A Comparison of Treatment Plans for Recurrent Nasopharyngeal Carcinoma

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SUMMARY

The purpose of this study is to assess intensity-modulated radiotherapy (IMRT) treatment plans with three-dimensional conformal radiotherapy (3D-CRT) plans for different sites of recurrent nasopharyngeal carcinoma. We treated 3 cases of different sites of recurrent nasopharyngeal carcinoma with IMRT techniques and 3D-CRT technique. These different plans were compared with respect to dose conformity, dose-volume histogram, dose to the sensitive normal tissue structures, and ease of treatment delivery. The planned dose distributions were more conformal to the sensitive normal tissue structures by IMRT plans in 3 different sites. Our experience concludes IMRT techniques provide improved tumor target coverage with significantly better sparing of sensitive normal tissue structures in the treatment of recurrent nasopharyngeal carcinoma. With improvement of the delivery efficiency, IMRT should provide the optimal treatment for recurrent nasopharyngeal carcinoma.

Key words: Dose-volume histogram; Intensity-modulated radiotherapy; Nasopharyngeal carcinoma; Three-dimensional conformal radiotherapy

Nasopharyngeal carcinoma (NPC) is a rare malignant neoplasm in Western countries, but it is a common form of head and neck cancer in Taiwan. Patients with NPC are typically treated with radiation therapy rather than surgery because of the anatomically challenging, difficult location and a demonstrated favorable response to irradiation and chemotherapy. The treatment results can achieve clinical local control rates for T1 and T2 tumors in the range of 70-90% [1]. However, recurrence of primary tumor is one of the major causes of death from this disease, especially with locally advanced diseases. The reported incidence of recurrence varies from 18% to 58%, with the median at 34% [2-5]. Although recurrent tumors of the nasopharynx could be reirradiated with some success [6-9], severe late complications have reported using conventional two-dimensional techniques by several literatures [7-9].

Three dimensional conformal radiotherapy (3D-CRT) technique has shown improvement in dose distribution conformity to the tumor target volume while concomitantly reducing the dose to the surrounding normal tissues, when compared to traditional techniques using bilateral opposed fields for primary NPC [10-11]. The limitation of the 3D-CRT technique, however, is that it heavily depends on the planner’s expertise, and requires manual iteration to achieve an optimal plan. In addition, it only controls the radiation beams in two dimensions.

Recent advances in computer technology have spurred the development of intensity-modulated radiotherapy (IMRT). The IMRT is an advanced form of 3D-CRT with two key enhancements that including computerized iterative treatment plan optimization using the inverse treatment planning and the use of intensity-modulated radiation beams. Furthermore, computer-controlled radiotherapy delivery systems allow efficient implementation of complex treatment plans [12-13]. Because of the proximity to surrounding critical structures, NPC is an ideal disease site to evaluate implementation of IMRT. In this study, we
evaluated the feasibility and difference for IMRT and 3D-CRT techniques for different site of recurrent NPC.

MATERIALS AND METHODS

In the 3 cases of recurrent NPC selected for this study, the gross target volume (GTV) was defined as the gross extent of the tumor demonstrated by imaging studies and physical examination. Whenever possible, fusion of the diagnostic MRI images and the treatment planning CT images was done to more accurately delineate the GTV and the surrounding critical normal structures. The clinical target volume (CTV) is defined as the GTV plus 0.5 cm margin for subclinical tumor. The planning target volume (PTV) includes the CTV plus 0.5 cm for daily patient set-up variation. The GTV, CTV and sensitive normal structures were delineated on a series of treatment planning CT images. The head of the patient was immobilized in a thermoplastic mask in the supine and mild extension position.

We select 3 cases as representative in different site. Case 1 is nasopharynx recurrence only. Case 2 is the recurrence over nasopharynx and neck. Case 3 is nasopharynx recurrence with intracranial extension. The previous treatments for these 3 patients were delivered by bilateral opposing technique with 6 MV photon beam. After 36 Gy, the neck was separated from primary tumor lesions and irradiated by AP/PA fields with central spinal cord block. The reduced boost fields cover only the primary lesion with the anterior oblique portals for an additional 24 Gy in 10 fractions. The total dose to primary tumor site is 70 Gy. The radiation dosages to brainstem and spinal cord were estimated to 46 and 40 Gy, respectively. The intervals between the previous RT and this treatment

Figures 1. The isodose distributions on axial images for these 3 recurrent nasopharyngeal study cases, generated with the 3D-CRT and IMRT plans. a. Nasopharyngeal recurrence only. b. Nasopharynx and neck recurrence. c. Nasopharynx recurrence with intracranial extension.
were 42, 36 and 59 months.

The planning systems were used by Corvus inverse treatment planning system for IMRT plans and Theraplan Plus (TPP) treatment planning system for 3D-CRT plans. The most challenging part of the planning was to deliver a tumorcidal dose to the tumor target volume while sparing the adjacent critical normal structures. In our paper, we focus on the treatment plans for the recurrent tumor target volume. Hence, the tolerance of these adjacent critical normal tissue structures made treatment planning for the recurrent tumor target volume very difficult.

The treatment goal was to deliver a prescribed dose of 70 Gy to at least 95% of GTV, and 60 Gy to at least 95% of CTV. The maximum doses to brain stem and/or spinal cord were limited to 20 Gy. The maximum doses to eye structures were limited to 30 Gy. We evaluated the result of the treatment plan result by radiation dose-volume-histogram (DVHs) to compare the difference between different treatment plans.

**RESULTS**

The isodose distributions on axial images for these 3 study cases generated with the 3D-CRT and IMRT plans were shown in figure 1. For the purposes of comparison, all treatment plans were normalized in such a way that a dose of 60 Gy was delivered to more than 95% of the CTV. One should notice that to meet this treatment goal, neither of these 2 plans could satisfactorily comply with the tolerance doses of the adjacent sensitive normal structures.

Figure 2-4 show the DVHs from these two plans with the 3 patients for the target (CTV), spinal cord, temporal lobe of the brain, brain stem, and bilateral eye structures, respectively. In general, all two plans had similar dose coverage for the CTV. However, the sensitive normal structures were significantly different. For the spinal cord, the dose distributions of IMRT were better than 3D-CRT in all 3 cases. The dose to the temporal lobe of the brain from IMRT was less than these of 3D-CRT in case 1 and 2 but no significant in case 3. For the brain stem, the dose from IMRT was also less than that from 3D-CRT in case 1 and 2. In case 3, the DVH curves were crossed. However, since the brain stem is biologically a serial structure, the curve in the high-dose region is more important than that in the low-dose region. Hence, the IMRT plan was better than 3D-CRT for brain stem in case 3. The dose to ipsilateral eye structures from IMRT was significantly less than that from 3D-CRT in case 3, slightly in case 1 and none in case 2. For the contralateral eye structures, the IMRT had no radiation dose distribution benefit in all 3 cases.

The average IMRT planning time including contouring for the tumor target and the normal sensitive

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**Figure 2.** The Dose-volume histograms comparing the IMRT and 3D-CRT for the patient with nasopharyngeal recurrence only
structures, beam definition, optimization of computer, evaluation and documentation was approximately 24-72 hours in comparison to an estimated 12-24 hours for the 3D plan. Daily patient setup and treatment times (including weekly verification films) averaged 20-30 minutes for IMRT in comparison with an estimated 15 minutes for the 3D conformal treatment plan.

Figure 3. The Dose-volume histograms comparing the IMRT and 3D-CRT for the patient with nasopharynx and neck recurrence

Figure 4. The Dose-volume histograms comparing the IMRT and 3D-CRT for the patient with nasopharynx recurrence with intracranial extension
DISCUSSION

Local control remains a significant problem for many patients with nasopharyngeal carcinoma, particularly those with advanced locoregional disease. Patients with recurrent NPC have a gloom prognosis if left untreated. Yan et al [14] reported only one 5-year survivor in a group of 276 patients with recurrent disease who received no further treatment. Reirradiation for local recurrences has been accepted as the most optimal treatment modality, which has no immediate life-threatening morbidity or mortality of surgery, and has frequently promising treatment results. Summarizing the reports on reirradiation, the local control rates were approximately 20% [8, 14-16]. Various reirradiation techniques were tried in an effort to limit the radiation doses to the surrounding critical normal structures, such as stereotactic radiosurgery (SRS) [16-19], fractionated stereotactic radiation therapy (FSRT) [20] and 3D-CRT [21].

Intensity-modulated radiotherapy involves the delivery of optimized, nonuniform irradiation beam intensities. It achieves a higher target dose conformity as compared with previous technologies. This characteristic provides the potential for improved tumor irradiation and sparing of the organs in the vicinity of the targets to an extent that was not possible before. On the other hand, nasopharynx is no organs motion compared with abdomen and pelvis regions, moreover, is adjacent to many critical and radiation-sensitive structures such as spinal cord, brain stem and optic apparatus. Hence, NPC represents an attractive site for IMRT.

In this study, the IMRT plans achieved better sensitive normal tissue structure sparing than 3D-CRT with similar dose coverage of the CTV, especially in nasopharynx recurrence with/without neck recurrence. Yan et al [14] had reported the sites of 219 recurrent NPC patients. Among various sites of recurrence and their combinations, recurrence in the neck was the most common, amounting to 42% of the whole series. They also reported a single recurrence in 62%, simultaneous recurrences at two sites in 23% and 15% at three sites. However, seventy-one percent of patients with neck recurrence only had further recurrence in the nasopharynx after second course of irradiation. Hence, they recommended that recurrences in the neck most often were combined with a local recurrence in the nasopharynx especially when repeatedly appearing. In our study, we used 3 cases in different recurrent sites. With similar dose coverage of the CTV, delivering a minimum dose of 60 Gy to more than 95% of CTV, the IMRT plans provided significant better sparing of the sensitive normal tissue structures especially the spinal cord, brain stem and temporal lobe of the brain in nasopharynx recurrence with/without neck recurrence. For nasopharynx recurrence with intracranial extension, the IMRT had only radiation dose distribution benefit in ipsilateral eye structures, and slightly in the spinal cord and brain stem.

RT for primary NPC often delivers doses equal to or greater than 70 Gy to gross tumor, intermediate doses of between 50 and 70 to tissues surrounding to the gross tumor, and about 50 Gy to electively irradiated tissues such as lymph node-bearing tissues at risk for subclinical or microscopic disease, however, the dosage for recurrent NPC has not been fully established. Wang [9] had reported that more radiation dose is crucial for salvage in recurrent disease. Chang et al [16] suggested that the radiation dose more than 50 Gy did significantly improve the survival. Pryzant et al [15] reported on 53 patients with locally persistent or recurrent NPC treated with megavoltage irradiation. The median dose was 57 Gy. The total cumulative dose (including initial treatment) ranged from 80 to 160 Gy. Lee et al [8] described results in 891 patients with local recurrence after definitive radiation therapy for NPC. The 586 patients were reirradiated with external irradiation alone. The median equivalent dose was 57 Gy, but 100 patients received doses greater than 60 Gy. Yan et al [14] also demonstrated that a higher dose gave better results. They suggested that the optimal dose seemed to lie above 50 Gy and preferably around 60 Gy for recurrent NPC. We agree the opinions of them. In this study, the treatment goal was to deliver a prescribed dose of 60 Gy to at least 95% of CTV.

Based on the comparison of dose distributions to sensitive structures, the advantage of the IMRT plans was evident. In practice, however, the planning of the IMRT treatments required more time than the conventional and 3D-CRT treatments. It usually took about 1-2 hours for a physician to delineate the tumor target and normal sensitive structures. For medical physics, it took about 24-72 working hours to get a good treatment planning depending on the maturity of physicist. Another time-consuming process was radiation delivery. It took about 20-30 minutes to complete IMRT treatment. The estimated treatment planning time included time spent for contouring and dose calculation. For IMRT plans, the planning time also included time for compute optimization. These estimated times for planning and delivering might be reduced with improvement in the efficiency of the delivery system and planning system, and with our
further experience with IMRT planning.

Because conventional evaluation of treatment plans is no longer adequate to address 3D-CRT technique, two general sets of tools for plan evaluation are used. One is based upon physical endpoints (DVH) and the other on biological indices, normal tissue complication probability (NTCP) and tumor control probability (TCP). The comparisons of DVH were mentioned as above. Though the NTCP and TCP are an alternative method for evaluating 3D-CRT treatment plans, there are some problems when they used in IMRT. First, many different types of normal tissues are included in the PTV with different $\alpha/\beta$ and some are parallel organs and others are serial organs. Hence, there are many challenges related to using Lyman’s NTCP model with inhomogeneous dose distributions in a normal organ found frequently with IMRT planning when the normal organ is adjacent to the PTV [22-23]. Second, in the application of $\alpha/\beta$ in the biological equivalent doses (BEDs) model, a simplification is often made to assume that $\alpha/\beta$ is the same for all parts of an organ and complications combination [24-27]. However, in IMRT treatment delivery, this assumption does not apply. Therefore, more data are necessary to establish the biological indices for IMRT. Mohan et al. [28] also mentioned it is recognized that there is considerable uncertainty in the available data and numerous assumptions in the linear-quadratic (LQ) model and isoeffect formalism, the validity of which has not been fully established. Therefore, the application of these models to estimate the dependence of response of tumors and normal tissues may be questioned. Just as emphasized by Ang et al. [29], “No isoeffect formula is sufficiently reliable to preempt clinical judgment, and in the final analysis, each new fractionation schedule must be tested clinically to establish its safety.”

Uncertainty in the demarcation of the target volumes is one of the major limitations to improve outcomes of head and neck cancer with RT. The extent of GTV determined clinically is not always easily defined, and the extent of CTV is much more uncertain. Therefore, target definition is more critical in IMRT treatment planning where the high dose volumes can be closely shaped to the target volumes. Until new imaging modalities become available producing more accurate gross tumor and subclinical tumor delineation, it is crucial that we carefully follow patients treated with IMRT to ensure that our best estimates of target volumes are not associated with a compromise in treatment outcome [30].

Modern RT technique tries to reach simultane-ously three goals: homogeneity, target coverage, and conformality. An often-mentioned disadvantage of IMRT is its increased degree of target dose heterogeneity when compared to 3D-CRT techniques. Although much more homogeneous plans could have been produced, increasing dose to the surrounding sensitive structures may occur and cause severe complications especial in recurrent NPC. Indeed, 3D-CRT selects to maintain homogeneity and structure sparing often at the expense of target coverage, on the other hands, IMRT usually elects to achieve target coverage and conformality while minimizing the importance of homogeneity. Pirzkall et al. [30] pointed out that an increase in heterogeneity was associated with highly conformal treatment deliveries. Because stiffness and fibrosis of neck is usually found in recurrent NPC patient, it is important that treatment delivery should be done as fast as practical. In summary, assessment and quantification of the potential clinical benefits of using IMRT to spare critical normal structures are needed to improve our understanding of the role of this new technology in the treatment of recurrent NPC. We showed that the dose coverage of the recurrent tumor was adequately maintained and normal sensitive structures sparing were improved as compared with 3D-CRT. With improvement of the delivery efficiency, IMRT should be highly recommended for all patients with recurrent NPC.

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鼻咽癌復發之治療計劃的比較

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本研究之目的是比較在不同部位復發之鼻咽癌，強度調控放射治療計劃與三度空間順形放射治療計劃之優劣。我們使用強度調控放射治療及三度空間順形放射治療兩種不同的技術設計三例不同部位復發的鼻咽癌病例。這些不同計劃比較其劑量均勻度、劑量體積柱狀圖、敏感正常組織結構之劑量以及計劃執行之難易度。在此三個不同部位的計劃劑量分布圖上，強度調控放射治療對敏感正常組織結構都較為適合。根據我們的經驗推斷對於鼻咽癌復發的治療上，強度調控放射治療技術不僅提供改善腫瘤標靶劑量的包含度，也對敏感正常組織結構有顯著較好的免除效應。在執效率改善之下，強度調控放療治療將提供為鼻咽癌復發時的最適切之療法。

關鍵詞：劑量體積柱狀圖，強度調控放射治療，鼻咽癌，三度空間順形放射治療