning comparisons of (photon) IMRT with IMPT. Using IMPT, mean doses to the organs at risk such as parotid glands, mandible, larynx, spinal cord and brain stem have been reduced by as much as 50%. The earliest published from Simon and colleage (Simon et al., 2011) showed significantly lowered the maximum doses to the spinal cored, brainstem and mean doses to the larynx and parotid glands of IMPT compared to IMRT and adaptive IMRT. A systematic review in the benefit of PT in head and neck cancer with respect to normal tissue sparing was reported (Water et al., 2011). There were 14 studies were identified and included in this review. Four studies included paranasal sinus cancer cases, three included nasopharyngeal cancer cases, and seven included oropharyngeal, hypopharyngeal, and/or laryngeal cancer cases. Seven studies compared the most sophisticated photon and proton techniques: intensity-modulated photon therapy versus

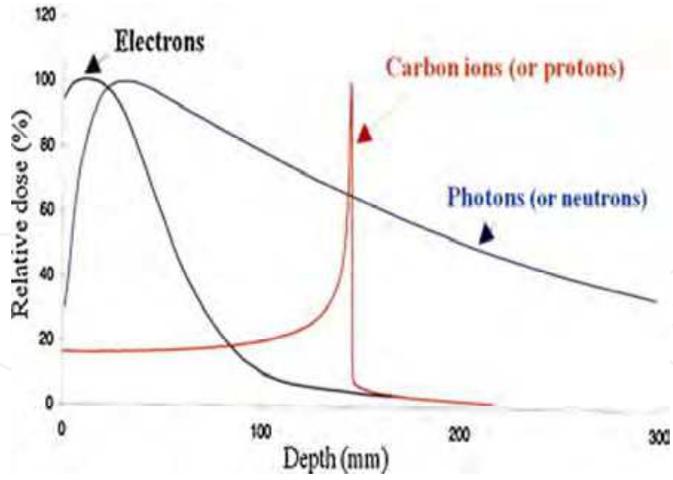


Fig. 8. Bragg peak in proton therapy radiation: comparison of deep dose distribution with other types of radiation treatment

intensity-modulated proton therapy (IMPT). Four studies compared different proton techniques. All studies showed that protons had a lower normal tissue dose, while keeping similar or better target coverage. Two studies found that these lower doses theoretically translated into a significantly lower incidence of salivary dysfunction. This result concluded that that PT have the potential for a significantly lower normal tissue dose, while keeping similar or better target coverage. IMPT probably offers the most advantage and will allow for a substantially lower probability of radiation-induced side effects. The areas in the head and neck such as paranasal sinus and nasopharynx that close to optic apparatus and brain and some radioresistant tumors such as uveal melanoma, chordoma, and chondrosarcoma could have clinical gain from proton therapy. However, the use of proton therapy in head and neck cancers requires special considerations in the simulation and treatment planning process, and currently available PT technology may not permit realization of the maximum potential benefits of proton therapy. Figure 9 shows a comparison of IMRT plan and a Proton therapy.

4.1 Clinical experience of proton therapy for head and neck cancers

Proton therapy in head and neck cancer is relatively new, so there still have few clinical data of proton therapy in head and neck cancer. The previous reports usually are small sample size and do not provide enough information to support the actual benefits in the therapeutic ratio from proton therapy compared with photon based radiation.

4.1.1 Nasopharyngeal carcinoma

The report from Massachusetts General Hospital on 17 patients treated with a combination of protons and photon untreated T4N0-N3 nasopharyngeal carcinoma and followed for a median of 43 months(Chan & Liebach' 2008) The median dose to the gross target volume was 73.6 Gy. The three-year outcomes were as follows: local-regional control, 92%; relapse-free survival, 79%; and overall survival, 74%. Toxicity was not described, so it is difficult to assess the therapeutic ratio, but the high disease control rates are very promising.

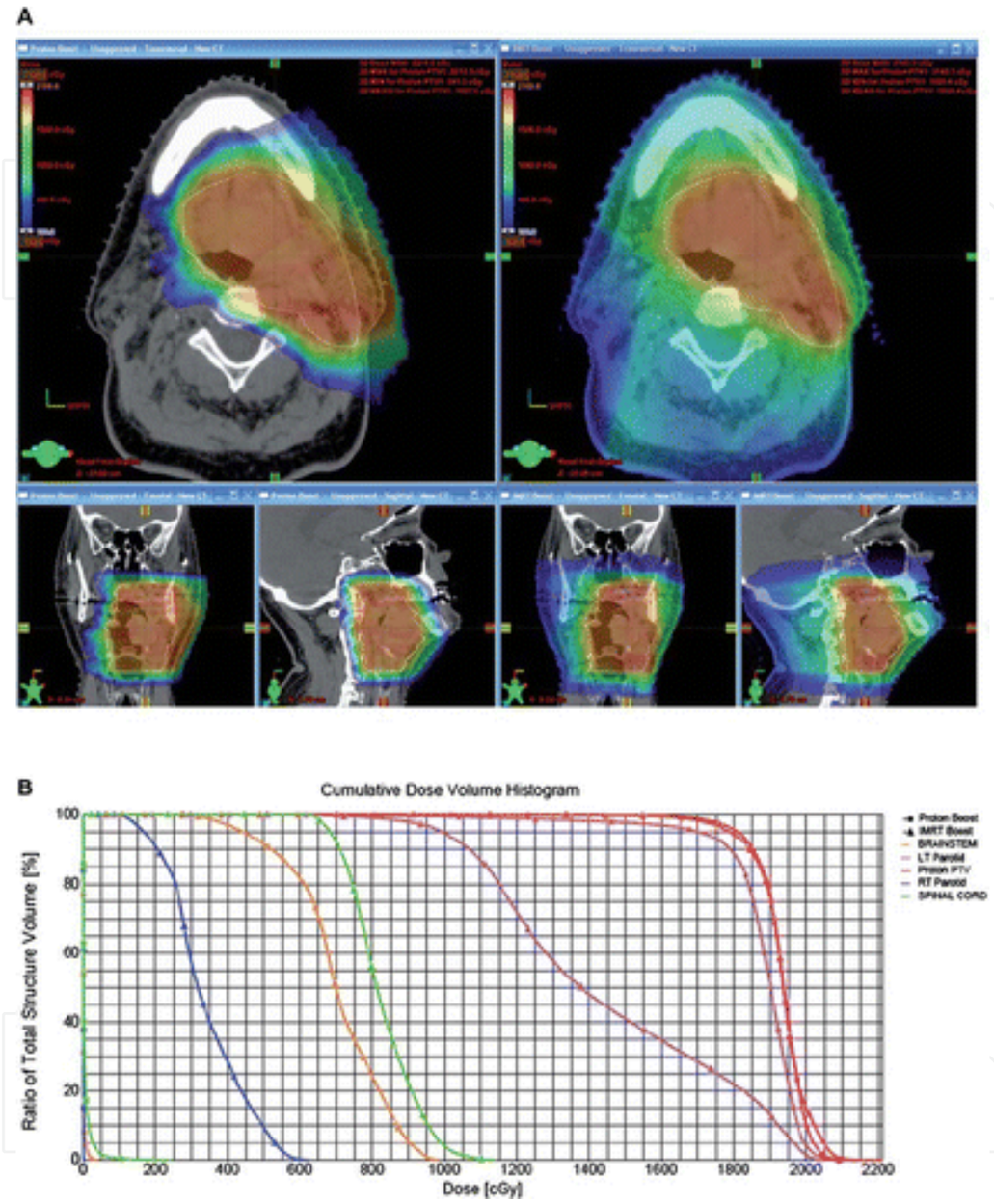


Fig. 9. (A) The dose distributions achieved with the PT plan (left) and the IMRT plan (right). There is greater integral dose with the IMRT plan. (B) The dose-volume histogram (DVH) comparison between the two plans; as apparent from the curves on the far right, the target coverage was the same for the two plans, but the PT plan delivered a significantly lower dose to the optic structures, including the chiasm, the lacrimal glands, the retina, and the optic nerves as well as the brainstem and parotids.

4.1.2 Oropharyngeal carcinoma

The reported from Loma Linda University Medical Center (Slater et al., 2005) on 29 patients with stage II-IV oropharyngeal cancer treated with a combination of protons and photons to 75.9 Gy/CGE in 45 fractions over 5.5 weeks. The 5-year actuarial locoregional control rate was 84%. The actuarial 2-year disease-free survival rate was 81%; at 5 years, it was 65%.Late Grade 3 toxicity was seen in 3 patients (10%).

4.1.3 Nasal cavity and paranasal sinuses

Chan and Liebsch reported on 102 patients with paranasal sinus cancers treated between 1991 and 2002 with PT to a median dose of 71.6 Gy at the Massachusetts General Hospital and followed for a median of 6.6 years (Chan & Liebach, 2008). Only 20% of patients had a complete resection prior to RT. The five-year local control rate was 86%; no toxicity information was offered in this report. Another study from MGH experience reported on 36 patients treated with proton/photon accelerated fractionated RT for paranasal sinus cancers to a median dose of 69.6 Gy (Weber et al., 2006), the median follow-up was 52 months. Thirteen patients developed late visual toxicity including cataracts in three patients.Late Effect Normal Tissue complication (LENT) grade I vascular retinopathy in one patient, LENT grade 1 optic neuropathy in one patient, lacrimal duct stenosis in three patients and dry-eye syndrome in five patients. No patients were reported to have lost vision. These excellent outcomes suggest the possibility of achieving both high rates of tumor control and low rates of severe toxicity with PT in sinonasal tumors.

4.1.4 Adenoid cystic carcinoma

The report from Massachusetts General Hospital (Pommier et al., 2006) on 23 patients treated for adenoid cystic cancer with skull base extension with photon/proton RT. The median follow-up was 64 months. Twenty patients (87%) had gross disease at the time of RT. The local control rate at 5 years was 93%. The rate of freedom from distant metastasis at 5 years was 62%. The disease-free and overall survival rates at 5 years were 56% and 77%, respectively. In multivariate analysis, significant adverse factors predictive for overall survival were change in vision at presentation (p= .02) and involvement of sphenoid sinus and clivus (p = .01).One patient developed grade 4 retinopathy. Three patients developed grade 3 complications requiring surgery including dacrocystorhinostomy in one patient, surgery for ectropion in one patient, and lens replacement for a cataract in one patient. These results suggest the possibility of both high rates of disease control and low rates of severe toxicity with PT alone in adenoid cystic cancer.

5. Stereotactic radiation: LINAC-based and gamma knife

Stereotactic Radiosurgery and radiotherapy are techniques to administer precisely directed, high-dose irradiation that tightly conforms to target to create a desired radiobiological response while minimizing radiation dose to surrounding normal tissue. In the case of radiosurgery (SRS), all of the radiation is done in a single session or fraction, while in stereotactic radiotherapy (SRT), more than one fraction of irradiation is administered. Stereotactic technique combines stereotactic localization with multiple cross-fired beams from a highly collimated high-energy radiation source.

5.1 Radiosurgery devices

Radiosurgery can be performed using various devices, including the GammaKnife, modified linear accelerators (Linacs) or particle beam devices.

5.1.1 Gamma knife radiosurgery

The source of GammaKnife come from Cobalt-60, this radioisotope decay and give high energy gamma ray for radiation treatment. The first prototype unit of Gamma Knife was created by Leksell and Larson in 1967. It uses a relatively hemispherical array of multiple fixed cobalt-60 201 sources, that are create small, relatively spherical treatment volumes of varied diameter with sharp dose falloff (Figure 10).

Fig. 10. GammaKnife unit and helmet for cobalt-60 201 sources

5.1.2 Linear accelerator based stereotactic radiotherapy (X-knife)

Linear accelerators (Linacs) (Figure 11)can be used for radiosurgery. Most early Linac-based radiosurgery techniques used multiple radiation arcs with circular collimators to create spherical dose distributions for three dimensional targets. Improved hardware and advanced planning software have been developed to enhance conformity. These include beam shaping with micromultileaf collimators, intensity modulation with inverse treatment planning algorithms.

5.1.3 Particle beam radiosurgery

The advantage of proton radiosurgery is that the beams stop at a depth related to the beam's energy (Bragg peak). The lack of an exit dose and the sharp beam profile of protons allow target irradiation with lower integral doses than are delivered with photon irradiation.

5.2 Clinical experience for stereotactic radiosurgery in head and neck cancer

More recently, stereotactic radiosurgery ncers both in primary cases (Kawaguchi et al., 2009) and in recurrent cases(Pai et al., 2002; Low et al., 2006; Roh et al., 2009) The complete response rates for these studies vary from 8.6-54% with 2-year overall survival rates ranging from 14.3-41% and 1-year overall survival rates of 18-52.1%. As the ranges of these outcomes suggest, the heterogeneity between these various studies is large. Various factors, including tumor stage, tumor volume, adequate irradiation dose, prior treatment, and anatomical site

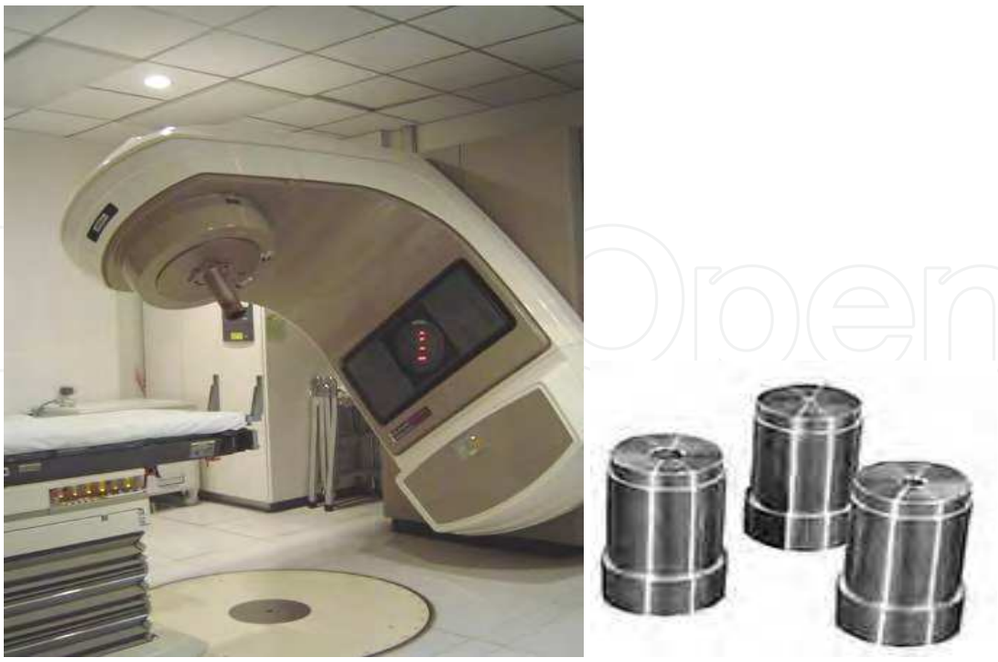


Fig. 11. Linac-based radiosurgery machine and circular collimators

complexly, influenced these reported outcomes. Kawaguchi et al (Kawaguchi et al., 2010) reported on 22 patients with advanced, recurrent head and neck carcinoma were treated with stereotactic radiosurgery with the marginal doses of 20-42 Gy delivered in two to five fractions. At an overall median follow-up of 24 months, for the 14 locally recurrent patients without lymph node metastases, 9 patients (64.3%) had a complete response (CR), 1 patient (7.1%) had a partial response (PR), 1 patient (7.1%) had stable disease (SD), and 3 patients (21.4%) had progressive disease (PD). For the 8 patients with lymph node metastases, 1 patient with a single retropharyngeal (12.5%) had CR; the remaining 7 patients (87.5%) all progressed. The overall actuarial 2-year survival for the patients with and without lymph node metastases is 12.5% and 78.6%, respectively.

6. Robotic radiosurgery (CyberKnife)

The CyberKnife (Accuray, Sunnyvale, CA, USA) is a frameless robotic radiosurgery system that has been utilized by numerous clinicians around the world to treat intracranial and extracranial tumors (Tate et al., 1999; Voynov et al., 2006; Le et al., 2003; Jansen et al., 2000). The CyberKnife system consists of a small and compact 6 MV Linac coupled to a multijointed robotic manipulator with 6 degree of freedom (Figure 12). The current generation of CyberKnife consists of two precisely calibrated diagnostic x-ray tubes fixed to the ceiling of the treatment room and two orthogonal flat-panel detector located under the floor. The CyberKnife depends on a co-registration of digitally reconstructed radiographs that are generated from CT images and x-ray projections that are captured during the treatment session. Changes in target position are relayed to the robotic arm, which adjusts pointing of the treatment beam. The robotic arm moves through a sequence of positions (nodes). At each node, a pair of images is obtained, the patient position is determined, and

adjustment are made. CyberKnife was based on tracking of the skeletal anatomy of the skull and spine. For treatment soft tissue lesion in the body such as lung, liver and prostate, implanted fiducial was need for target localization and respiratory tracking. The advantages of the CyberKnife include the ability to deliver radiation without a frame, the feature of increased fractionation flexibility, and the ability to treat extracranial lesions. Figure 13 shows isodose distribution in nasopharyngeal cancer treated with CyberKnife.

Fig. 12. CyberKnife Robotic Radiosurgery system

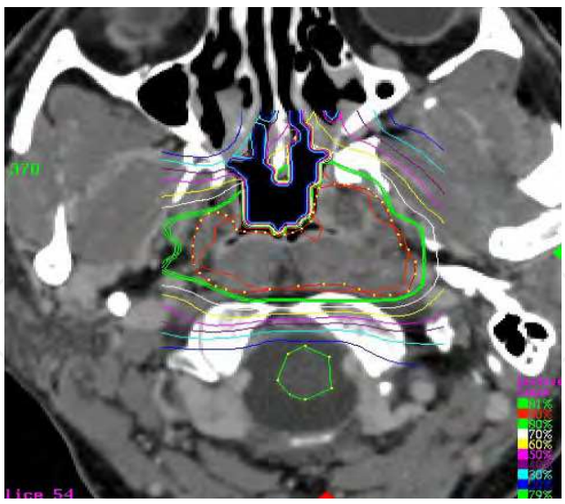


Fig. 13. Isodose distribution for nasopharygeal CA treated with CyberKnife.

6.1 Clinical experience of CyberKnife for head and neck cancer

The use of CyberKnife for head and neck cancer is relatively new. Cengiz and colleage (Cengiz et al., 2010) reported 46 recurrent, unresectable, and previously irradiated head-and-neck cancer patients treated with CyberKnife. The local disease control was achieved in

31 patients (83.8%). The median overall survival was 11.93 months and the median progression free survival was 10.5 months. One-year progression-free survival and overall survival were 41% and 46%, respectively. In this study, 8 (17.3%) patients had carotid blow-out syndrome, and 7 (15.2%) patients died of bleeding from carotid arteries. The author discovered that this fatal syndrome occurred only in patients with tumor surrounding carotid arteries and carotid arteries receiving all prescribed dose. Another report from Korea (Seo et al., 2009) shown 35 patients with locally recurrent NPC treated using CyberKnife. The overall survival (OS) rate, local failure-free survival (LFFS) rate, and disease progression-free survival (DPFS) rate at 5 years were 60%, 79%, and 74%, respectively. Twenty-three patients achieved complete response after CyberKnife. Only T stage at recurrence was an independent prognostic factor for OS and DPFS. Five patients exhibited severe late toxicity (Grade 4 or 5).

7. Conclusion

Modern in Radiation therapy has significant considerable promise to improve cancer treatment. The benefit of these technologies is able to deliver more radiation to the tumor and better spares normal tissue and critical structure. It is expected that these modern radiation therapy will yield improvements in all important outcomes including overall survival, disease free survival, local control and quality of life for patients. However, most modern technologies have not been proven to change patients' ultimate outcome. In addition, modern radiation therapy may be associated with significant increases in cost to the patients and the medical system. Therefore, continued careful studied and quantification of the effects of modern radiation therapy on treatment outcomes is needed so that definitive statements may be made about its necessity in everyday radiotherapy.

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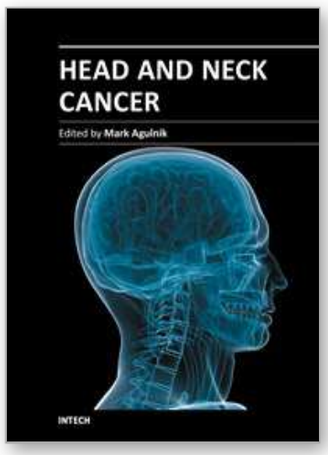

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Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

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