Hyperfractionated Re-irradiation using a 3-Dimensional Conformal Technique for Locally Recurrent Carcinoma of the Nasopharynx: Preliminary Results

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To evaluate the efficacy of hyperfractionated re-irradiation using a three-dimensional conformal radiotherapy (3-D CRT) technique in patients with locally recurrent carcinoma of the nasopharynx. Four patients with locally recurrent nasopharyngeal cancer were retreated with a hyperfractionated schedule using a 3-D CRT technique. Re-irradiation was delivered in 1.1-1.2 Gy fractions twice per day (BID), with interfraction intervals of more than 6 hours. The total dose ranged from 59.4 to 69.2 Gy. A 3-D CRT technique with 5- or 6-field coplanar and/or non-coplanar beams were employed during the entire treatment procedure. All four patients achieved complete remission of locally recurrent lesions, with marked improvement of subjective symptoms, immediately after re-irradiation. All are alive and well without evidence of disease after limited follow-up periods, which range from 7 to 20 months. So far, there have been no radiation-induced neurologic complications. Four patients with locally recurrent carcinoma of the nasopharynx were successfully treated by hyperfractionated re-irradiation using a 3-D CRT technique. A relatively high re-irradiation dose of more than 60 Gy may be safely delivered with no serious acute or late radiation-induced complications in patients with local recurrences and who were initially treated with doses greater than 70 Gy.

Key Words: Carcinoma of the nasopharynx, re-irradiation, Hyperfractionation, three-dimensional conformal radiotherapy.

INTRODUCTION

Patients with locally recurrent carcinoma of the nasopharynx have an extremely poor prognosis if they are not properly treated. Although salvage surgery, re-irradiation, chemotherapy, or a combination of these modalities have been employed in the treatment of these patients, re-irradiation treatment is still accepted as the most effective modality for salvaging nasopharyngeal recurrence. Various radiotherapeutic techniques, including external-beam radiotherapy or brachytherapy, either alone or in combination have been applied with the intention of producing worthwhile symptomatic palliation or possible cure in selected cases. Despite the fact that the majority of patients with local recurrence had been previously given radiation doses of over 70 Gy, several investigators have recommended that re-irradiation doses of greater than 60 Gy are necessary to achieve a significant cure rate for locally recurrent nasopharyngeal cancer. However, there is no doubt that such higher doses are usually accompanied by a substantial risk of radiation-induced late complications. Recently, a few investigators have explored the possibilities of a re-irradiation trial using the technique of stereotactic radiosurgery in order to overcome such problems, but the efficacy of the technique remains unclear, partly because of the physical limitations imposed by the size of the collimators and partly because of radiobiological limitations caused by the lack of fractionations.

On the other hand, 3-dimensional conformal radiotherapy (3-D CRT) is a technique which is capable of conforming the higher doses of spatial distribution to the irregular shape of a locally recurrent tumor, while minimizing the risk of late...
effects on the surrounding tissues. \textsuperscript{36,37} Nevertheless, very little information is now available on the efficacy of such technique in the management of nasopharyngeal cancers. Furthermore, no data has been published in the English literature concerning re-irradiation using 3-D CRT for the management of locally recurrent nasopharyngeal cancer. In addition, the use of hyperfractionated radiotherapy schedules can be expected to allow an overall escalation of total radiation doses, thereby increasing the tumor control rate whilst maintaining acceptable levels of late normal tissue toxicities. In an attempt to enhance the treatment outcome and to minimize radiation complications, we designed a pilot study to investigate the efficacy of hyperfractionated radiotherapy using a non-coplanar 3-D CRT technique in the management of patients with locally recurrent nasopharyngeal carcinoma. In this report, we present our preliminary experiences with this technique in four patients.

\section*{MATERIALS AND METHODS}

Between 1996 and 1998, four patients with locally recurrent nasopharyngeal carcinoma were seen at the Yonsei Cancer Center, Yonsei University, College of Medicine in Seoul, Korea. All those who had previously received high-dose radiotherapy employing 4 MV photon beams were retreated with a hyperfractionated schedule incorporating 3-D CRT technique. The radiation doses delivered during the first irradiation ranged from 50.4 Gy to 74 Gy during 6-9 weeks. The initial TNM classifications, previous treatments, sites of recurrence, disease-free intervals to recurrence, and retreatment TNM classifications (rTNM) for each patient were variable. Patients characteristics are listed in detail in Table 1. Before treatment, the natural history of the recurrent tumor, the different retreatment option, and the purpose of our treatment strategy were discussed with individual patient. Re-irradiation using our technique was initiated after obtaining informed consent. Each patient had the baseline work-up consisted of a complete physical examination, nasopharyngoscopy, complete blood count, chest X-ray, and head and neck computerized tomography (CT) or magnetic resonance imaging (MRI). To exclude distant metastasis, whole body bone scan and liver ultrasound were conducted before the re-irradiation was undertaken.

The patients with locally recurrent tumor were retreated with 6 or 10 MV X-ray. The hyperfractionated schedule, twice a day, 5 days per week, for 6-7 weeks was used with a minimum 6-hour interval between the two treatments. In each fractional treatment, 1.1 or 1.2 Gy was delivered with a daily tumor dose of 2.2 or 2.4 Gy. The total dose for a continuous course of re-irradiation ranged from 59.4 to 69.2 Gy.

Our 3-D CRT planning procedure has been described previously. \textsuperscript{38} Briefly, the patients were immobilized with thermoplastic, and planning CT slices were obtained at intervals of 0.5 cm from the top of the vertex to the level of the hyoid bone. Then the CT data was transferred to a

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Case & Age (yr) & Initial TNM classification & Initial RT Dose (Gy) & Sites of failure & Interval to Recurrence & rTNM & Survival after reirradiation \\
No. & /Sex & & & & & & \\
\hline
1 & 51/M & T4N0M0 & 70.0 & Cavernous sinus & 94 mo & rT4N0M0 & 1.2 & 61.2 & 14 mo NED \\
2 & 49/M & T4N0M0 & 74.0 & Posterior wall & 66 mo & rT3N0M0 & 1.2/1.6 & 69.2 & 20 mo NED \\
3 & 57/M & T2aN1M0 & 70.0 & Lateral wall & 19 mo & rT1N0M0 & 1.2 & 60.0 & 7 mo NED \\
4 & 69/M & T2aN1M0 & 50.4 & Cavernous sinus & 14 mo & rT4N0M0 & 1.1 & 59.4 & 11 mo NED \\
\hline
\end{tabular}
\caption{Clinical Features and Outcome of Four Patients with Locally Recurrent Nasopharyngeal Cancer}
\end{table}

rTNM, TNM classification of the recurrent tumor; RT, radiotherapy; NED, no evidence of disease

\textsuperscript{1} Total radiation dose to ipsilateral neck node area: 59.4 Gy

3-D radiotherapy planning system (ADAC-Pinnacle). The gross target volume (GTV) and clinical target volume (CTV) were outlined on each CT slice. The planning target volume (PTV) was set as the CTV with an additional 0.5 cm of margin. Adjacent critical organs such as the brain stem, spinal cord, pituitary gland, optic chiasm, both optic nerves, temporo-mandibular joints, and parotid glands were simultaneously delineated on the same CT slices. After 3-D image reconstruction, the beam's eye-view displays were generated to design the beam direction and field-shaping, which adequately encompassed the PTV, while excluding the brain stem and spinal cord completely and as much of the temporal lobes and parotid glands as possible. Five or six-field coplanar and/or non-coplanar beams were usually employed to ensure adequate coverage to all known or probable disease extensions (Fig. 1). The radiation dose was prescribed to the maximum isodose surface which completely enveloped the PTVs. Isodose display in axial, sagittal, and coronal planes was routinely generated for isodose prescriptions (Fig. 2). Each CT slice was reviewed at the completion of a plan to ensure adequate coverage of the PTV by the 95% isodose, and for proper blocking of critical structures. In addition, a cumulative dose volume histogram (DVH) was constructed for each defined PTV and the various normal tissue organs (Fig. 3). The plan evaluation and comparison consisted of a review of axial, sagittal, and coronal isodose distributions, followed by a comparison of the dose statistics, DVHs, and biological indices for each PTV and each critical organ. After comparing the rival plans, the best 3-D CRT plan was selected and implemented. To assess treatment accuracy, all patients had verification film taken weekly with an electronic portal imaging device system.

RESULTS

All four patients with a locally recurrent nasopharyngeal cancer who received re-irradiation treatment with hyperfractionated radiotherapy using 3-D CRT achieved a successful outcome and complete remission of the recurrent lesion was observed immediately after the completion of the re-irradiation. Our novel technique was well tolerated by all patients. Acute reactions of normal tissues including mucosa were negligible. Although the follow-up periods ranged from 7 to 20 months was too short to comprehensively evaluate the treatment outcomes, all patients are currently alive with no evidence of disease or neurologic complications.

A man, aged 51 years, presented a T4N0M0,

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Fig. 1. (a) A beam's eye view display showing the field shaping which adequately encompasses the PTV, while excluding the brain stem, ipsilateral optic nerve, and a part of the optic chiasm. (b) Six-field non-coplanar beams making the spatial distributions of radiation dose were used to minimize the potential toxicities to the normal tissues of the high radiation dose, which had been previously delivered (Patient 1).
Fig. 2. Isodose display in the axial, sagittal, and coronal planes. 95% isodose line (thick white line) encompasses the PTV (scrapped area) adequately. Radiation dose was prescribed to the 95% isodose line (Patient 1).

Fig. 3. Cumulative dose volume histograms (DVHs) for each defined PTV and various normal tissue organs. All four patients.
undifferentiated carcinoma of the nasopharynx with extension to the skull base bone in May, 1985. He received 2 cycles of neoadjuvant chemotherapy consisting of cisplatin and 5-fluorouracil (FP) regimen, followed by definitive external-beam radiation therapy (70.2 Gy total dose/8 weeks, 1.8 Gy/fraction). After achieving a complete response to initial treatment, he had been lived well with no evidence of disease for approximately 8 years. When he revisited our institution, he had a 3 month history of severe headache, eyeball pain, diplopia, and a limitation of lateral gaze of the right eye. He was pathologically proven to have a recurrent squamous cell carcinoma of the nasopharynx with a disease-free interval of 94 months. The patient was restaged as rT4N0M0, accompanied by cranial nerve signs that invaded the clivus and ipsilateral cavernous sinus. Prior to the salvage re-irradiation, 6 cycles of neoadjuvant chemotherapy with a taxol and ifosfamide regimen were administered, but there was no significant improvement in patient’s symptoms. During the 3-D CRT planning process for re-irradiation, the ipsilateral optic nerve and cavernous sinus were included within the PTV, whereas the optic chiasm and contralateral optic nerve were excluded as much as possible. The beam arrangements for 3-D CRT were composed of a combination of 5 non-coplanar ports. Two 30° wedge filters were added to compensate dose homogeneity within the PTV. Dose statistics and DVHs for the PTV and adjacent critical normal tissues were satisfactory within the tolerance dose limits. Re-irradiation using 3-D CRT was performed using a hyperfractionated schedule, consisted of 1.2 Gy per fraction, twice a day, with interfraction intervals of more than 6 hours, and a total dose of up to 61.2 Gy. The patient tolerated the entire procedure very well, without interruption of the planned treatment schedule. In contrast to the severe acute toxicity observed during the first radiation treatment, the acute mucosal reaction during re-irradiation was negligible. All the subjective symptoms except an intermittent eyeball pain were significantly improved during the radiotherapy. A complete regression of the tumor was also observed on follow-up CT scan (Fig. 4). He is currently alive and well, without any ophthalmologic or neurologic complications 14 months after completion of salvage re-irradiation.

The second patient, a 49-year-old man with undifferentiated carcinoma of the nasopharynx was initially presented with left facial pain and left ear fullness, which had persisted for 6 months. His MRI at the time of initial admission showed an infiltrative mass at the left Rosenmuller fossa, extending to the sphenoid sinus and parapharyngeal space. He was initially staged as T4N0M0 accompanied by the involvement of the maxillary division of the left trigeminal nerve. After initial treatment with concurrent chemoradiotherapy, an FP regimen and a total radiation dose of 74 Gy, he had lived well for 62 months, until a recurrent

Fig. 4. A complete regression of the recurrent tumor mass, which involved the right side cavernous sinus was observed on follow up CT scan (Patient 1).
mass developed at the left lateral wall of the nasopharynx around the posterior choana extending to the sphenoid sinus (rT3N0M0) was detected. Following 4 cycles of the salvage neoadjuvant chemotherapy with a FP regimen, the re-irradiation trial using 3-D CRT was performed, using the BID schedule for the locally recurrent lesion. Five non-coplanar beams, including a vertex port were employed. The dose distributions of PTV for a 3-D CRT plan were closely tailored to the shape of the PTV with relative sparing of the surrounding normal structures. Since the recurrent tumor was localized anteriorly at the left lateral wall of the nasopharynx near the posterior choana, there were no technical difficulties during the 3-D CRT planning. Important critical structures such as the brainstem, spinal cord, temporal lobes, and temporo-mandibular joints were easily spared by using a vertex port. In addition, the radiation doses to the optic chiasm and both optic nerves presented an acceptable range in terms of the dose statistics and DVHs for the 3-D CRT plan. Hyperfractionated radiotherapy of 1.1 Gy per fraction BID was delivered up to 48.4 Gy, and then followed by 1.6 Gy per fraction BID to a total dose of 69.2 Gy. After salvage radiation treatment, all the recurrent lesions disappeared and he has been living well for 20 months after salvage radiotherapy without any radiation-related complications.

The third patient, a 57-year-old man was initially seen with a bulging neck mass, measuring 5 cm × 4 cm at level II of the right lateral neck. His head and neck CT scan revealed an exophytic mass involving the right Rosenmuller fossa and oropharyngeal wall, and an enlarged lymph node correlating to the clinically palpable area. This patient with T2aN1M0 squamous cell carcinoma of the nasopharynx received 70.2 Gy of radiation with conventional fractionation. Follow-up nasopharyngoscopy and CT scan showed complete remission both in the nasopharynx and neck. Unfortunately, however, a small recurrent tumor (rT1N0M0) was discovered at the left lateral wall of the nasopharynx seven months after the first radiotherapy. He underwent salvage re-irradiation employing the same 3-D CRT technique up to a total dose of 60 Gy with the hyperfractionated schedule by 1.2 Gy per fraction BID with the same interfraction intervals. The 3-D CRT plan provided an excellent coverage of target volume with homogeneous dose distribution within the PTV. Additionally, a recurrent lesion of small volume confined to the left lateral wall facilitated the sparing of the critical normal structures during 3-D CRT planning procedure. After achieving a complete remission of the recurrent tumor, he is alive with no evidence of disease after seven months.

The fourth patient, was a 68-year-old man who presented with multiple non-tender palpable mass in the left neck, which was pathologically proven to be undifferentiated carcinoma. Despite an intensive search, the primary site was not identified. After left modified radical neck dissection, he received external-beam radiotherapy to the both neck node areas and possible primary sites including nasopharynx. The involved neck node area received 59.4 Gy, but the subclinical disease area received 50.4 Gy. Eleven months later, a recurrent tumor was found at the nasopharynx extending to the left cavernous sinus. Neurologic examination showed deficits of abducens and oculomotor nerves. 3-D CRT was performed with a combination of 6-field non-coplanar ports. A total dose of 59.4 Gy was delivered in 1.1 Gy per fractions BID. After the salvage re-irradiation using the hyperfractionated 3-D CRT technique, this patient is alive and has been well for 11 months without evidence of re-recurrence or any neurologic complication.

**DISCUSSION**

Improved treatment outcome for locally recurrent nasopharyngeal cancer is usually dependent on various factors, such as early detection of recurrent lesions, histologic subtypes, site of the disease at recurrence, disease-free interval to recurrence, and treatment modalities. Of the various re-treatment options, the role of salvage chemotherapy has not yet been clarified for the treatment of such patients. Although a number of reports have suggested that recurrent or metastatic nasopharyngeal carcinomas are highly responsive to a cisplatinum-based combi-
nation chemotherapy, the prognosis of patients treated by chemotherapy-alone is generally poor due to a high incidence of local recurrence and distant metastasis. On the other hand, this form of surgical salvage has also been used successfully in selected patients with recurrent nasopharyngeal carcinoma in the primary site. Fee et al. and Wei et al. reported that a considerably high rate of local control could be achieved in patients who underwent surgical resection. However, serious complications such as palatal fistulas, osteoradionecrosis of the skull base, and/or bleeding from the internal carotid artery had been frequently observed in the patients involved in both studies. Moreover, some of the patients had required an additional brachytherapy because of inadequate resection margins. In fact, a complete resection of the most recurrent lesions with an acceptable margin is not easy for locally recurrent nasopharyngeal cancers, despite an aggressive and hazardous surgical approach; hence, sterilizing doses of radiotherapy are occasionally required.

Instead of chemotherapy or surgery, salvage re-irradiation has more frequently been successfully applied in these patients. Given the several collective reviews, a higher radiation dose, of more than 60 Gy, has been recommended, even for those patients who were initially treated with doses higher than 70 Gy. Of the numerous re-irradiation techniques described, one of the most commonly used radiotherapeutic technique for recurrent nasopharyngeal carcinoma is intracavitary brachytherapy, in which radioactive sources are afterloaded into a pair of cuffed pediatric endotracheal tubes, a Teflon ball, or a plastic tube, with double lumen, placed in the nasopharyngeal cavity by a transnasal approach. Although this approach is a convenient tool and capable of effectively treating a smaller volume than external-beam radiotherapy, it is of little value in the management of recurrent tumor with intracranial extension beyond the nasopharynx. A more invasive technique, which involves implantation with either gold or seeds is also occasionally adopted. This approach has the benefit of allowing the direct visualization of the tumor volume during the procedure, but it is more invasive than intracavitary brachytherapy, because of the complex anatomy which abounds in the critical structures potentially injured by this procedure. When the base of the skull may be involved or intracranial extensions may be present, retreatment should be primarily by external-beam irradiation rather than by using these brachytherapy techniques.

Recently, radiosurgery utilizing a gamma knife or linear accelerator has been used for the management of recurrent nasopharyngeal carcinoma. Kondziolka and Lunsford explored gamma-knife radiosurgery for a patient with recurrent cancer of Rosenmuller's fossa, in whom significant tumor shrinkage was achieved with no treatment-related morbidity. Buatti et al. also reported 3 patients with locally recurrent nasopharyngeal carcinoma treated with linac-based stereotactic radiosurgery, but with limited success. However, substantial risks of serious neurological complications had resulted in two of three cases, which were probably due to the higher single-dose delivered by stereotactic radiosurgery. Instead of a higher single-fraction dose, Ahn et al. reported recently preliminary results of fractionated stereotactic radiosurgery (FSRT) for three locally recurrent nasopharyngeal carcinomas. In all three patients, the total doses to the recurrent tumors were delivered to 45-50 Gy in 18-20 fractions, with a dose per fraction of 2.5 Gy, in two of these cases concurrent chemotherapy was given. Unfortunately, however, no beneficial effects of FSRT in the treatment of recurrent nasopharyngeal carcinoma was found despite a satisfactory symptomatic improvement, remarkable objective tumor regression, and no neurologic side-effects. The authors speculated that these results could be explained on the basis that it was not easy to completely encompass the full extent of a recurrent cancer with an infiltrative nature by radiosurgery alone, partly due to the complex anatomy, which is surrounded by many critical normal structures, such as the cranial nerves III-VI, optic chiasm, pituitary fossa, and the temporal lobes.

In contrast to stereotactic radiosurgery, our 3-D CRT technique with multiple coplanar and non-coplanar beams is likely to have several advantages for more generously and more precisely encompassing the irregular-shaped target vol-

Moreover, it was found possible to adequately apply to radiation to a recurrent tumor of an irregular shape, regardless of the size of the target volume. Additionally, there are no mechanical limitations dependent upon the extension sites of the tumors. The selection of 3-D CRT as an available treatment modality does not depend on the anatomical site, regardless of the existence of extracranial or intracranial components. Since a 3-D CRT could more easily conform the entire target volumes with the spatial distribution of the radiation dose, allowing a concomitant reduction to critical normal tissues, this approach permit escalation of the radiation dose for the recurrent tumors while decreasing the probability of normal tissue toxicity. We believe this technique may be a promising treatment strategy in the management of these patients.

Apart from a 3-D CRT, we employed a hyperfractionated schedule in an endeavor to minimize the radiation-induced toxicity in the management of patients with locally recurrent nasopharyngeal cancer, who had previously received a high-dose radiotherapy. As is already well known, the basic rationale of hyperfractionation is that the use of small dose fractions allows higher total doses to be administered within the tolerance dose limits of the late-responding normal tissues, and that this translates into a higher biologically effective dose to the tumor. Clinical experiences and laboratory studies have demonstrated that it is possible to increase the tolerance of late responding tissues, more than would be predicted from the fractionation response of acutely responding tissues or tumor cell populations. Although it is still unproven clinically whether or not this approach could reduce the incidence of severe late sequelae, serious late radiation-induced complications were not been observed in any patients who received a re-irradiation dose of 60 Gy, which was delivered on an average with a fraction of 1.1 or 1.2 Gy, with interfraction intervals of more than 6 hours. In addition, all four patients in our study tolerated the treatment well without any interruptions of the treatment schedule.

By combining the hyperfractionated fractionation schedule and the 3-D CRT technique, we attempted to achieve higher rates of local control and to maximally reduce the risk of radiation complications. All four patients are currently alive with quite acceptable treatment-related morbidity during the follow-up periods ranging from 7 to 20 months. None of our patients have experienced any locoregional re-recurrence or distant metastasis. However, we cannot draw definite conclusions at this time because of the limited follow-up. It is clear that our follow-up period is short in consideration of the natural history of locally recurrent nasopharyngeal cancer and the chronologic evolution of late radiation-induced complications. Furthermore, our patients had several favorable prognostic factors. Two of four patients had a long disease-free interval to the recurrence over five years and the one of the remaining two patients experienced an early small volume recurrence. Even though such prognostic factors are closely associated with favorable outcomes, the preliminary results were so encouraging that we believe our approach deserves further development and continued study.

In conclusion, four patients with locally recurrent carcinoma of the nasopharynx were successfully treated with hyperfractionated re-irradiation using the 3-D CRT technique. A higher re-irradiation dose of above 60 Gy could be safely delivered with no serious acute or late radiation-induced complications in patients with local recurrences who were initially treated with doses greater than 70 Gy. However, it is evident that our observations are premature because of the insufficient number of patients and the limited follow-up. Therefore, these results should be confirmed in a larger study and long-term follow-up.

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REFERENCES


30. Zhang YW, Liu TF, Fi CX. Intracavitary radiation
treatment of nasopharyngeal carcinoma by the high
dose rate afterloading technique. Int J Radiat Oncol Biol
31. Vikram B. Permanent iodine-125 implants for recurrent
carcinoma of the nasopharynx: Early results. Endocur-
32. Withers HR, Peters LJ, Thames HD, Fletcher GH.
8:1807-9.
33. Thames HD, Withers HR, Peters LJ, Fletcher GH.
Changes in early and late radiation responses with
altered fractionation: implication for dose-survival