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Stereotactic Reirradiation of Recurrent Nasopharyngeal Carcinoma Using Robotic Stereotactic Body Radiotherapy System: Preliminary Results

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ABSTRACT

Local recurrence of nasopharyngeal carcinoma (NPC) represents a major cause of mortality and morbidity with or without systemic illness. Fractionated Stereotactic radiotherapy (FSRT) is an option for salvage treatment. This study reviewed the treatment outcomes of recurrent NPC in terms of efficacy and toxicity.

Between February 2009 and December 2009, 12 patients (8 men and 4 women), median age at diagnosis was 49, (range 18-69) with biopsy proven (10 of 12 patients) locally recurrent NPC were treated using FSRT with CyberKnife (Accuray Inc. Sunnyvale, CA). Median prescribed dose was 25 Gy (range 24-30) delivered to median 75% isodose line (range 70%-80%) in 5 to 6 fractions. GTVs were delineated using PET-CT images in 5 patients and MRI in 7 patients (median GTV 29.4 ml, range 4.9-78.7). Median follow-up was 11.5 months (range 6-18).

Complete response rate after FSRT was 66.7% (8 patients), partial response rate was 33.3% (4 patients). One-year local failure-free survival (LFFS) and overall survival rates were 85% and 75% respectively (2 patients with complete response after FSRT developed local relapse, 4 patients died; the reason for death was disease progression in other sites in 3 patients and treatment related complication in 1 patient). Treatment related grade 3 or more toxicity was observed in 5 patients (33% early and 9% late, total 42.3%).

Our preliminary results provided acceptable outcomes with FSRT as a salvage treatment of NPC with regard to early response rate and toxicity.

Keywords: Stereotactic radiotherapy, Recurrent nasopharyngeal carcinomas, Robotic stereotactic body radiotherapy

ÖZET

Tekrarlamış Nazofarenks Karsinomlarının, Robotik Stereotaktik Radyoterapi Sistemi Kullanılarak İkincil Işınlanması: Ön Sonuçlar

Beraberinde sistemik hastalık olsun olmasın, nazofarenks karsinomlarının (NFK) lokal nüksü önemli bir mortalite ve morbidite sebebidir. Fraksiyone stereotaktik radyoterapi (FSRT) salvaj tedavi için bir seçenektir. Bu çalışma ile, nüks NFK'nin tedavi sonuçları etkinlik ve toksisite açısından değerlendirilmiştir.

Şubat 2009 ile Aralık 2009 arasında 10 tanesi biopsi ile konfirme edilmiş lokal olarak nüksetmiş NFK'lu 12 hasta (8 erkek, 4 kadın; tanı anındaki yaş aralığı 18-69, ortanca 49) Cyberknife (Accuray Inc. Sunnyvale, CA) kullanılarak FSRT ile tedavi edildi. Hastalar, 5-6 fraksiyonda, ortanca 25 Gy (24-30) ışınlandı (%70-%80'lik isodoz). Gros tümör volümü (GTV) 5 hastada Pozitron emisyon tomografi/ Bilgisayarlı tomografi (PET/BT), 7 hastada Magnetik rezonans görüntüleme (MRG) görüntüleri kullanılarak belirlendi (Ortanca GTV volümü 29.4 ml, 4.9-78.7 ml arası). Ortanca takip süresi 11.5 ay (6-18 ay).

FSRT sonrasında tam cevap oranı %66.7 (8 hasta), kısmi cevap oranı %33.3'dü (4 hasta). Bir yıllık lokal hastalıksız sağkalım ve genel sağkalım sırasıyla %85 ve %75'di (FSRT sonrasında komplet cevap veren 2 hastada lokal nüks gelişti, 4 hasta öldü; ölüm sebebi 1 hastada tedavi ile ilişkili komplikasyon diğerlerinde hastalık progresyonuydu). Tedaviye bağlı 3. derece ve üzerinde komplikasyon 5 hastada gözlendi (%33 erken, %9 geç toksisite toplam %42.3).

Bu çalışmanın ön sonuçları, FSRT'nin NFK'nin salvaj tedavisinde erken cevap oranı ve toksisite açısından kabul edilebilir olduğunu gösterdi.

Anahtar Kelimeler: Stereotaktik radyoterapi, Tekrarlamış nazofarenks karsinomu, Robotik stereotaktik radyoterapi

INTRODUCTION

Nasopharynx is one of the most difficult regions where surgery is challenging, because of its relationship to base of skull and nearby critical structures.[1] Primary treatment of nasopharyngeal carcinoma (NPC) is radiation therapy or concomitant chemo-radiotherapy (CRT).[2-4] Local recurrence rates after primary treatment is 8-58% in 5 years.[2,5] Because of the difficulty and unsatisfactory results of salvage surgery[6], and low response rates with systemic chemotherapy[3,4], re-irradiation has become main palliative and curative choice in recurrent NPC.[7-15].

Historically re-irradiation evolved from two dimensional narrow portals to brachytherapy of nasopharynx[7,8], three dimensional conformal radiotherapy (3DCRT)[9,10], intensity modulated radiotherapy (IMRT)[11,12], and stereotactic radiosurgery (SRS).[13-15]. Today with the help of new technological equipments, it is possible to re-irradiate locally recurrent NPC with fractionated Stereotactic radio surgery (FSRT), without exceeding critical organ tolerance doses.[16-25]. Before Cyberknife, Stereotactic radiosurgery of the NPC has been performing with linear accelerator based systems and Gamma knife.[15] SRS with Gamma Knife is available among the cancers which are limited to base of skull, where cranium should be stabilized with a metallic frame. It is an invasive procedure for patients and needs extra working time for health workers. On the other hand, transportation to the hospital for fractionated therapy is hard for the patient who is carrying a heavy metallic frame. Cyberknife, frame-less SRS system (Accuray Inc. Sunnyvale, CA) is a miniaturized 6-MV linear accelerator which has an ability of moving robotically in six different spatial axis. System has capable of doing isosentric and nonisosentric treatment and real time image tracking. Spatial mechanic precision for robot is 0.12 mm and all 3-D treatment precision is between 0.4-1 mm.

METHODS AND MATERIALS

Twelve locally recurrent nasopharyngeal carcinoma patients (8 men, 4 women) who were reirradiated using FSRT with Cyberknife (Accuray Inc. Sunnyvale, CA) at Ankara Oncology Hospital between February 2009 and December 2009 were retrospectively reviewed. All patients had been previously treated either with radiation (RT), or cisplatin based chemoradiation (CRT) for curative-intent. One of the patients had also been treated with conformal radiation for the second local recurrence. The time interval between the first diagnosis and the recurrence was 11-168 months, with a median of 41 and the start of FSRT ranged from 0.5 months to 10 months, with a median of 3 months. Almost all recurrences were pathologically confirmed by biopsy except two which were accompanied with obvious distant metastatic lesions seen on positron emission tomog-

Table 1. Patient characteristics

Properties	**Number** Median (Range)
Female: Male	4 : 8
Age	51 (25-71)
Previous-Rxt (Gy)	70 (66-71.4)
Previous-CRT-and/or-CT	
Yes: No	9 : 3
RT-recurrence interval(year)	3 : 1-16
Original-T-stage	
T1 : T2 : T3 : T4	2 : 4 : 4 : 2
Original-N-stage	
N0 : N1 : N2 : N3	2 : 4 : 4 : 2
Times of recurrence	
1. recurrence: 2.reccurence	11 : 1
Re-treatment T stage	
rT1 : rT2 : rT3 : rT4	2 : 4 : 4 : 2
Re-treatment distant metastasis	
Yes : No	3: 9
Re-treatment neck involvement	
Yes: No	2 : 10
Re-treatment lung metastasis	2
Re-treatment bone metastasis	1
Pathology	
Undifferentiated carcinoma	5
Keratinizing carcinoma	5
Malign mesenchymal carcinoma	1
Adenoid cystic carcinoma	1
SRC-concomitant CT	1

raphy/computed tomography (PET/CT). At the time of FSRT, 4 patients had already have systemic disease who needed palliation at the nasopharyngeal site. Recurrent lesions were restaged according to the 2002 (6th) American Joint Committee on Cancer Stage Classification (AJCC). Patients characteristics are summarized in Table 1.

Table 2. FSRC Physics Planning Characteristics

Characteristics	**Number** Median (Range)
Prescribed total dose (Gy)	25 (23.94-30)
Times of fraction	
5 : 6	11: 1
Type of optimization	
Sequential: iterative	11: 1
Type of collimation	
Iris: Fixed	11 : 1
Treatment duration/fraction (min)	49 (27.5-62.8)
GTV (ml)	29.4 (4.89-78.7)
Prescribed isodose (%)	75 (70-80)
Coverage of GTV (%)	98.27 (95.6-99.85)
Indexes	
Conformality Index (CI)	1.75 (1.3-1.9)
New Conformality Index (NCI)	1.79 (1.3-1.8)
Homogeneity Index (HI)	1.32 (1.2-1.4)

GTV: Gross Tumor Volume
CI; PIV/TIV, nCI; $PIV(TV)/(TIV)^2$, HI; $D_{max}(\%100)/(Rx\ Dose)$,
Coverage; TIV/TV, PIV; Prescription Isodose Volume
TIV: Target Isodose Volume TV: Tumor Volume

Before taking planning CT images, thermoplastic head and neck immobilization devices and knee support pads were applied. Gross tumor and critical organ volumes were defined according to the fused images of planning CT with PET and magnetic resonance imaging (MRI) (Figure 1). Gross tumor volumes (GTVs) ranged from 4.9 to 78.7 ml (median 29.4 ml) and planning target volumes (PTVs) were obtained by adding a 1 mm margin to GTV as appropriate. The planning and delivery of FSRT were performed using sequential/iterative optimization, and '6-D Skull Tracking' method. Treatment plans were composed of three different size collimator in one patient and 'Iris' which is a variable collimator in 11 patients. Planning and treatment parameters are summarized in Table 2.

Prescribed doses of 24 to 30 Gy (median:25.5 Gy) with a coverage of 95.6% to 99.8% in 75% to 80% isodose lines were applied to PTV. FSRT was perfor-

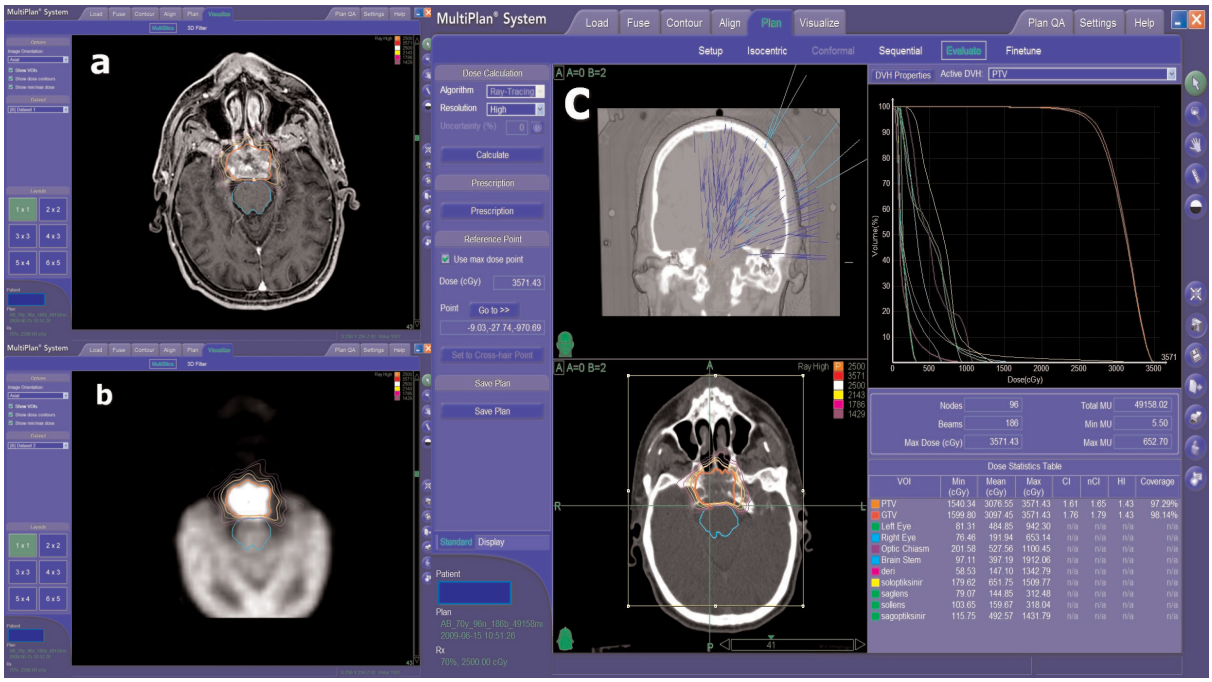

Figure 1. Planning image of recurrent NFC which is done by sequential method. Triple fusion. **a)** MRI. **b)** FDG-PET. **c)** Planning overview screen showing beam paths, DVH and isodose lines.

med in 5 to 6 fractions (median 5) which was completed in 5 to 9 days (median 7). Because, almost all patients were treated with 2D techniques previously, doses of first radiation to the critical organs were not known exactly. So, critical organ doses of FSRT were tried to keep as low as possible. Critical organ doses are listed in Table 3.

Patients were evaluated every 3 months with physical examination, fiberoptic nasopharyngoscopy and radiological imaging (PET/CT and/or MRI) (Figure 2). Tumor response was assessed by using 'New Response Evaluation Criteria in Solid Tumors' (RECİST1.1).[27] Local failure was defined as an increase in tumor size in partial responders or new lesion in or around the radiation field in complete responders. Early and late side effects were defined by using Radiation Therapy Oncology Group (RTOG) toxicity grading system.

Early response rate, local failure free survival and overall survival were the final endpoints of this study in order to determine efficacy FSRT using Cyberknife. All statistical analysis was performed using SPSS, version 13.0 (SPSS, Inc., Chicago, IL, USA). Survival analysis was based on Kaplan-Meier curve.

RESULTS

Response evaluation was done at first follow-up according to initial diagnostic scans (PET/CT or MRI) and nasopharyngoscopic biopsies. Based on these procedures; 8 patients (66.7%) were assessed as complete response (CR) and 4 patients (33.3%) were assessed as partial response (PR). The follow-up duration ranged from 6 to 18 months (median 11.5 months). By the time of analysis, 4 patients died and 2 patients who initialy achieved complete response developed recurrence. One of the recurrent patients died 11 months after FSRT as a result of treatment-related complication and the other one is still alive at 15 months follow-up The cause of mortality was systemic disease in 3 cohort and grade 5 mucositis in one. One-year local failure-free survival (LFFS) and overall survival rates were 85% and 75% respectively.

FSRT was well-tolerated by all patients. Satisfactory palliation was obtained in metastatic patients. Treatment related grade 3 or more acute toxicity was observed in 4 patients (33%). Two of them had grade 3 mucositis, severe dysphagia and malnutrition and required hospitalization for a short period (4-7 days). One of them had hearing loss and another had facial

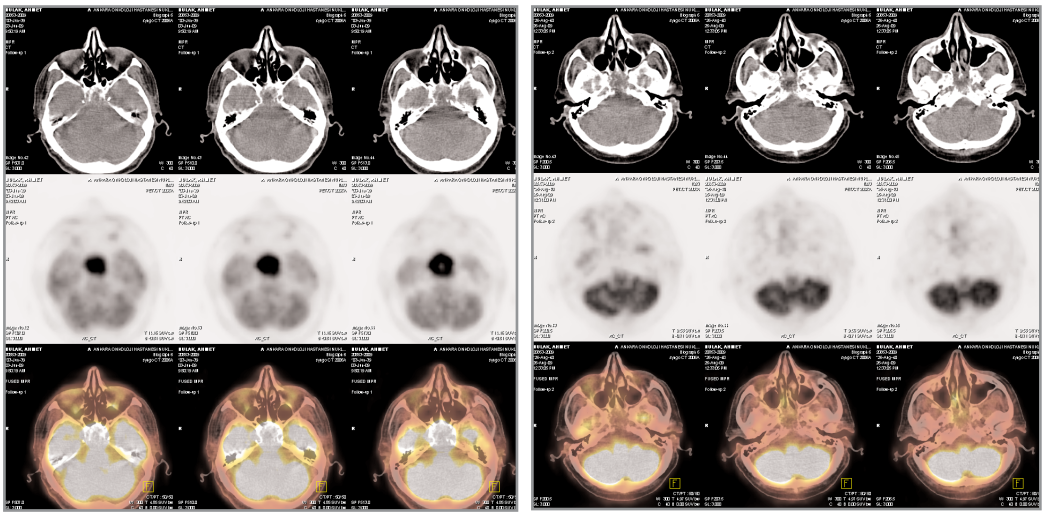

Figure 2. Imaging of FDC-PET/CT with NFC before treatment (left side), 2 months after treatment (right side)

paralysis. Severe late radiation toxicity (grade 5) was observed in one patient. He had oropharyngeal ulceration complicated by infection which could not be controlled with medical therapies and leading him to death. No other late complications (temporal lobe necrosis, massive hemorrhage in the carotid artery, etc.) were noted during follow-up.

DISCUSSION

Despite radical irradiation, local recurrence remains a major problem for patients with NPC. The reported incidence varies from 8 to 58%, with the median at 34%.[1,2,5] Local failure may be due to the intrinsic radioresistance of the primary tumor, insufficient dose, or a geographic miss during the initial radiotherapy.[1,2,5,25,27] Early detection of recurrence is of great importance, because the outcome of salvage treatment varies with the extensiveness of local disease.[19] Recent studies indicate that 18-flouro-2-deoxyglucose (FDG)- PET is more accurate in detecting local recurrence after curative radiation or chemoradiation than MRI.[29] In a retrospectively evaluated 891 patients with recurrent NPC, the patterns of failure was local alone in 70%, local/regional in 25% and distant metastasis in 8%.[2]

Table 3. Critical organ doses

Critical Organ	**Median** Median (Range) (cGy)	**Maximum Point Doses** Median (Range) (cGy)
Chiasm	354 (183-818)	557 (391-1338)
Skull base	374 (185-721)	883 (596-1912)
Left eye	189 (66-484)	426 (315-942)
Right eye	192 (56-452)	560 (301-932)
Left optic nerve	439 (315-723)	784 (889-1213)
Right optic nerve	492 (55-794)	801 (123-1772)
Left lens	97 (28-129)	180 (30-345)
Right lens	139 (28-225)	294 (35-545)

In historical series, external reirradiation with curative intent is often ineffective owing to insufficient imaging modalities and inadequate radiotherapy techniques. Besides reported different kinds of toxicities ranging from 6% to 85%, the outcome is poor, with a 5-year survival rate of 8-36%, and local control rate of 19-38%.[2]

Conventional external beam RT delivered in 2-D technique yields a higher complication rate than 3-D conformal RT or intensity-modulated radiation therapy (IMRT). The rate of severe complications observed in conventional group were 23%, but only 9% in conformal RT group. With conventional RT, 14% of patients were found to have brain necrosis, and no brain necrosis occurred in conformal RT group.[9] Late toxicities are still common after IMRT but generally milder than conventional RT.[13]

SRS is a highly precise form of radiation therapy, which necessitate accurate delineation of tumoral volume with guidance of MRI and PET/CT. There are several series emphasizing the role of (SRS) in the treatment of recurrent NPC.[13-15] Reports from these series have proven satisfactory local control but high rates of severe late toxicity.[8,14] FSRT is a modification of SRS, which has the same mechanical precision with the radiobiological advantage of fractionation especially in advanced T stages when larger tumor volumes located at nearby critical structures are of concern.

Chua et al. retrospectively reviewed the records of 125 NPC patients who received salvage stereotactic radiation. He used a matched-pair design to select patients with similar prognostic factors who received stereotactic re-irradiation using single fraction (SRS) or multiple fractions (SRM). Median dose was 12.5 Gy in single fraction by SRS, and 34 Gy in 2-6 fractions by SRM. Local control rate was better in SRM group although overall survival rates were similar. Incidence of severe late complications was 33% in SRS group vs. 21% in SRM group, including brain necrosis (16% vs. 12%) and hemorrhage (5% vs.2%).[12,13]

Another article that was published by To-Waı Leung et al.[20] whose claimed that it was necessary above the 55 Gy total equivalent dose (TED) (which was calculated by the linear quadratic formula, α/β= 10 Gy) to get local control with acceptable complication rates. In their study, they reported 8 grade 3-4 complications; 2 patients with lethal massive hemorrhage in the nasopharynx which occurred at 9 months after FSRT and 3 patients with brain stem necrosis which was confirmed by MRI at 5,10 and 15 months, 3 patients with temporal lobe necrosis at 5-63 months after completion of FSRT.

Wu et al. reported the outcomes of 56 recurrent NPC patients treated with FSRT. The median FSRT dose was 48 Gy in 6 fractions. Complete response rate was 63%, and 3-year LFFS was 75%. Multivariate analysis showed that large tumor volume were independent factor that predicted poorer disease-specific survival. Severe late complications (massive hemorrhage and necrosis at the nasopharyngeal site, brain stem necrosis etc.) were observed in 25% of patients.[16]

Seo et al., reported a series of 35 patients with locally recurrent NPC treated using FSRT with Cyberknife. The prescribed dose ranged from 24 to 45 Gy in 3 or 5 fractions. Gross tumor volumes ranged from 2.6 to 64.0 ml (median, 7.9 ml). Of all patients, 72% achieved complete response. LFFS was 79% and OS was 60% at 5 years. Severe late toxicities which was accepted as grade 4 or grade 5 were seen in 16% of patients.[19]

This study also used FSRT with Cyberkife. The precision of Cyberknife can facilitate delivery of higher doses resulting better tumor control without an increase in normal tissue toxicity. The flexibility for non-isocentric beam delivery allows optimal dose conformity without compromising dose homogeneity despite irregularly shaped lesions.[17] In our study, we applied 5 times 5 Gy to a median 29.4 ml GTV volume on consecutive days. But generally a weekend separated fraction schedules and the total treatment time prolonged by 2 days (total treatment time; median; 7 days). Our TED was calculated by the linear quadratic formula as 30.2 Gy (α/β= 10 Gy) and the value was well below the 55 Gy TED which Leung et al. suggested.[20] In spite of this we got 66.7% early complete response rate. Overall response rate was encouraging and complications regarding acute and late toxicities were acceptable. The poorer outcomes in terms of survival function may be attributable to the fact that four patients had already have regional and/or distant failure before FSRT and the GTV volume1s were ranged from 4.9 to 78.7 ml with a median of 29.4 ml which were relatively larger.

Early response rates with CyberKnife FSRS was satisfactory and acute side effects were in acceptable limits. In the near future, as the number of cases and follow up time increase we will be able to reach more data about FSRS dose, fractionations and late side effects.

CONCLUSION

The role of FSRT in the reirradiation of locally recurrent NPC remains to be established. Although promising, more clinical randomised studies and longer follow-up are needed to determine the relationship between effective dose per fraction and tumor control without causing severe toxicity.

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