Chapter

# Treatment of Head and Neck Cancers Using Radiotherapy

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## Abstract

Radiotherapy is one of the major treatments for head and neck cancers. This chapter discusses the importance of radiotherapy in treating the common types of head and neck cancers, which can be used as a primary treatment or as a postoperative adjuvant treatment to increase the survival of head and neck cancer patients. Because head and neck cancers are likely to be closely surrounded by radiation-sensitive vital organs, the dosimetric superiority of intensity-modulated radiotherapy (IMRT) to achieve highly conformal dose to the planning target volume (PTV) and avoidance of organs at risk (OARs) helps maintain the cornerstone role of radiotherapy in treating the disease. The rationale of IMRT and the treatment planning technique are introduced. Treatment planning of radiotherapy is one of the key procedures in IMRT. The inverse planning process involves many decision-making steps, including PTV and OAR delineation, beam arrangement settings, objective function setting, etc. These important steps are all illustrated in the chapter, with a specific discussion of planning challenges relevant to head and neck cancers. Finally, the promises for further development of IMRT in terms of OARs dose sparing and PTV dose escalation are briefly discussed and reviewed.

**Keywords:** radiotherapy, treatment planning, head and neck cancers, IMRT, VMAT

## 1. Introduction

This chapter aims to provide background information about head and neck cancers, including their respective treatment options and radiotherapy techniques. It is divided into 4 parts. Part 1 summarizes the information about head and neck cancers and the use of radiotherapy for head and neck cancers. Part 2 introduces the intensity-modulated radiotherapy (IMRT) which is commonly used in the treatment of head and neck cancers. Part 3 reviews the planning techniques of IMRT. Finally, part 4 discusses the current challenges of head and neck cancers radiotherapy and the promises to overcome the challenges.

## 2. Head and neck cancers

### 2.1 Epidemiology statistics

Head and neck cancers refer to the carcinomas that originate from any parts of the upper aero-digestive tract. They also include the cancers of the thyroid and salivary glands. Although head and neck cancers no longer rank among the top 5 cancers in the latest report [1], they are still regarded as major types of cancer in Hong Kong [2]. One of the main reasons for this recognition is that nasopharyngeal cancer (NPC) is ranked sixth in terms of the number of new cases in the male population in Hong Kong [1]. The NPC worldwide figures illustrated by the age-standardized rate (ASR) was 1.2 per 100,000 [3], which were much lower than the incidence in Hong Kong which was 7.4 per 100,000 in the year 2012 [1]. The high incidence of NPC in Hong Kong is attributed to its special geographical epidemiology pattern that 76% of new cases were found in east and south-eastern parts of Asia, in which Hong Kong is situated [4]. Other head and neck cancers recorded in the Hong Kong Cancer Registry include cancers of the lip, oral cavity, pharynx, nasal cavity, middle ear and accessory sinuses, larynx, and thyroid gland. Altogether, there were 2617 new cases of head and neck cancers reported in 2016 in Hong Kong, which accounted for 8.3% of all cancer new cases [1]. NPC was the most common type of head and neck cancer, accounting for 46.6% of all new cases. It was followed by the cancer of the tongue and larynx which accounted for 13.9% and 11.4%, respectively [1]. Although there have been some variations in the trend of ASR between sub-sites, the overall ASR of head and neck cancers in Hong Kong has remained around 21 per 100,000 in the past decade. Because of the relatively high incidence of head and neck cancers, their treatment remains one of the major burdens in the health care services in Hong Kong [2].

### 2.2 The role of radiotherapy in major types of head and neck cancers

The role of radiotherapy in the radical treatment of five types of head and neck cancers including cancers of the nasopharynx, oral cavity, larynx, maxillary sinus, and parotid gland is discussed in this section. Intensity-modulated radiotherapy is a standard radiotherapy technique used. The benefit of IMRT is that it is capable of delivering highly conformal doses to the target while sparing the nearby organs at risk (OARs).

#### *2.2.1 Nasopharynx*

Radiotherapy is the major treatment modality for nasopharyngeal carcinoma (NPC). It is because the primary tumor site of NPC is difficult to be accessed by surgical intervention, and the tumor cells of NPC are sensitive to radiation [5]. The use of radiotherapy alone is effective to treat stage I to II NPC, while concurrent chemotherapy is added for higher stages disease to achieve better local-regional control and survival outcome [6]. IMRT is the preferred radiotherapy technique and the late side effect of xerostomia in patients receiving IMRT was significantly reduced [7]. The current standard of the prescribed total dose to the primary tumor is to give 70 Gy in 33–35 fractions [8]. With the use of simultaneous integrated boost, the prophylactic dose which is lower than the dose to the primary tumor is prescribed for the potential microscopic spread of the primary tumor and selected cervical lymph nodes

regions. The prophylactic prescription can be varied in different local practices, it was reported that the prescriptions for the intermediate and low-risk cervical lymph nodes were about 60 Gy and 50 Gy, respectively [8, 9].

### *2.2.2 Oral cavity*

The cancer of the oral cavity includes various sub-sites such as the anterior tongue, buccal mucosa, hard palate, soft palate, alveolus, and floor of the mouth. The primary treatment of the cancer of the oral cavity varied according to the stage, which can be briefly divided into early and advanced. For early-stage which refers to T1 and early T2 tumors, radiotherapy entirely or partly delivered by brachytherapy can result in similar local control as in surgery [10, 11]. However, a recent retrospective study reported that primary radiotherapy to early-stage oral cavity cancer patients resulted in higher mortality as compared with those who received primary surgery [12]. It has also been reported in the same article that the majority (more than 95%) of early-stage oral cavity cancer patients received primary surgery. The small proportion of patients receiving primary radiotherapy in this group of patients was attributed to the fact that brachytherapy services were not available due to lack of expertise and suitability of applicator for insertion [10]. Hence, most early-stage oral cavity cancer patients receive surgery for primary treatment, although radiotherapy is also an alternative. Postoperative radiotherapy is only indicated for positive or close margins after resection [13]. For advanced oral cavity cancer, surgery is often the standard primary treatment whenever resectable [14], and then followed by adjuvant radiotherapy or chemo-radiotherapy. For non-resectable advanced oral cavity cancer, radical radiotherapy is offered in conjunction with chemotherapy or targeted therapy to improve disease control [15]. The total prescribed dose is 70 Gy to the gross tumor or 66 Gy to the tumor bed after resection, delivered with 2 Gy per fraction. Similar to NPC, prophylactic irradiation to the cervical lymph nodes regions is also used, where 60 Gy and 54 Gy are prescribed to the intermediate-risk and low-risk regions, respectively [16].

### *2.2.3 Larynx*

A specific consideration when treating cancer of the larynx is preserving organs and function. Radiotherapy alone or concurrent chemoradiotherapy is the most widely applied approach in organ preservation therapy [17]. Radical surgery is the rival choice for the patients, the outcome would lead to sub-optimal quality of life because it would result in loss of voice, swallowing problem, and often a permanent tracheostomy. To achieve a better quality of life after treatment, organ preservation therapy using radiotherapy or chemoradiotherapy is recommended for early-stage disease and some advanced cases of T3 and T4 [17, 18]. The consideration of offering surgery instead of radical chemoradiotherapy for advanced cases includes patients' condition and the extent of the disease and should be assessed by an expert panel of clinicians from different disciplines [19, 20]. Even when surgery is chosen as the treatment option, radiotherapy still has the role in providing postoperative adjuvant treatment for high-grade tumors, positive margins, cervical lymph nodes involvement, and tumor invasion beyond the larynx [21]. The prescribed dose ranged from 66 Gy to 76 Gy to the primary tumor site and involved lymph node, and the prescription for the selective lymph node with suspected microscopic involvement is at least 50 Gy [22].

*2.2.4 Maxillary sinus*

Although the primary treatment of the cancer of the maxillary sinus is surgery, postoperative radiotherapy is indicated for stage 2 and stage 3 disease, and for stage 1 disease when the surgical margin is insufficient [20]. For locally advanced disease, induction chemotherapy and then concurrent chemoradiotherapy have been suggested for non-resectable patients [23]. The treatment outcome for these patients would be better if the tumor can be down-staged and subsequent resection is possible [23]. The concern of the radiotherapy to the maxillary sinus includes the preservation of the optic apparatus which are near to the tumor [20]. It has been reported that 37% of the patients who received conventional radiotherapy developed radiotherapy-induced blindness [24]. IMRT is the preferred technique. It has been reported that IMRT could significantly spare nearby organs than those in 3DCRT. The dose to the optic chiasm can be significantly reduced from over 60 Gy in 3DCRT to less than 40 Gy in IMRT [25], while the tumor coverage by the prescribed dose is increased from 83% in 3DCRT to 95% in IMRT. The prescribed dose to the primary tumor site ranged from 66 to 70 Gy.

*2.2.5 Parotid gland*

The primary treatment for the cancer of parotid gland is surgical resection. Radiotherapy is used for adjuvant postoperative treatment except in small and low histological risk tumor with clear surgical margins [26]. In addition, radiotherapy is also indicated as radical treatment in advanced parotid gland cancer cases when resection of the tumor is not possible [27]. The prescribed dose to the primary site is about 66 Gy. IMRT is advocated as the treatment technique to improve OARs sparing [28].

## 3. Intensity-modulated radiotherapy

As discussed, IMRT has commonly used for radiotherapy of head and neck cancers The concept of IMRT has been introduced as early as 30 years ago [29], when the method of optimizing the intensity distribution of the incident beams with the purpose to achieve the required dose distribution in the targets was described. The following points summarize the concept of the delivery of IMRT: (1) There are multiple radiation beams with specially decided nonuniform intensity in beamlets, also known as intensity modulation. (2) The multiple radiation beams are applied from different directions, and the region of the convergence of the beams can achieve the desired dose distribution based on the modulated beam intensity. (3) Calculation of the modulated beam intensity usually follows an inverse approach, in which the final dose distribution indicated by planners is used by the computer to calculate the intensity of each beamlets in the treatment field of the IMRT plan.

The delivery of intensity-modulated beams is largely contributed by the dynamic multi-leaf collimator (MLC). The MLC can change the field shape automatically and the summation of numerous sub-fields in different shapes then generate a field with intensity modulation. A simplified rationale of intensity modulation is illustrated in **Figure 1**. Assume there is no OAR surrounding the target, the intensity of the beam should be proportional to the target thickness from the perspective of each beam. Although beam modifying devices such as wedges and compensators have been used in 3DCRT, their flexibility of beam intensity modification is far less than that in the

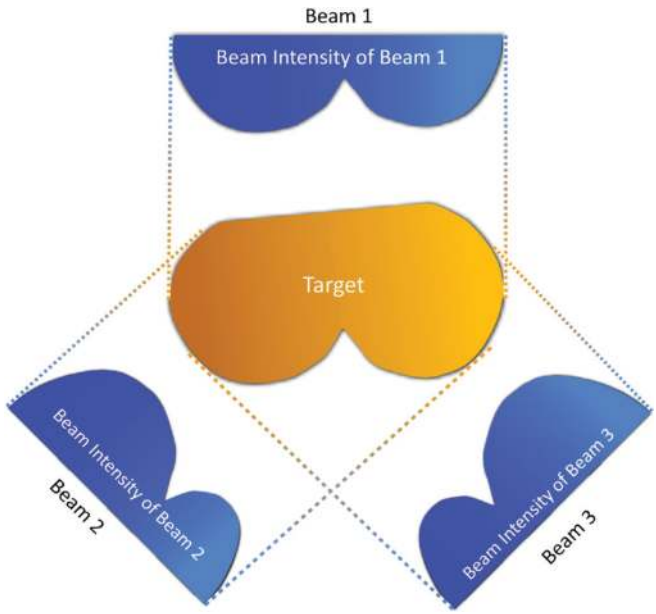


**Figure 1.**
*Illustration of the relationship of beam intensity and target thickness.*

IMRT. This is best illustrated by the fact that IMRT can produce concave shape isodose distribution which 3DCRT can hardly generate. The freedom of intensity modulation has a great impact on the dosimetric superiority of IMRT, in which better target coverage and less dose to the OARs can be achieved.

The superiority of IMRT over 3DCRT is illustrated in **Figure 2**, which shows radiotherapy plans for NPC patients. The dose-volume histogram (DVH) and the isodose distribution show that IMRT is more capable of sparing the dose delivered to both parotid glands while delivering an adequate dose to the PTV.

## 4. IMRT planning

To achieve the dosimetric superiority of IMRT described in the last section, the planning procedure adopts an inverse approach. Inverse planning is a process to determine the optimal beam intensity. Numerous inverse planning approaches have been proposed and they can be classified as dose-volume based or biological index based [30]. The inverse planning procedure starts with the delineation of the regions of interest (ROI) which includes the PTV and OAR, followed by the beam configuration, objective function setting, and computer optimization. The workflow of IMRT planning is illustrated in **Figure 3**.

The procedures which require human input, including the setting of ROI delineation, beam configuration, and objective function, and evaluation of the plan are further discussed in the following sections.

### 4.1 Target delineation

Target delineation is the first and a very important step in IMRT planning to ensure effective treatment. The delineation of targets in head and neck cancers includes the high-risk, intermediate-risk, and low-risk planning target volume (PTV) [31]. The

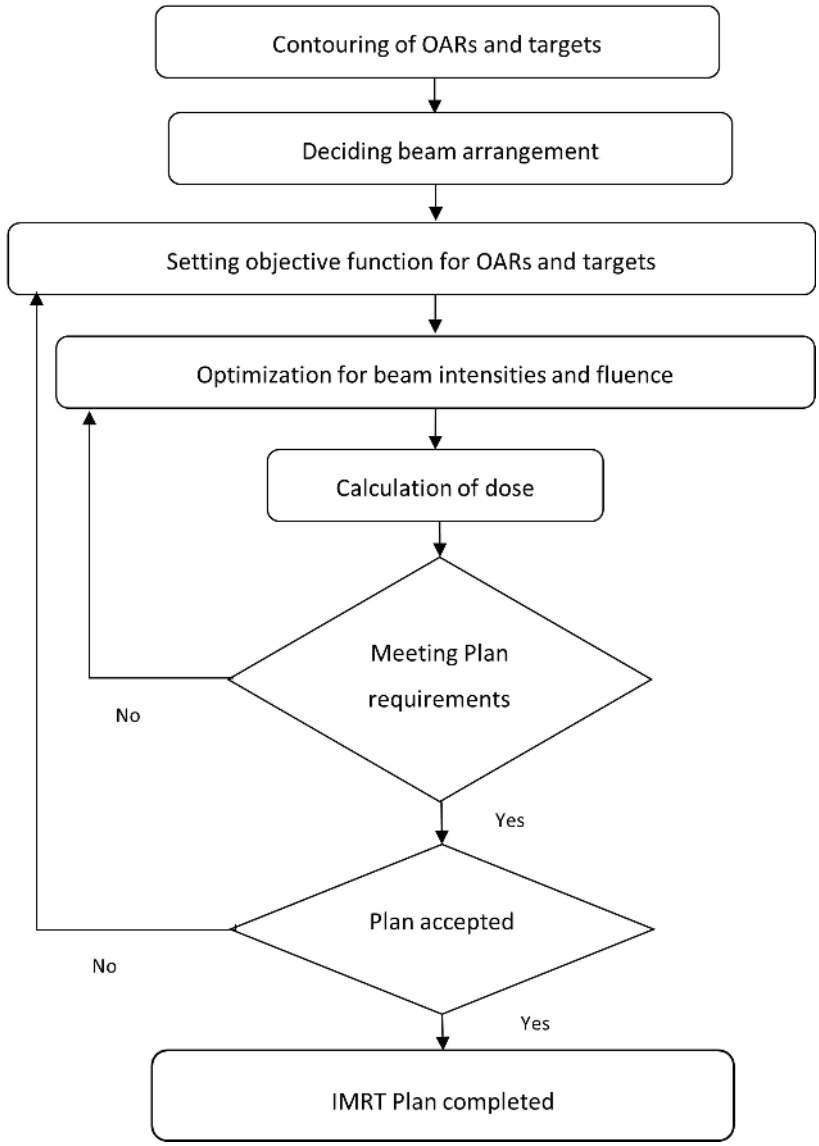


**Figure 2.**
*Procedure of IMRT planning.*

intermediate-risk PTV refers to the regional lymph nodes and the isotropic margins of the high-risk PTV, the low-risk PTV refers to selective negative lymph nodes for prophylactic treatment, and the high-risk PTV encompasses the primary tumor or tumor bed and the positive lymph nodes. The consensus guideline on the delineation of elective lymph nodes levels is well-established [32]. The guideline classifies the regional lymph nodes in the head and neck region into 10 levels and defines their anatomical boundaries. While the selection of lymph nodes levels to be treated largely depends on different oncologists' judgment and individual patients' conditions, there have been published guidelines to review the criteria for the lymph nodes levels selection for treatment in different types of head and neck cancers [32, 33]. Contrary to the well-established consensus in the delineation of PTV for the regional lymph

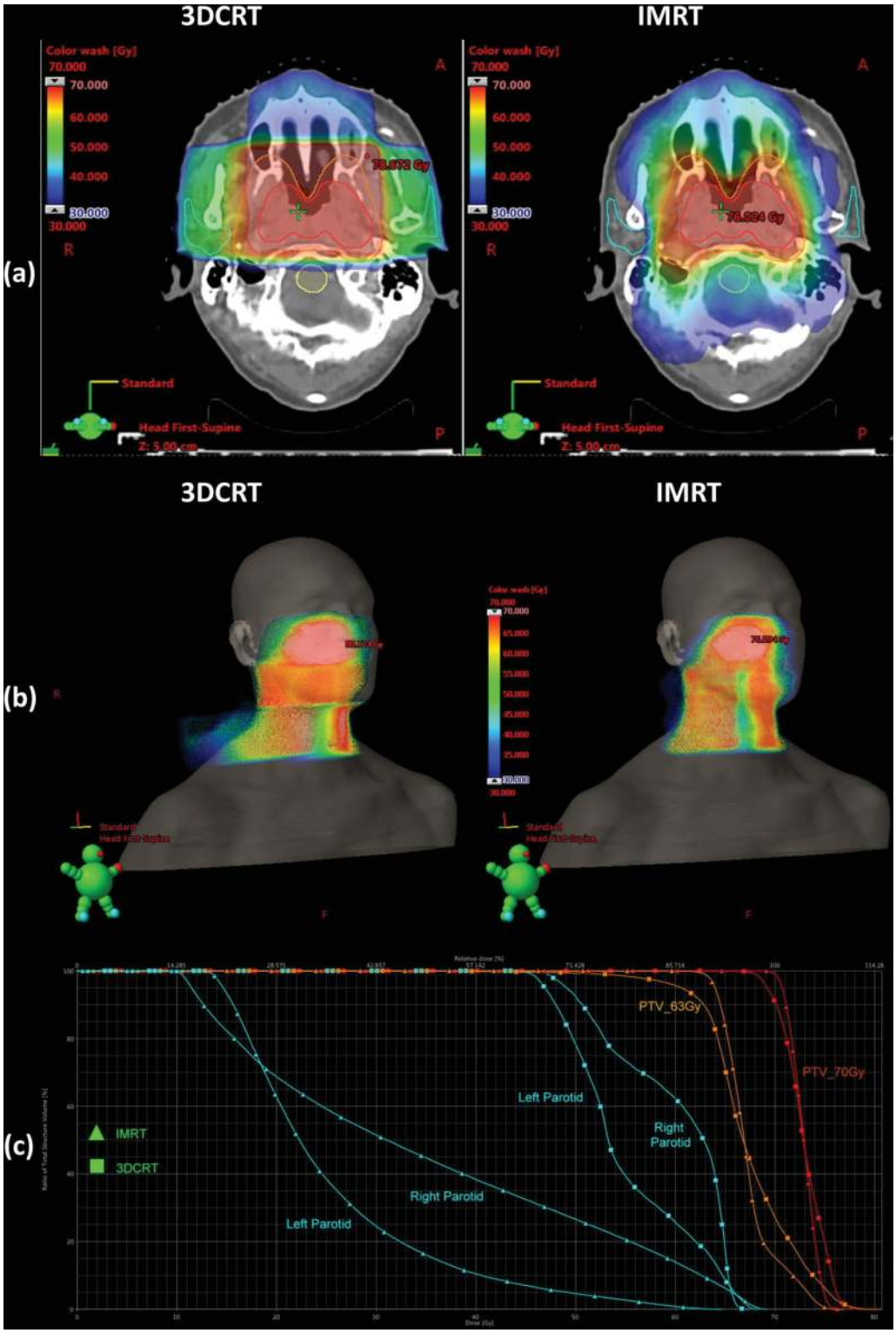


**Figure 3.**
*Comparisons in NPC patients with 3DCRT and IMRT plans. (a) Isodose distribution; (b) 3-dimensional dose color wash; (c) dose-volume histogram.*

nodes, the high-risk PTV delineation technique varies among oncologists. It can either be based on the isotropic expansion of the gross tumor volume or the inclusion of anatomical sub-sites [31]. The method of isotropic expansion to form PTV and the margins needed has been described [34]. The aim of the margins is to account for the uncertainties in the delivery of radiation to avoid target miss. On the other hand, the aim of the inclusion of anatomical subsites in the high-risk PTV in addition to the gross tumor volume is to include regions with possible microscopic extension [33].

The delineation of PTV is closely associated with the dose optimization regarding the skin dose. Usually, oncologists contour a clinical target volume (CTV) that covers all clinical and subclinical malignancy to be irradiated [35]. PTV, on the other hand, would add geometrical margins to CTV to ensure that the prescribed dose is adequately delivered. The CTV to PTV margins can be determined by previously reported margin recipes, accounting for systematic and random error during irradiation [36]. It is worth to note that there is a common circumstance when the head and neck cancers CTV stops just below the skin surface, i.e. no disease in the skin, while the PTV would cover the skin surface or even go beyond it after adding the CTV to PTV margins. In this case, the inverse planning procedure of IMRT would unnecessarily attempt to deliver an extra dose into the skin surface region [37], leading to excessive dose to the skin and adverse skin reactions [38]. Special attention is suggested to these cases, where the target is close to but not involving skin surface so PTV margins should be modified to avoid excessive skin surface normal tissue dose. Many imaging modalities contribute to the delineation of the target. It is important for the definition of tumor extent, the assessment of lymph nodes involvement, and the evaluation of perineural spread [39]. The common modalities include computed tomography (CT) and magnetic resonance imaging (MRI). Both CT and MRI are imaging modalities that provide sectional images with 3-dimensional reconstruction. Each of them has their unique strengths and therefore can provide complementary information in the localization of tumors and organs at risk.

Although both CT and MRI generate sectional images, their image generation mechanisms are not the same. The CT generates images using X-ray. By rotating the X-ray tube, a fan beam of X-ray is irradiated around the patients. After passing through the patient's body and being attenuated differentially by different body tissue with various densities, the X-ray detector receives many projections from the scanned body region. The computer then generates cross-sectional images based on the information gathered from the detected X-ray projections [40]. The resultant images are shown in grayscale according to the tissue density, which can be illustrated by appearing white for bone (high density), gray for soft tissue (medium density), and black for air (low density) [40]. In addition to the visualization of internal anatomy for the diagnosis purpose, the grayscale which is derived from the CT numbers and the robust geometrical information make the CT images suitable to be used for the dose calculation in radiotherapy planning [41].

On the other hand, MRI works by detecting the reaction of the MR-active nuclei in different parts of the body, mainly hydrogen, to the magnetic fields generated by the MRI machine [42]. MR-active nuclei refer to the particles that have net spins of the protons and neutrons, which create magnetic fields on the nuclei [43]. These MR-active nuclei, therefore, react to the strong magnetic field applied by the MRI machine. The image formation is first done by the application of magnetic field to patients' body to align the spinning axis of the MR-active nuclei in the body tissue. Then, by the application of short pulse radiofrequency, the alignment is displaced and then relaxed. This procedure, called relaxation, leads to the release of energy detected

by the receiver coil [42, 44]. The two main types of relaxation are longitudinal relaxation time (T1) and transverse relaxation time (T2). T1 determines the rate of the spinning axis of the MR-active nuclei to realign to the MRI machine magnetic field, while T2 determines the rate of the MR-active nuclei to lose phase from the alignment [43]. The detection of the energy released can then be processed by computers to generate the cross-sectional images. The differences in the relaxation time (T1 or T2) and the density of the nuclei contribute to the tissue contrast in MRI images [43].

Utilization of both CT and MRI images in head and neck cancers is common because they are complementary to each other. In general, MRI is better in soft-tissue contrast while CT is better in detecting bone erosion. For example, T1 weighted MRI images are the most suitable to delineate NPC tumors because of better soft-tissue contrast and more sensitive in detecting the perineural extension of the tumor [45]. However, MRI images may fail to detect subtle skull base bone erosion, which can be complemented by coronary CT images in the bone window [46]. Also, in the cancer of the oral cavity, contrast-enhanced T1 weighted MRI images are the best for the delineation of tumor margin [47], while CT images are useful for the detection of the small lytic lesion in the cortical mandible [48].

In addition, PETCT also provides useful information to the commonly used CT and MRI images. The PETCT utilizes the mechanism of the increased uptake of the fluorodeoxyglucose (FDG) in tumor cells than in normal cells because of their higher metabolic activity [49]. The FDG uptake site can then be localized by scanners by detecting the radioactivity of the FDG. There are several circumstances that PETCT can provide supplementary information in addition to CT and MRI images. PETCT has been reported to have superior performance than CT and MRI in the detection of involved cervical lymph nodes. This is illustrated by the sensitivity of 90% and specificity of 94% in PETCT, compared with about 80% sensitivity and specificity in MRI and CT [50]. Also, PETCT is better in the detection of the unknown primary tumor, which is essential to decide the treatment regimen [51]. Furthermore, PETCT is useful in determining the presence of distant metastasis. It has the sensitivity and specificity of 89% and 95% respectively which indicates a very accurate diagnosis of the metastatic stage of the disease [52].

### 4.2 Organs at risk delineation

Inverse planning of IMRT involves the estimation of OAR dose for the calculation of the beam modulated intensity. The accuracy of the OARs delineation is crucial for the estimation of OARs dose, and hence the inverse planning procedure. There has been a consensus guideline on the OARs delineation in the head and neck regions [53]. This guideline listed the anatomical boundaries of 25 OARs in the head and neck region for the purpose of consistency in the delineation. Detailed atlas has also been supplemented for reference. **Figure 4** shows part of the atlas provided by the guideline

### 4.3 Beam arrangement

In the early application of IMRT, an equally spaced beam arrangement was commonly used [54, 55]. There are two other beam arrangement options available in the Eclipse treatment planning system (Varian Medical System, Palo Alto, USA). These include volumetric modulated arc therapy (VMAT) that enables rotational beams and beam angle optimization (BAO) that automatically chooses optimal static beam angles in either coplanar or non-coplanar beam arrangements.

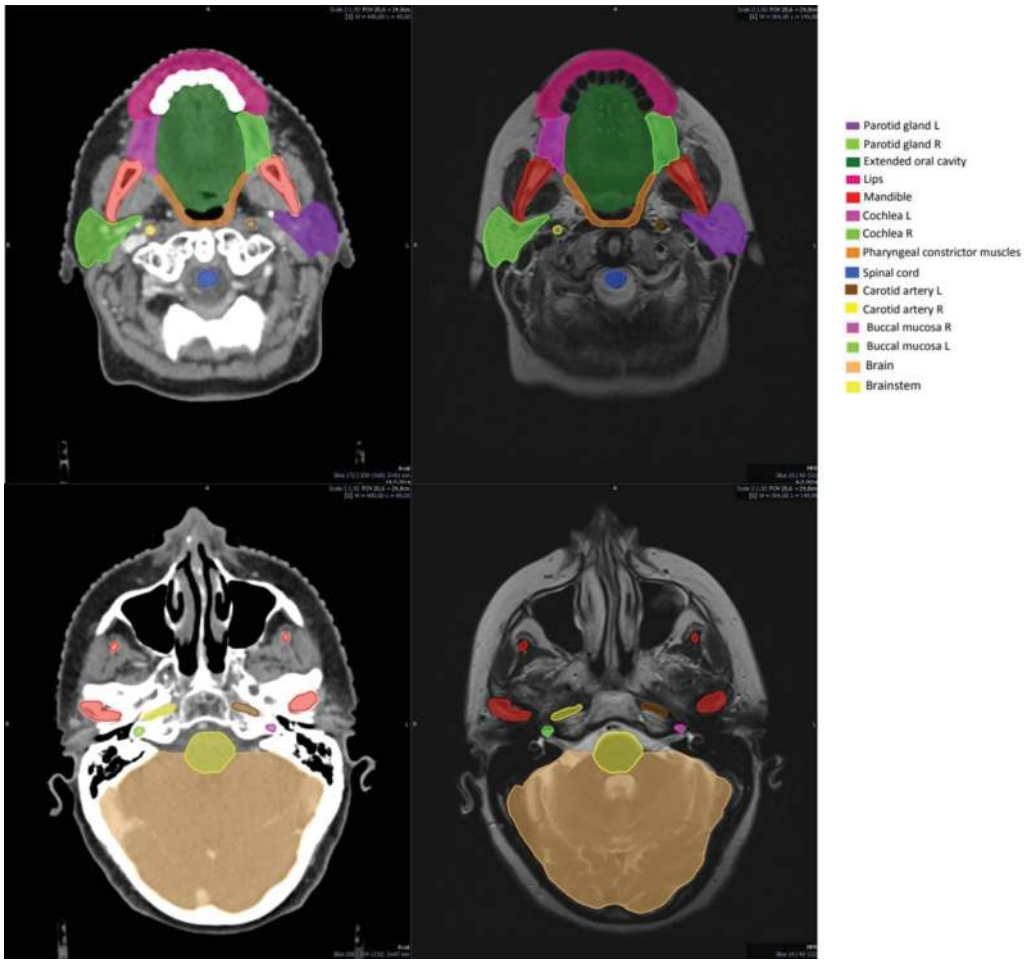


**Figure 4.**
*Part of the OAR delineation atlas. Adapted from [53]. Copyright 2015 the Authors.*

### *4.3.1 Equally spaced beams (ESB)*

The delivery of IMRT requires several beams to achieve the assigned dose distribution [29]. It has been a common practice to use the 5–9 beams arrangement in IMRT for head and neck cancer [55, 56]. Theoretically, a greater number of beams can have a higher chance to achieve the planned dose distribution, which increases the time for delivery and quality assurance. Hence, effort should be put to minimize the number of beams to use. Another concern in the beam placement is that opposing beams should be avoided in IMRT because it reduces the effectiveness of the optimization [57]. Furthermore, it has been calculated that the optimal number of beams is 7–9 after striking a balance between the gain in dose distribution and the expenses of treatment time in further addition of beams [58].

### *4.3.2 Beam angle optimization (BAO)*

Selecting optimal beam orientations can help to improve the dose distribution in complex plans [59]. BAO is a function available in the Eclipse treatment planning system that a built-in algorithm can automatically choose the optimal beam

arrangements in static beam IMRT. The mechanism of selecting the beams is by elimination of beams from up to 400 pre-assigned beams orientations. Then, the calculation of fluence optimization iterations can help to eliminate the beams that cause the least contribution to the pre-set objective functions until the number of desired beams is reached. Planners must customize the resulting number of beams, coplanar or non-coplanar arrangement, and the number of initial beams. Also, objective functions for each target volume and OARs must be set beforehand for the purpose of fluence optimization in the beam elimination process. The user interface of BAO is shown in **Figure 5**.

### *4.3.3 Volumetric modulated arc therapy (VMAT)*

VMAT is a technique that enables the delivery of IMRT in one or more rotations of the linear accelerator gantry. The delivery time is shorter than static gantry methods while maintaining at least comparable dosimetric quality [60]. It is done by simultaneous modulation of the position of the multi-leaf collimator (MLC), dose rate, and gantry speed, while the gantry is rotating around the patient during treatment. The VMAT plan optimization is done on the same user interface as the fixed beam IMRT plan, which is the photon optimizer in the Eclipse treatment planning system. While individual optimal fluence for the beam intensity modulation is optimized for the fixed beam IMRT, the VMAT optimization considers the full rotation of the gantry by dividing it into 178 equally spaced control points [61]. Assuming that the radiation

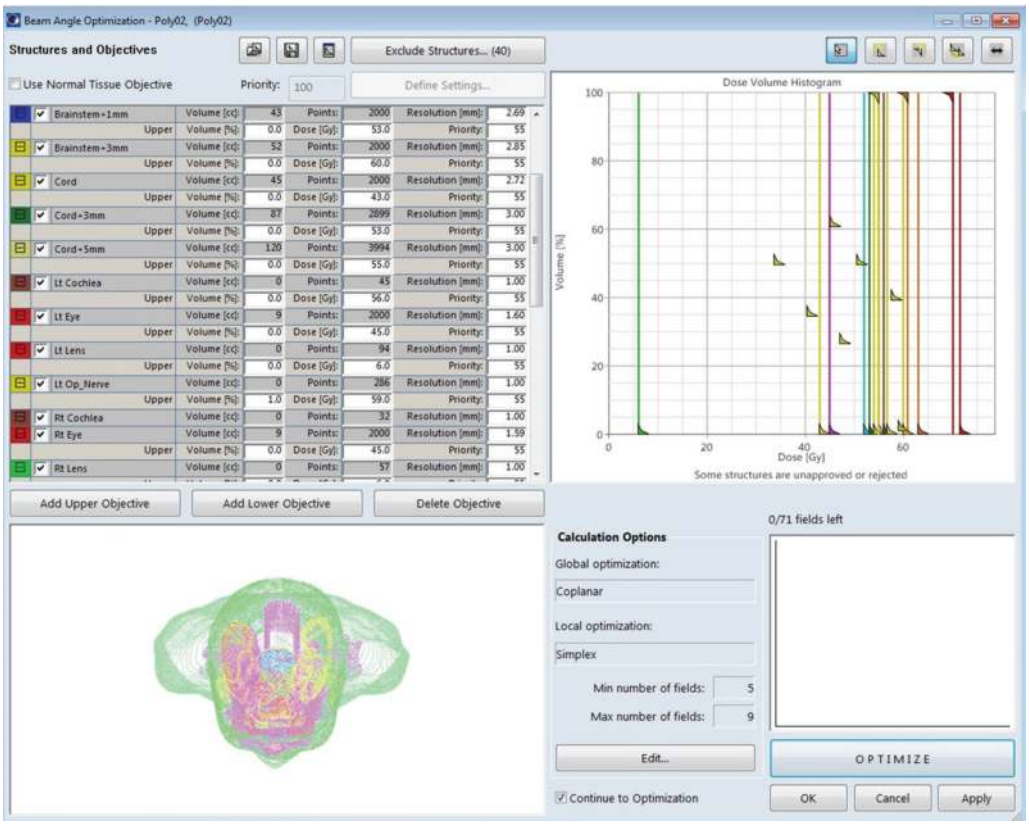


**Figure 5.**
*User interface of BAO in Eclipse treatment planning system.*

from each control point is delivered from a static gantry, the optimizer then generates the information of the MLC position, dose rate, and gantry speed altogether for the dose distribution calculation. The photon optimizer user interface for the optimization of IMRT in the Eclipse treatment planning system is shown in **Figure 6**.

### 4.4 Optimization objectives and procedures

The setting of dose objective is a crucial step in inverse planning because it defines the doses to be delivered to various delineated structures. The computer then calculates the intensity modulation of the treatment field based on the definition of dose objectives [62]. While both dose-volume based objectives and biological objectives can be input in the current commercially available system, dose-volume based objectives were more commonly used. This is because it has been demonstrated that the use of generalized equivalent uniform dose (gEUD) objectives would lead to poorer homogeneities [63]. Inverse planning was first proposed in 1982 [64], in which the dose distribution was defined by planners for the calculation of beam intensity to deliver the desired dose. It is an "inverse" process when compared with the conventional "forward" approach, in which the planners define beam parameters for the calculation of dose distribution [62]. There are upper objective, lower objective and mean objective in the definition of dose-volume based objectives for a structure. A priority number is assigned for each objective to indicate their relative importance. Because the objectives to achieve target dose coverage and to avoid dose to OARs sometimes oppose to each other, the setting of priority provides information for the computer system to decide the "trade-off" between conflicting objectives.

### 4.5 Dose constraints of targets and OARs

In general, there are 3 types of dose constraints settings before the optimization. They are the PTVs, serial OARS, and parallel OARs respectively. For the PTV, it requires the setting of at least one upper objective and one lower objective as shown in

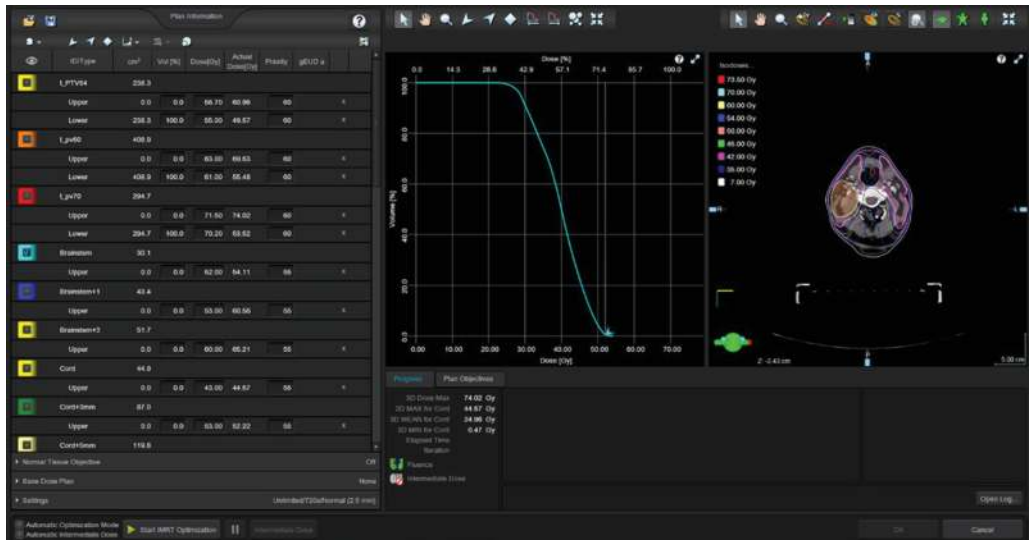

**Figure 6.**
*User interface of photon optimizer.*

**Figure 7**. The resultant dose-volume histogram (DVH) should show that the majority of the PTV receives the desired dose with little volume receive the higher dose, and the shape should look like a plateau at 100% volume with an extremely steep cliff at the end when it reaches the prescribed dose.

The dose constraints setting for serial OARs only requires an upper objective to limit its maximum dose, as shown in **Figure 8**.

For parallel OARs, since the dose received by the various proportion of volume is the concern for late side effects, setting of upper objectives to limit the maximum dose is not enough. It can be done by setting multiple upper objectives at different dose-volume levels or setting the mean objectives. The purpose is to limit the received dose at all volume levels and to push the DVH to its left end as much as possible. A sample objective setting for a parallel OAR is shown in **Figure 9**.

### 4.6 Practical difficulties of optimizing a radiotherapy plan for head and neck cancers

Although the planning procedures are driven by treatment planning computer calculations in an inverse planning process, it is not a completely automatic procedure and there are difficulties in the planning. The difficulties in planning are largely related to the number of OARs and the geometric relationship between the PTVs and the OARs. In the optimization process of the inverse planning, it is usually not possible to achieve all the lower objectives for the PTVs while fulfilling all the upper and mean objectives for the OARs because they naturally contradict each other when the PTVs and OARs are in the vicinity [65]. In head and neck cancers, there are many OARs near to the PTVs including but not limited to the brain stem, the spinal cord, the parotid gland, and the optic nerves. Because of this, the treatment planning system optimization usually has no optimal solution that can fulfill all the set objective functions. Therefore, planners need to intervene in the procedure by evaluating the optimized treatment plans using their own experiences, and to balance the trade-off among all the nonoptimal objective functions of the PTVs and OARs.

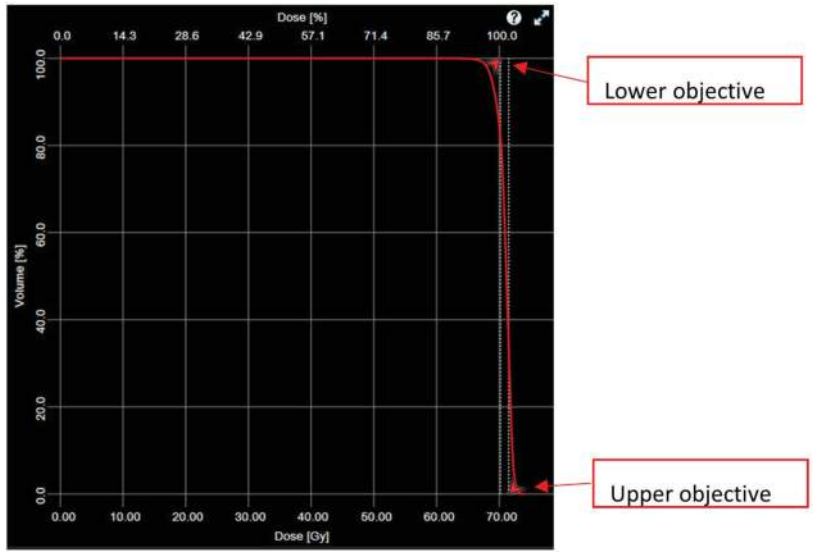


**Figure 7.**
*Dose constraints setting of PTV.*

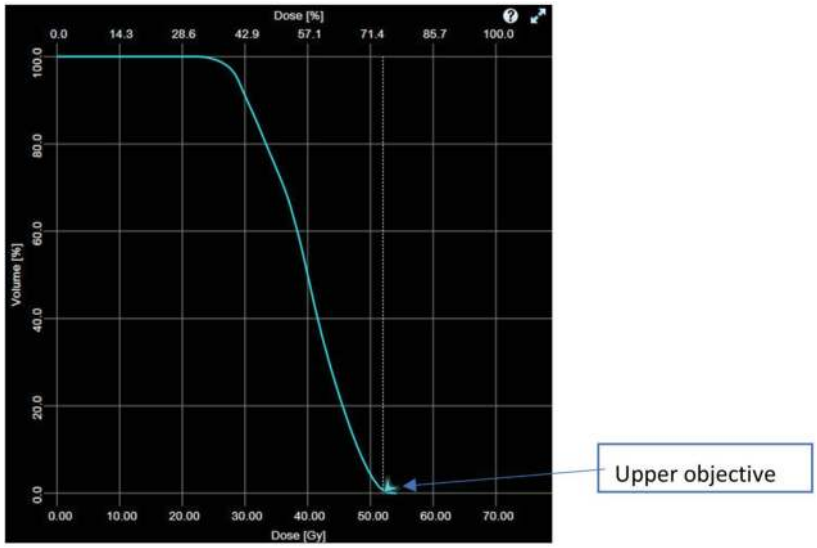


**Figure 8.**
*Dose constraints setting of serial OARs.*

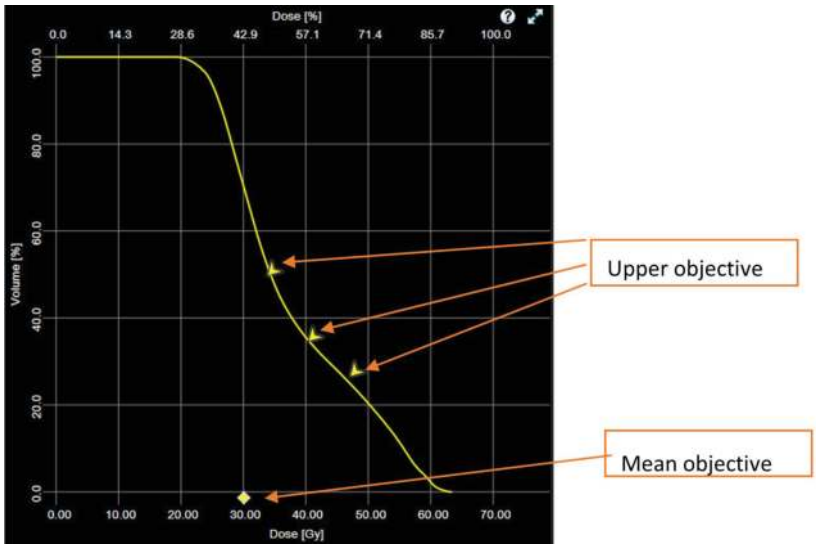


**Figure 9.**
*Dose constraints setting of parallel OARs.*

## 4.7 Plan evaluation

In the evaluation of radiotherapy plan dosimetric quality, there are four main parameters to be evaluated: (1) PTV coverage, (2) OAR dose, (3) PTV homogeneity, and (4) PTV conformity [66]. PTV coverage refers to the minimum proportion of PTV covered by the prescribed dose. OAR dose is to see whether it is within the organ tolerance. PTV homogeneity is used to assess the dose uniformity within the PTV whereas PTV conformity is to evaluate whether the prescribed dose level encompasses and follows the shape of the PTV. Examples of different PTV coverage, homogeneity, and conformity situations are illustrated in **Figure 10**.

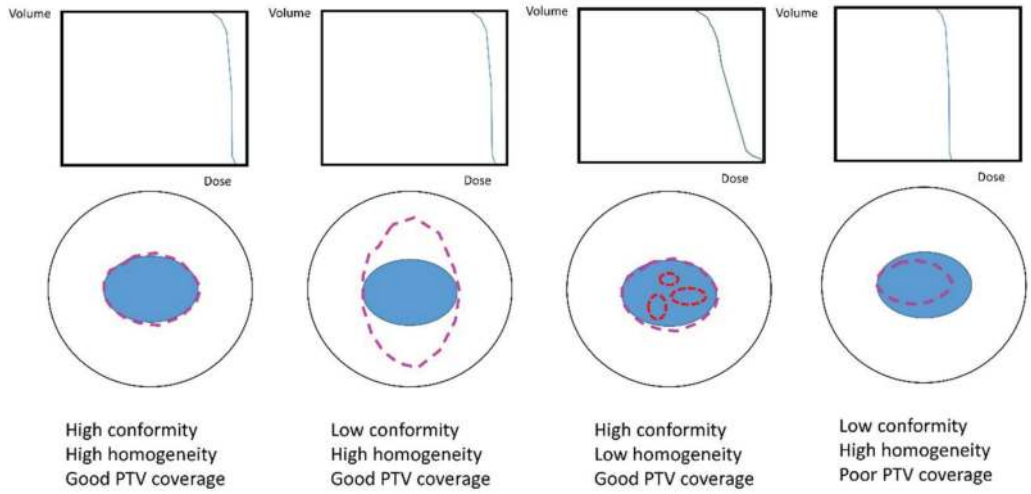


**Figure 10.**
*Examples of different PTV coverage, homogeneity, and conformity situations. The PTV is in blue solid lines and the body is in black solid lines. The purple dashed lines are the prescribed isodose and the red dashed lines are the hot spots isodose. Their respective dose-volume histograms are shown above.*

The evaluation of PTV coverage and OAR dose is conducted using the dose-volume histogram (DVH). PTV homogeneity and conformity are assessed by indices known as the homogeneity index [67] and conformity index respectively [68].

## 5. Current challenges and promises in head and neck cancer radiotherapy

As illustrated, IMRT offers the opportunity for better treatment outcome and less side effects in radiotherapy of head and neck cancers when compared with 3DCRT. A positive aspect of IMRT is that it can increase the dose conformity and homogeneity to the PTV while better sparing of the OARs [69, 70]. The following challenges are needed to be addressed for further development of the advantages of IMRT.

### 5.1 Organs at risk (OARs) dose estimation

In the treatment planning of IMRT, the inverse planning process requires planners to define the dose limits of various PTVs and OARs for the optimization of the beam intensity modulation. This process is regarded as the setting of the objective function, which includes the dose constraints and priority of the PTVs and OARs as discussed in Section 4.5. In general, the setting of PTVs objective functions are guided by the prescription whereas those for the OARs are set according to their dose tolerance [71]. In practice, however, the objectives for OARs sparing are often in conflict with the objectives to achieve PTV dose coverage [72]. This is because OARs and PTVs are often in close proximity and sometimes may even overlap one another. In this condition, we may have to deliver OARs doses that are close to or even higher than their dose tolerance in order to achieve PTV adequate dose coverage. On the contrary, when the OARs are far from the PTV, the actual OARs dose would be well below their tolerance. It is logical to deduce that the OARs dose is related to their anatomical relationship with PTVs, and this relationship varies greatly among different patients.

### *5.1.1 Knowledge-based radiotherapy and 4pi VMAT*

Knowledge-based radiotherapy planning has recently emerged as rapidly developing area with the aim to improve the IMRT planning process [73]. Knowledge-based planning refers to the strategy to incorporate past plans data (known as knowledge) into the treatment planning process. Six different categories of purpose in knowledge-based planning have been summarized in a review article, which includes (1) the determination of DVH, (2) specific dose metrics, (3) voxel-level doses, (4) objective function weights, (5) beam parameters and (6) quality assurance metrics [73]. The development of knowledge-based radiotherapy planning enables planners to determine the setting of objective functions in a more systematic approach, less dependent on personal experience, and therefore higher consistency of plan qualities.

The technology of delivering 4pi VMAT is emerging. 4pi radiotherapy refers to the incorporation of beams distributed on the imaginary isotropically expanded spherical surface around the iso-center during plan optimization [74]. The 4pi VMAT can be delivered by non-coplanar arc beams using a static couch or synchronizing the arc rotation of the gantry with a rotating couch [75, 76]. It has been shown that 4pi VMAT has the potential to further decrease the dose to OARs compared with coplanar VMAT. For example, a study on head and neck cancers reported that the mean $D_{max}$ to the brain stem and spinal were decreased by 6 Gy and 3.8 Gy respectively using 4pi VMAT [77]. In addition, the method of delivering 4pi VMAT with synchronized gantry and couch rotation enabled more sophisticated arc trajectories compared with the static couch method. It was expected to deliver a highly conformed dose to the PTV with a reduction of OARs dose and 50% isodose volume in the patient body [76]. Although the treatment time will increase by 30% in current linear accelerators compared with coplanar VMAT [75], the potential of 4pi VMAT can be unleashed with the advancement of the future linear accelerators with automatic couch and gantry motion capabilities for faster 4pi VMAT delivery [78].

## 5.2 Tumor dose escalation

IMRT offers the possibility to escalate the dose to the tumor because of its better ability to spare the OARs. In fact, dose-escalation has already been implemented in IMRT in the treatment of NPC when the gross tumor dose was raised from 66 Gy in conventional radiotherapy to about 70 Gy [79]. NPC is known for its radiosensitivity and the existence of dose-tumor-control relationship beyond routine cancericidal dose [80], hence increasing the dose to the tumor volume is able to increase the local control rate. It has been reported that in the group of predominantly locally advanced NPC (T3-4 N0-1), 61.8% of the failure was caused by local relapse [81]. Another study also revealed that 80% of the recurrent cases had the relapse sites at the region delivered with the median dose of 70.4 Gy in the previous treatment [82]. Clinical investigations on the dose escalation in the treatment of NPC using external beam radiotherapy [83] and brachytherapy have been reported [84]. Although it has shown good local control and survival in both reports, treatment side effects were the concern. For example, grade 3 mucositis was observed in about 80% of the cases [83]. Also, by assessing the acute toxicity, it has been suggested that the maximal tolerable dose in IMRT of head and neck cancers was 2.36 Gy per fraction to a total of 70.8 Gy [85].

### *5.2.1 Application of radiomics to selection of NPC cases for dose escalation*

Radiomics refers to the extraction of features in the regions of interest (ROI) from medical images [86]. The extracted features can be the image voxel intensity, ROI texture and shape features, etc. [87]. These extracted radiomics features can be used to correlate with clinical data such as recurrence and metastasis status of patients, so as to develop tools for predicting treatment outcome in future patients based on individual patients' image radiomics features. Research articles have been published to evaluate the chance of local recurrence in NPC patients, and it was reported that local recurrence can be predicted using pre-treatment imaging with a concordance index of over 0.8 [88, 89]. The future direction could be to incorporate radiomics study for more accurate and individualized patient selection instead of based on their staging. With the attempt to generate own local recurrence prediction model based on radiomics features, NPC patients indicated for GTV dose escalation could be more accurately identified.

## 6. Summary

Radiotherapy is necessary for the treatment of various head and neck cancers either as a primary treatment or adjuvant treatment after surgery to cure the disease. To achieve optimal radiotherapy treatment, we need to understand the rationale of IMRT and the procedure of treatment planning. With the help of treatment planning computer, inverse planning procedure can accomplish treatment plans with highly conformal radiation dose to PTV and dose avoidance from OARs. Because of the conflicting nature of the 2 major dosimetric goals: high PTV dose and low nearby OARs dose, the optimal radiotherapy treatment is usually achieved by experienced planners who are able to carefully balance the trade-off between the conflicting goals. Nevertheless, the present development of knowledge-based planning could provide a guidance for planners to decide the trade-off in a more objective manner. In addition, the development of 4-pi VMAT and research of radiomics may strengthen the advantage of IMRT in terms of OARs sparing and tumor dose escalation.

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