RESEARCH ARTICLE

Reirradiation with Robotic Stereotactic Body Radiotherapy for Recurrent Nasopharyngeal Carcinoma

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Abstract

Background: Recurrent nasopharyngeal carcinoma (NPC) after previous radiotherapy is challenging. There is no standard approach for salvage treatment. Here we present toxicity and treatment results for recurrent NFC patients who underwent fractionated stereotactic radiotherapy (FSRT) as second line radiotherapy (RT). Materials and Methods: Between April 2009 and July 2012, 24 patients, with a male to female ratio of 3:1, were treated with CykerKnife® FSRT for recurrent NFC in our institution. Seven out of 24 patients had metastatic recurrent disease. Median age was 53 years (range, 20-70 years). Initial RT dose was 70Gy. The time period between initial RT and FSRT was a median of 33.2 months. The median prescription dose for FSRT was 30Gy (range, 24-30 Gy) in a median of 5 fractions (range, 4-6). Results: The median follow-up for all patients was 19.5 months (IQR: 12.2. -29.2 months). The locoregional control; progression free survival and overall survival (OS) rates for 1-, 2- and 3-year were 64%, 38%, 21%; 60%, 30%, 17% and 83%, 43%, 31%, respectively. Median OS for the entire cohort was 22 months (95% CI: 16.5-27.5). On multivariate analysis recurrent tumor stage was the only prognostic factor for OS (p=0.004). One patient exhibited grade III temporal lobe necrosis. One died because of grade IV mucositis and overlapping infection. Conclusions: The treatment of recurrent NPC is controversial. Fractionated stereotactic radiotherapy is promising. However, the published trials are heterogeneous with respect to the selection criteria and treatment details. Prospective studies with long term follow-up data are warranted.

Keywords: Recurrent nasopharyngeal carcinoma - stereotactic radiotherapy - CyberKnife

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Introduction

Recurrent nasopharyngeal carcinoma (NPC) in a previously irradiated volume remains a challenging problem. There is no level I clinical evidence available to inform decision making of physicians and patients, given the heterogeneity of the current literature. The localisation of the nasopharynx and high doses of radiotherapy (RT) and chemotherapy given for primary therapy make retreatment difficult (DeConti and Schoenfeld, 1981; Hong et al., 1985; Fontanesi et al., 1989). Options for the treatment of recurrent NPC include external irradiation, brachytherapy, chemotherapy, nasopharyngectomy and various combinations of these modalities. Nasopharyngectomy can be performed for only patients with T1-2 recurrences with no distant metastases (Wei, 2003; Chang et al., 2004; Danesi et al., 2007; Hao et al., 2008). Chemotherapy alone is suggested for palliative treatments even though there is no evidence that shows superiority over supportive-care (Jin et al., 2012; Kua et al., 2013).

Recurrent NPC reirradiation causes several concerns due to limited tissue tolerances and the high radiation doses used previously. Brachytherapy (BT) has been used in salvage treatment of recurrent NPC for several decades but can be applicable only to a small volume within the nasopharynx (Law et al., 2002). Reirradiation with or without chemotherapy became more popular with the advent of new techniques in RT planning and delivery such as intensity modulated radiotherapy (IMRT) with or without stereotactic application facilities. CykerKnife® (Accuray, Sunnyvale, CA) is a robotic stereotactic radiosurgery (SRS)/fractionated stereotactic radiotherapy (FSRT) device using a 6-MV linear accelerator. Computed-operated robot gives opportunity to use several beam entrances from different nodes. Rapid dose fall-off at target periphery makes it a proper candidate for reirradiation of the lesions that are close to critical structures. There is not enough data in the literature about the effectiveness and toxicity of SRS/FSRT in recurrent NPC treatment.

Here, we present our experience for the first 24 patients with recurrent nasopharynx squamous cell carcinoma who were treated with with CykerKnife® FSRT in our department.

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Materials and Methods

Patients

Between April 2009 and July 2012, 24 patients, with a male to female ratio of 3:1, were treated with CykerKnife® FSRT for recurrent NPC at Ankara Oncology Hospital. The charts and follow up information of the patients were reviewed retrospectively. All previously irradiated 24 patients underwent FSRT with CykerKnife®. Informed consent was obtained from all patients before reirradiation. All patients had histologically confirmed recurrent disease except 2 with radiological diagnosis. Before CykerKnife® FSRT, all patients underwent restaging with magnetic resonance imaging (MRI) of nasopharynx and neck, bone scintigraphy, thorax computed tomography (CT), abdominal ultrasonography or 18-fluorodeoxyglucose-positron emission computed tomography (PET-CT). American Joint Committee on Cancer 2010 system was used for re-staging.

FSRT

The delivery of FSRT was performed with CykerKnife® for all patients. Patients were immobilized in the supine position with a thermoplastic head and neck mask. All patients underwent a treatment planning CT and planning MRI with a 1.5mm slice thickness. The planning target volume consisted of gross disease identified on MRI with an expansion of 0-2mm at the discretion of the treating physician. The standard dose was 30Gy in 5 fractions; however, the treating physicians individualized this according to tumor size, localisation and patient characteristics. The doses of critical structures and target volume conformity and homogeneity was analysed for plan evaluation. Biologically effective dose (BED) was calculated for each treatment according to the Linear Quadratic (LQ) model (Fowler, 1989).

Follow-up

All patients completed planning treatment. During follow-up, a post-treatment surveillance PET-CT scan and/or MRI scan was performed 2-3 months after the completion of FSRT and then every 3 months for the first year and every 6 months thereafter. Fiberoptic nasopharyngoscopy was conducted at the control visits, with biopsy as indicated. The Common Terminology Criteria for Adverse Events v3.0 was used. All grade ≥3 toxicities were reported.

Statistical analysis

Locoregional control (LRC), progression free survival (PFS) and overall survival (OS) were primary endpoints. All events were measured from the time of recurrent disease diagnosis to locoregional or distant failure, death, or last follow up. The univariate effects of covariates on survival were investigated using log-rank test. Factors found to influence prognosis on univariate analysis were subjected to multivariate analysis using Cox's proportional hazard regression model with backward selection, in order to determine independent predictors of survival. A 5% type-I error level was used to infer statistical significance. All calculations were performed using SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline patient and treatment characteristics are detailed in Table 1. All patients initially received 70Gy of RT with or without concurrent chemotherapy. Seven out of 24 patients had metastatic recurrent disease. Median

Table 1. Patient and Treatment Characteristics.

Characteristic		Value
Total Patients (n)		24
Gender (n,%)	Male	18 (75%)
	Female	6 (25%)
Age (years)	Median	52.4
	IQR	(39.7-60.7)
Histology (n,%)	Undifferentiated carcinoma	18 (75%)
	Squamous cell cancer	5 (20.8%)
	unknown	1 (4.2%)
T (n,%)	T1	0 (0%)
	T2	11 (45.8%)
	T3	3 (12.5%)
	T4	4 (16.7%)
	unknown	6 (25%)
Stage (n,%)	I	0 (0%)
	II	8 (33.3%)
	III	5 (20.8%)
	IV	4 (16.7%)
	unknown	7 (29.2%)
Chemotherapy with initial RT (n,%)		
	Induction	1 (4.2%)
	Induction+Concurrent	3 (12.5%)
	Induction+Concurrent+Adjuvant	1 (4.2%)
	Only concurrent	8 (33.3%)
	Concurrent+Adjuvant	5 (20.8%)
Initial RT dose (Gy)	Median	70
	IQR	(70-70)
Interval between initial RT and CyberKnife (months)		
	Median	33.2
	IQR	(20.4-56.7)
Locoregional Recurrence Type (n,%)		
	Local	18 (75%)
	Regional	1 (4.2%)
	Locoregional	5 (20.8%)
rT (n,%)	rT0	1 (4.2%)
	rT1	8 (33.3%)
	rT2	4 (16.7%)
	rT3	6 (25%)
	rT4	4 (16.7%)
	unknown	1 (4.2%)
rStage (n,%)	I	8 (33.3%)
	II	2 (8.3%)
	III	6 (25%)
	IV	7 (29.2%)
	unknown	1 (4.2%)
Gross Tumor Volume (cc)		
	Median	28.2
	IQR	(18.3-51.8)
Chemotherapy with CyberKnife (n,%)		
	Induction	2 (8.7%)
	Adjuvant	11 (47.8%)
CyberKnife dose (Gy) (median, IQR)		30 (25-30)
CyberKnife dose BED10 (Gy) (median, IQR)		44.3 (38.3-48)
CyberKnife dose/fraction (Gy) (median, IQR)		6 (5-6)
Number of fractions (median, IQR)		5 (5-5)
Prescription isodose line (%)(median, IQR)		80 (75-90)
Conformity Index (median, IQR)		1.6 (1.5-1.8)
Homogeneity Index (median, IQR)		1 (1-1)
Number of nodes (median, IQR)		107 (97-117)
Number of beams (median, IQR)		248 (212-319)

*Abbreviations; RT, Radiotherapy; IQR, Inter Quartile Range; r, recurrent; BEDn, biologically effective dose based on an α/β ration of n

time from initial RT to CykerKnife® FSRT was 33.2 months. Magnetic resonance imaging and PET-CT were used for staging. All but two patients had histological diagnosis at the time of recurrence. CykerKnife® FSRT fractionation schema was 25-30Gy delivered over 5 days with 1 day intervals. Median prescription isodose was 80% (IQR:75%-90%).

The median follow-up for all patients was 19.5 months (IQR: 12.2.-29.2 months), for surviving patients 27 months (IQR: 19-47 months). The LRC; PFS and OS rates for 1-, 2- and 3-year were 64%, 38%, 21%; 60%, 30%, 17% and 83%, 43%, 31%, respectively for all patients. Four patients were alive with no evidence of disease, 2 patients were alive with local progressive disease at the time of reporting. Seventeen patients died because of disease progression (n=15) and toxicity (n=2).

Median LRC and PFS were 16 months (95% CI: 9.25-22.74 months) and 12 months (95% CI: 5.35-18.64 months), respectively (Figure 1A-1B). Median OS for the entire cohort was 22 months (95% CI: 16.5-27.5) (Figure 1C).

Univariate analyses revealed that OS was significantly better in patients with Gross tumor volume (GTV) <40cc, recurrent tumor T (rT) 1-2 and recurrent tumor stage (rStage) 1-2 (Table 2). In multivariate analyses rStage was the only prognostic factor for OS (p=0.004; HR:0.151; 95% CI: 0.042-0.545). The actuarial 3-year OS rate was

Table 2. Univariate Analysis of the Association of Different Variables and Survival Data

Variable			Locoregional control survival	Progression free	Overall survival
			p value	p value	p value
Age (y)	<60 *vs* ≥60	18 *vs* 6	0.218	0.343	0.851
Sex	Male *vs* Female	18 *vs* 6	0.426	0.29	0.662
Histology					
	U/D *vs* SCC	18 *vs* 5	0.493	0.721	0.672
rGTV Volume (cc)					
	<40 *vs* ≥40	16 *vs* 8	0.74	0.896	0.035*
rT	0-2 *vs* 3-4	13 *vs* 10	0.527	0.169	0.020*
rStage	I-II *vs* III-IV	10 *vs* 13	0.332	0.113	0.001*
BED	<44 *vs* ≥44	12 *vs* 12	0.308	0.237	0.976
Conformity index					
	<1.5 *vs* ≥1.5	7 *vs* 17	0.386	0.236	0.703
Time from initial RT to CyberKnife					
	≤2 years *vs* >2	9 *vs* 15	0.912	0.975	0.916
Chemotherapy for recurrence					
	Any *vs* no	13 *vs* 11	0.896	0.712	0.851

*Abbreviations; U/D, undifferentiated carcinoma; r, recurrent; GTV, gross tumor volume; BED, biologically effective dose

Table 3. Literature Review for Stereotactic Reirradiation of Recurrent Nasopharyngeal Carcinoma

Author	Year	No.	Median follow-up (months)	Rairradiation technique and dose Gy*	Local control rate	Overall survival rate
Ozyigit	2011	24	23	FSRT: 30 Gy in 5 fr	2y 82%	2y 64%
Seo	2009	35	25	FSRT: 24-45 Gy in 3-5 fr	5y 79%	5y 60%
Wu	2007	56	20.3	FSRT: 10-24 Gy in 2-4 fr	3y 75.1%	3y 45.9%
Low	2006	36	50	SRS: 18 Gy in 1 fr +BT: 12 Gy in 2 fr	5y 65%	5y 62%
Chua	2005	31	11	IMRT: 50-60 Gy in 25-30 fr ±SRS: 8.5-12.5 Gy in 1 fr	1y 56%	1y 63%
Xiao	2001	50	20	FSRT: 14-35 Gy in 6-15 fr	NR	3y 59.6%
Dizman	Current	24	19.5	FSRT: 25-30 Gy in 5 fr	3y 21%	3y 31%

*for the reports with various irradiation techniques, we used EBRT as a general term; Abbreviations; FSRT, fractionated stereotactic radiation therapy; EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; BT, brachytherapy; IMRT, intensity modulated radiation therapy; NR, not reported

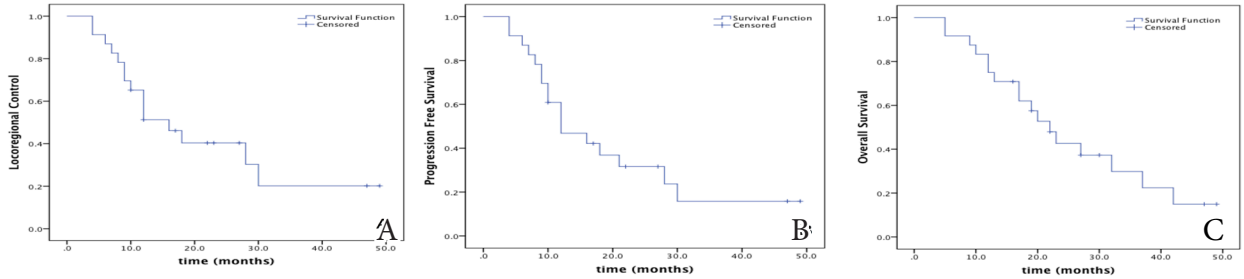

Figure 1. A) Actuarial Locoregional Control, B) Progression Free Survival and, C) Overall Survival for All Patients

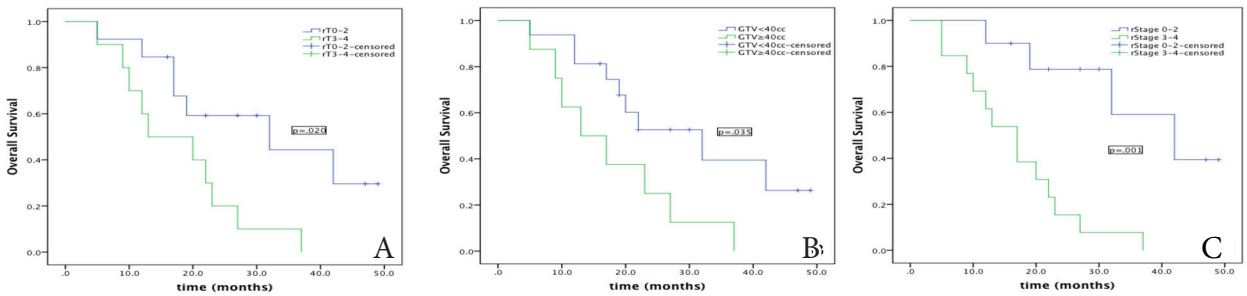

Figure 2. Actuarial Overall Survival for Patients with rT 0-2 and for those with rT3-4 (A); for Patients with GTV<40cc and for those with GTV ≥40cc (B); for Patients with rStage 0-2 and for those with rStage 3-4 (C)

60% for patients with rStage 1-2, 0% for those who have rStage 3-4 diseases.

One patient exhibited grade III temporal lobe necrosis. One patient died because of grade IV mucositis and overlapping infection. Grade I-II toxicities were not reported.

Discussion

Despite the developments in head and neck cancer treatments, locoregionally recurrent tumors in previously irradiated areas remain as a challenging problem with a morbidity rate as high as 50-60% (DeConti and Schoenfeld, 1981; Hong et al., 1985; Fontanesi et al., 1989; Hao et al., 2008; Huang et al., 2012). Deep localisation of the tumor and previously given high doses obstructs the treatment. There is no standard treatment approach among physicians. Tumor and patient characteristics are important in decision making of the physician. Usually treatment selection depends on physicians' experiences and the hospital facilities.

Nasopharyngectomy is an option for carefully selected patients with T1-2 non-metastatic disease. Recently reported surgical reports presented LRC and OS rates as high as 72% and 54%, respectively (Wei, 2003; Chang et al., 2004; Danesi et al., 2007; Hao et al., 2008). Brachytherapy is also appropriate for early stage recurrent NPC (Cheng et al., 2013). Law et al. (2002) achieved local control at 5-years, up to 85% but with a complication rate of 53%. Lee et al. (1993) showed improved local control with combined external beam radiotherapy (EBRT) and BT, as high as 45% at 5 years.

The advent of new technologies in RT in the last decades brought a new interest in curative and palliative reirradiation of recurrent NPC. Old series were mainly with BT or with conventional techniques. Reirradiation doses with conventional techniques were quite low because of the risk of high toxicity on close critical structures. However, dose escalation has been found relevant with improved survival in previous studies (Wang, 1987). The use of IMRT has shown encouraging results with a survival rate of 60-62% at 5 years (Low et al., 2006; Seo et al., 2009; Koutcher et al., 2010; Chee Ee Phua et al., 2013; Phua Chee Ee et al., 2013; Xiang et al., 2013;).

Stereotactic radiosurgery has been accepted as an effective model with high dose delivery option; however, high risk of toxicity remains a challenging problem (Chua et al., 2003; Low et al., 2006; Wu et al., 2007). The rapid dose falloff at target periphery enables to protect close critical structures while giving high doses of radiation to the target. On the other hand, single fraction RT leads to increased late toxicity. Thanks to the methods that give fractionation options, nowadays we can use the mechanic advantages of stereotaxy and radiobiologic advantages of fractionation at the same time. Table 3 summarizes the treatment techniques and results of studies with stereotactic reirradiation of NPC. The majority of the reported series are retrospective analyses with heterogeneous patient and treatment profiles. The only prospective study on recurrent NPC reirradiation is a phase II trial from Chua et al. (2005), using median 54 Gy of IMRT with FSRT boost in 22% of the cases with a single dose 8.5 to 12.5Gy, they reported 1-year OS and local control of 63% and 56% in 31 patients, respectively.

We previously reported our treatment results of CykerKnife® FSRT reirradiation of the first 12 patients with heterogeneous histologies of recurrent nasopharynx tumor that also consists 9 of the cases in this present study (Cetindag et al., 2012). One-year local control and OS rates were 85% and 75%, respectively. In the present study with 24 patients with recurrent differentiated or undifferentiated squamous cell carcinoma of the nasopharynx, 1-year LRC and OS rates are 64% and 83%, respectively. However, it is not possible to compare the results since the first report also consists diseases with mesenchymal and adenoid cystic histologies.

In the reported reirradiation studies except those with BT alone, the majority of the recurrences are at advanced stage with a ratio of 15-73.3% and 8-53% for rT3-4 tumor and rStage-4 diseases, respectively (Lee et al., 1997; Xiao et al., 2001; Lu et al., 2004; Chua et al., 2005; Wu et al., 2007; Seo et al., 2009; Koutcher et al., 2010; Ozyigit et al., 2011). In our series the 41.7% of the cases were with rT3-4 and 29.2% were with rStage-4 disease. Recurrent tumor T stage has been presented as a prognostic factor in many previously reported series (Chua et al., 2005; Oksuz et al., 2009; Koutcher et al., 2010; Ozyigit et al., 2011; El-Sherbieny et al., 2011; Sun et al., 2012) . The poor outcome with advanced rT lesions may be related to poor target coverage due to nearby critical structures. In our study, although rT stage was a prognostic factor for survival in univariate analyses, multivariate analyses revealed no further significance. We were able to achieve comparable outcomes between limited and advanced rT lesions.

There are many other covariates that may affect treatment outcome in recurrent NPC reirradiation. Sex, age, reirradiation dose, rStage, time interval between 2 irradiations, concurrent chemotherapy is the most investigated ones in previous reports Chua et al. (2005; 2009) and Seo et al. (2009) reported age as a prognostic factor for survival. In our series, we did not observe any local control or survival advantage in favour of patients younger than 60 years old.

Reirradiation dose was found to be prognostic in some previously reported series. Higher reirradiation dose (≥60 Gy) was associated with better survival outcome in some series (Wang, 1987; Pryzant et al., 1992; Lee et al., 1997; Teo et al., 1998). Chang et al. (2000) reported improved survival with ≥50Gy. Lu et al. (2004) reported excellent local control rate with 68-70Gy of IMRT. However, Teo et al. (1998) reported high incidence of complications due to toxicity with doses ≥60Gy. The interpretation of the results is difficult because of the short follow-up data and lack of information on late toxicities. In our analyses, we used LQ model to compere the results with different RT schemas of FSRT. Although LQ model has not been validated for hypofractionation, we considered using this model in order to predict possible late side effects on the normal tissue as supported by Brenner (2008) and Kirkpatrick et al. (2008). We did not find any survival advantage for doses

with BED10>44Gy over BED10<44Gy. The relationship between reirradiation dose and late toxicities could not be evaluated at the moment. Grade III temporal lobe necrosis and grade IV mucositis were morbid toxicities in our series. In the literature severe late complication were reported to be between 15% and 73% (Lee et al., 1993; Chang et al., 2000; Pai et al., 2002; Chua et al., 2005; Koutcher et al., 2010). Koutcher et al. (2010) reported improved toxicity with the combination of BT with EBRT to EBRT alone (8% *vs* 78%). Longer follow-up data is required in order to evaluate late toxicities more clearly.

Although similar follow-up periods, reirradiation techniques and doses, our results for OS was poor compared to current literature (Table 3). In our institution, all patients were treated under strict guidance with experienced physicians. All patients but one were followed with 3 monthly intervals with PET-CT and/or MRI imaging. Our unfavourable outcomes may appear to be due to involvement of the metastatic cases and to have only recurrent but not persistent disease in our analyses. However, some of the previous reported series involve persistent disease and exclude metastatic disease. Therefore, it is difficult to compare the results with the current literature. There is no level I clinical evidence for NPC reirradiation as salvage treatment. Although there are some single institutional data with encouraging results for reirradiation with new techniques, all these reports are with limited number of patients and short follow-up data.

In conclusion, The treatment of recurrent NPC is challenging. There is no prospective clinical data to guide physicians. With the advent of new technologies, reirradiation with FSRT or SRS became more popular. However, we need prospective multi-institutional clinical trials with long-term follow-up data to clarify the role of these approaches among other treatment techniques in the treatment of recurrent NPC.

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