

High Dose 3-Dimensional Re-Irradiation for Locally Recurrent Nasopharyngeal Cancer

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This is to report the results of 3-dimensional (3D) high dose re-irradiation (re-RT) for patients with locally recurrent nasopharyngeal cancer. Between May 1995 and Dec. 2000, 21 patients with locally recurrent cancer of the nasopharynx received high dose 3D re-RT at Samsung Medical Center. The median 55 (45 - 70) Gy was applied by daily fractions of 2.5 Gy or 3.0 Gy. The median survival period, the rates of local control, overall survival and disease-free survival at 5 years, of all patients, were 21 months, 71.8%, 32.3%, and 21.2% respectively. The number of patients who experienced treatment failures at any site was 14 (67.0%): eight patients (38.1%) experienced distant hematogenous metastases; five patients (23.8%) experienced recurrences within the current re-RT treatment volume; and seven patients (33.0%) had recurrences outside this volume. Five patients (23.8%) experienced severe late radiation-induced complications of RTOG grade IV or V, and these were brainstem necrosis (2), temporal lobe necrosis (1), mucosal necrosis (1), and massive epistaxis (1). For locally recurrent nasopharyngeal cancer patients, high dose 3D re-RT could lead to improved results when compared with the historic data by conventional re-RT techniques. Further treatment refinements, that would be necessary, may include optimization in patient selection, improvement in target localization and patient immobilization, and the addition of systemic agents, either as a radiation sensitizer or a radiation protector.

Key Words: 3-dimension, re-irradiation, recurrence, nasopharyngeal cancer

INTRODUCTION

Nasopharyngeal cancer is usually radiosensitive and a high rate of local control can be achieved by high dose radiation therapy (RT). Even though there has been a positive dose-response relationship, loco-regional failures, however, occur in 10-50% (median 34%) of the patients following curative RT.¹ The prognosis after loco-regional recurrence with no treatment is usually very poor.^{1,2} Salvage neck dissection is usually the preferred treatment for isolated, persistent or recurrent disease in the cervical lymphatics. A surgical approach, however, is usually difficult to perform for recurrent disease at the primary site. High dose re-irradiation (re-RT) for a local recurrence appears to be most effective, especially in patients with longer disease-free intervals.^{3,4} The anatomical proximity of recurrent lesions to the surrounding normal structures has prohibited a meaningful dose escalation when using conventional 2-dimensional (2D) RT techniques.⁵ The organs at risk in high dose re-RT usually include the optic apparatus, the brainstem, the spinal cord, the pituitary gland, the temporal lobes, the temporo-mandibular joints and the parotid glands. Delivery of a high radiation dose, solely by conventional 2D techniques, used to lead to limited success and significantly higher rates of severe neural complications. Newer techniques of 3-dimensional (3D) RT are regarded as the promising alternative to conventional techniques, with improved therapeutic ratio for patients with locally recurrent cancer of the nasopharynx. Our experience of high dose re-RT, using a fractionated stereotactic radiation therapy (FSRT) technique for the first three patients with local recur-

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rence, has already been reported.⁶ This paper is to report our expanded experience, using either FSRT or 3-D conformal radiation therapy (CRT), in 21 patients with locally recurrent nasopharyngeal cancer.

MATERIALS AND METHODS

Between May 1995 and Dec. 2000, 21 patients with locally recurrent cancer of the nasopharynx received high dose 3D re-RT at Samsung Medical Center. 4 MV X-rays from a linear accelerator were used and the beam arrangements were so determined, that each beam adequately covered the target while minimizing the inclusion of normal structures throughout its path. Eighteen patients received FSRT, which can be summarized as multiple, non-coplanar, arc rotations of circular cones, focused on the isocenter using XKnife-3[®]. For an irregularly shaped target which was close to critical neural structures, beam shaping by the "ball-in-ball" technique and independent jaw closure was used to deliver an improved radiation dose profile around the target.⁷ The three most recent patients received 3-D CRT with multiple, non-coplanar, static shaped beams using the Prowess[®] radiotherapy planning system.

The follow-up periods were measured from the first day of the current re-RT. The rates of local control, overall survival, and disease-free survival were calculated using the Kaplan-Meier method. Possible prognostic factors that might have influenced the rates of local control, overall survival, and disease-free survival were subjected to univariate analyses by log rank test. These factors were; the gender, the age, the initial T stage, the histologic type of cancer, the patients' performance status, the recurrent T stage, the extent of disease, the disease-free interval from the patients first RT and the cumulative radiation dose in BED conversion. The shortest distances between the margins of the target volume and the nearest neural structure, were measured on the RT planning system which is based on CT images, and the significance on the occurrence of neural complications was analyzed.

RESULTS

Fourteen patients (66.7%) were male and seven were female (33.3%). Their ages ranged from 29 to 69 years and the median age was 54 years. The histologic types of cancer were undifferentiated carcinoma (WHO type III) in twelve patients (57.1%) and squamous cell carcinoma (WHO type I) in nine patients (42.9%). The clinical target volume ranged from 5.9 to 80 (median 30) cc. The initial stages, according to the 1997 AJCC staging system,⁸ were Stage II in seven (33.3%), Stage III in six (28.6%), Stage IV in six (28.6%), and unknown in two patients (9.5%). Cisplatin-based chemotherapy was added to the first RT in 13 patients (61.9%), of whom eight received sequential chemotherapy and RT while five received concurrent chemoradiotherapy. The total dose of the first RT ranged from 37.8 to 76.0 (median 70.2) Gy. The dose per fraction was mainly 1.8 Gy. The extent of the recurrence was confined to a single site only, in 15 patients (71.4%) and more than one site in six patients (28.6%). The anatomical structures harboring the recurrence, in the patients with a single site recurrence, were the nasopharynx in 14 patients and the retropharyngeal lymph node in one patient, while those structures in the patients with more than one site recurrence were, local + regional in five patients and local + distant in one patient. The T stages at the recurrence were rT0 in one (4.8%), rT1 in two (9.5%), rT2 in seven (33.3%), rT3 in four (19.0%), and rT4 in seven patients (33.3%) (Table 1).

In 16 patients (76.2%), the current re-RT was their second RT and in five patients (23.8%) it was their third RT. The median disease-free interval from the first RT till the current re-RT in all patients was 28 (5-68) months and that from the second RT till the current re-RT in five patients was 12 (2-39) months. The dose per fraction of the current re-RT was 2.5 Gy in 15 patients (71.4%) and 3.0 Gy in six patients (28.6%). The fractionation schedule was to give once daily treatments for 5 days per week, with the total dose actually delivered being 45-70 (median 55) Gy. The fraction size and the total dose were determined on an individual basis considering the extent, size, and location of the recurrent lesions, as well as the aim of the current re-RT. The median biological

Table 1. Patient Profiles

Characteristics	Number of patients (%)
Age (years)	29 - 69 (median 54)
Sex	
Male	14 (66.7)
Female	7 (33.3)
Histology	
Undifferentiated carcinoma	12 (57.1)
Squamous cell carcinoma	9 (42.9)
Initial treatment	
Sequential chemotherapy+RT	8 (38.1)
Concurrent chemo-RT	5 (23.8)
RT alone	8 (38.1)
T stage at recurrence	
rT0	1 (4.8)
rT1	2 (9.6)
rT2	7 (33.3)
rT3	4 (19.0)
rT4	7 (33.3)
Disease extent at recurrence	
Single site only	15 (71.4)
More than one site	6 (28.6)

effective dose (BED) of the current re-RT for the early responding tissues (assuming α/β ratio=10) and the late responding tissues (assuming α/β ratio=3) was 70 (56 - 88) Gy and 108 (83 - 128) Gy respectively. The median cumulative BED for the early and late responding tissues of 16 patients, receiving the current re-RT as their 2nd RT, was 155 (107 - 172) Gy and 225 (152.0 - 243) Gy respectively, while that of five 5 patients receiving the current re-RT as their 3rd RT was 208 (175 - 244) Gy and 308 (244 - 354) Gy respectively.

The median follow-up period was 49 (11 - 85) months. Twelve patients (57.1%) died during the follow-up period: nine (42.9%) died from either local or distant disease progressions; two (9.5%) died from radiation-related neural complications at 7 and 11 months following the current re-RT; and one (4.7%) died of sudden massive epistaxis at 3 months following the current re-RT, without definite evidence of disease progression.

The number of patients who experienced treatment failures at any site was 14 (67.0%) (Fig. 1). Eight patients (38.1%) experienced distant hematogenous metastases, seven patients (33.0%) had recurrences outside the current re-RT treatment

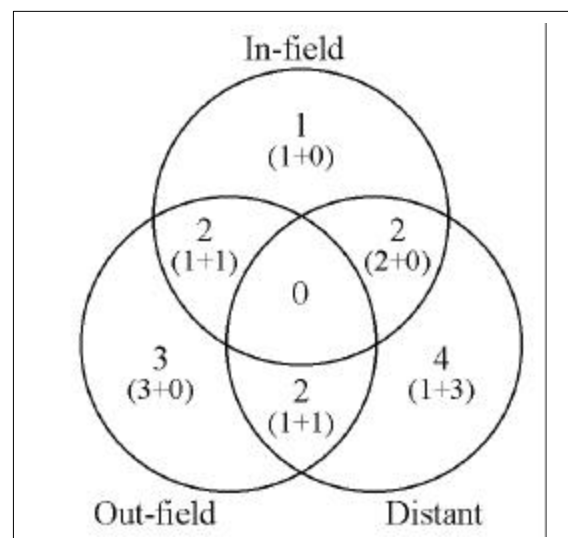


Fig. 1. Schematic diagram showing the patterns of failures after re-RT for locally recurrent nasopharyngeal cancer. The numbers in parentheses are the numbers of failures among those patients with a single site recurrence only, + with more than one site recurrence.

volume and five patients (23.8%) developed recurrences within the treatment volume. Local in-field recurrences were apparently more common in

those patients with single site recurrence only, than those patients with recurrences at more than one site (26.7% vs. 16.7%, $p=0.552$). To the contrary, the out of treatment-field disease progressions, including regional and distant failures, were apparently more frequent in patients with recurrences at more than one site, than in those with single site recurrence only (83.3% vs. 40.0%, $p=0.094$). The median survival period, the rates of local control, overall survival and disease-free survival at 5 years, of all patients, were 21 months, 71.8%, 32.3%, and 21.2% respectively (Fig. 2). The median survival period was significantly prolonged in those patients with single site recurrence only, compared to those with recurrences in more than one site (24 vs. 14 months, $p<0.0001$). Neither the BED's of the current re-RT, nor the cumulative BED's, were significant determinants with respect to the rates of local control, overall survival, disease-free survival, or the risk of severe neural complications. The local control rate of the undifferentiated carcinoma type was significantly better than that of the squamous cell carcinoma type (87.5% vs. 53.3%, $p<0.05$) (Fig. 3). There was no prognostic factor that significantly influenced the overall survival rate. The disease-free survival rate of the undifferentiated carcinoma histology was significantly better than that of the squamous cell carcinoma histology ($p<0.01$), while the disease-free survival rate of the patients with single site recurrence only was significantly better than that of those with recurrences at more than one site ($p<0.0001$) (Fig. 4).

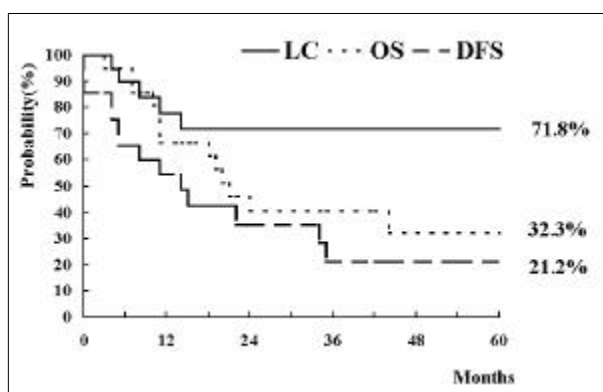


Fig. 2. Local control rates, overall survival, and disease-free survival at 5 years by high dose 3D re-RT were 71.8%, 32.3%, and 21.2% respectively.

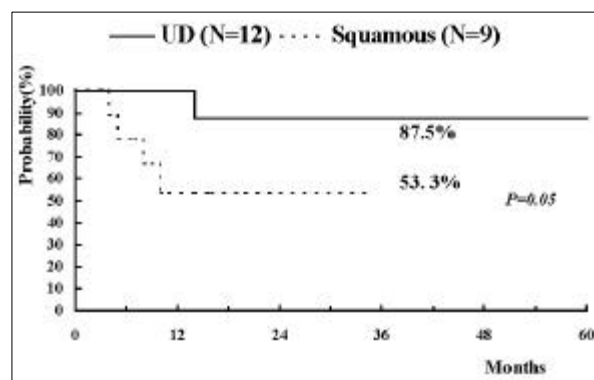


Fig. 3. The local control rate in those patients with undifferentiated carcinoma was significantly better than that in those with squamous cell carcinoma.

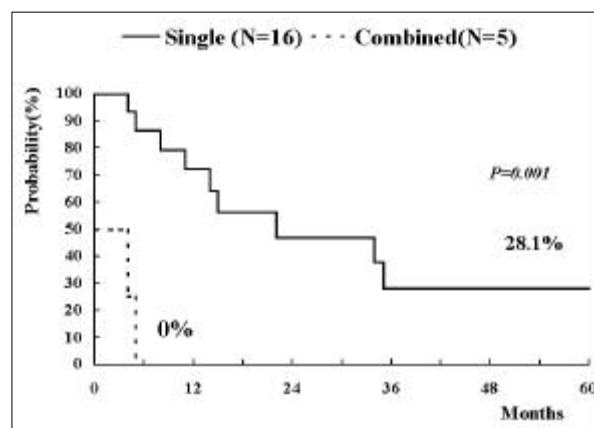


Fig. 4. The disease-free survival rate of the patients with a single site recurrence only, was significantly better than that of those with more than one site recurrence.

Even though most patients experienced moderate to severe, local mucositis adjacent to the target volume, there was no incidence of an unplanned treatment break during the RT courses. There were, however, five patients (23.8%) who experienced severe late radiation-induced complications of RTOG grade IV or V, occurring at 3-35 (median 7) months after the current re-RT. Two grade IV complications were brainstem necrosis and mucosal necrosis. Three fatal, grade V complications were, massive epistaxis, temporal lobe necrosis and brainstem necrosis occurring at 3, 7, and 11 months post treatment, respectively. The shortest distances between the margins of the target volume and the nearest neural structure, were relatively smaller in those patients who

experienced severe neural complications than in those who didn't (6.0 ± 6.0 mm vs. 17.4 ± 7.16 mm), but the difference was not statistically significant. Three of nine patients, in whom this distance was smaller than or equal to 15 mm, developed grade IV or V neural complications, while none among 12 patients, in whom the distance was greater than 15 mm, developed such complications ($p=0.063$).

DISCUSSION

RT has been the most important treatment modality for the management of nasopharyngeal cancer. In the past two decades, many reported improved treatment results using RT. There are several factors that might have contributed to these improvements. Increased accuracy in diagnosis and staging have enabled early detection, early treatment and the selection of patients with better prognoses for curative RT. Improvements in RT planning based on CT images and the subsequently better dose distribution, availability of mega-voltage RT equipment and the use of chemotherapy for radiation sensitization have also contributed to the better results. Local control rates, in general, varied depending on the T stages, which are in the ranges of 71 - 93% for T1-2 and 40 - 68% for T3 - 4 lesions.⁹⁻¹¹ Local control rates, using the conventional RT techniques, especially in locally advanced stage nasopharyngeal cancer, however, were far from satisfactory. About one-third of the patients, on average, still suffered from local failure. The treatment options for local recurrence included surgery, chemotherapy and re-RT.

Surgery has been employed in some selected patients with local recurrence.^{12,13} A variety of surgical techniques have been described and used, these include the transpalatal, transmaxillary, transcervical, and the transcervico-mandibulopalatal approaches. Surgery, however, usually resulted in surgical mortality or substantial functional disability post operatively with limited success in respect to long-term survival. Therefore, surgery should be cautiously limited to those patients with rather small and superficial recurrences and should be performed by highly expe-

rienced surgeons.

The efficacy of chemotherapy for recurrent nasopharyngeal cancer, either as a sole treatment or in combination with RT, has usually been disappointing. The survival outcomes after the most potent cisplatin-based combination chemotherapy alone were extremely poor, although the objective responses were apparently favorable.¹⁴ These poor results with chemotherapy alone might well have been anticipated by the patient selection bias, where those with far advanced lesions and more likelihood of harboring chemotherapy-resistant clones, tended to receive chemotherapy alone. The role of chemotherapy should be further investigated, considering the high incidence of local as well as distant failures following local treatment modality alone.

Brachytherapy alone, or in combination with external beam RT, was used for small and superficial lesions with some degree of success.^{4,15} The use of this modality, however, for the more advanced lesions that not infrequently involve the deep tissues and the skull base, may evidently be inadequate, considering the rather short radiation range. Although re-RT has been accepted as the most optimal modality for local recurrence, the salvage results of the conventional RT techniques have remained usually disappointing, where the long-term rates of local control and survival ranged between 15.2 - 40% and 7.6 - 45%^{1,2,16-22} There are a few factors that might have contributed to the suboptimal outcomes by re-RT. First, the recurrent tumors may be composed of more cells that are inherently radiation resistant than radiation-naïve tumors. Second, less aggressive attitudes, with respect to the re-RT, might have been taken in the past. It has been speculated that lower levels of diagnostic accuracy, for the patients with recurrence, could have resulted in inaccuracies of tumor localization and inadvertent geographic misses in RT targeting.²³ It is also likely that less sophisticated RT techniques were employed for the convenience of the health care providers and a lower total dose than could achieve adequate local control rates was delivered, in fear of the possibility of disabling complications subsequently.

There are, however, several reports on the increase in survival and local control rates by

increasing the re-RT dose.^{2,4,19,20} Lee et al.²⁰ reported that the risk of local failure decreased with the increase of the BED of re-RT, while Wang et al.⁴ reported that patients receiving re-RT doses higher than 60 Gy showed a significantly better 5-year survival rate than those receiving doses lower than 60 Gy (45% vs. 0%, $p=0.0001$). The major limitation of re-RT by conventional techniques is the risk of severe normal tissue complications, as the recurrent lesions in the nasopharynx are usually infiltrative in nature and surrounded by several radiation sensitive structures such as the optic apparatus, the cranial nerves III-VI, the brainstem, the temporal lobe and the pituitary fossa. The application of the 3D RT techniques has the advantage of delivering a higher and more focal radiation dose, that conforms to the target shape, than conventional 2D techniques.

Higher rates of local control and survival were achieved by employing more aggressive and higher radiation dose through FSRT and 3D CRT techniques than the previously reported series.^{1,2,16-22} Based on the authors' observations, histologic type of squamous cell carcinoma was a significantly adverse prognostic factor with respect to the rates of local control and disease-free survival. Pryzant et al.¹⁹ also reported a significantly better survival in those patients with lymphoepithelioma than in those with squamous cell carcinoma. The usual proportion of squamous cell carcinoma histology, at the time of the initial diagnosis, is much lower than that of undifferentiated carcinoma histology.²⁴ The fact that the proportion of squamous cell carcinoma patients in our series was 42.9%, which was almost twice as many as in the initial presentation, might indirectly suggest that this histologic type is more subject to local recurrence than the undifferentiated carcinoma. Moreover, even after the uniformly high dose re-RT as in our series, the fact that the squamous cell carcinoma histology was a significantly adverse prognostic indicator of local control, again might reflect that radiation resistance was more common in squamous cell carcinoma than in undifferentiated carcinoma.

The disease extent at the time of recurrence was also a significant prognostic factor for local control

and survival. The patients with limited disease, which was confined to the nasopharynx, showed better local control and survival results than those with advanced disease.^{4,15,20-23} In our series, the occurrence of distant metastases was apparently more common in those patients with recurrences in more than one site than in those patients with a single site recurrence only. It may be natural to reason that the patients with more advanced lesions may have a higher risk of distant metastases than those with a less primary tumor burden.

The incidence of severe complication after conventional 2D re-RT techniques ranged from 6% to 34%, those risks were usually proportional to the total cumulative dose, the dose per fraction and the cumulative BED.^{19,20,25} In the present series, the cumulative total dose and the cumulative BED were more or less uniform in all patients and did not show any significant influence with respect to the occurrence of severe complications. This lack of influence may stem from the fact that irradiation of neural structures using the 3D RT techniques was intentionally avoided. The distance between the target and neural tissue, however, was suspected as an important determinant of the risk of neural complications. It may be necessary to pay more attention to further reduction of the dose to neural structures, when they are very close to the target lesions, even when using the 3D RT techniques.

In summary, the authors employed high dose re-RT by 3D techniques for patients with locally recurrent cancer of the nasopharynx and could achieve improved outcomes when compared with the previously reported data. The innate radiation resistance of some cancer types, is suspected to be an important factor with respect to local control. More attention needs to be paid to the procedure, when the distance between the target and the neural structure is very small to reduce the risk of severe neural complications. Further treatment refinements that may be necessary would include, the optimization in the patient selection, the improvement in target localization and patient immobilization and the addition of systemic agents, either as a radiation sensitizer or a radiation protector.

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