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Original Article

Re-irradiation results of fractionated stereotactic radiotherapy (FSRT) with cyberknife for locally-advanced nasopharengeal carcinoma (NPC)

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Abstract

Aim: Recurrent nasopharyngeal carcinoma (NPC) after previous radiation therapy is a major problem. This study was conducted to determine the survival benefits and potential benefits of the effects of severe late toxicities by re-irradiation with fractionated stereotactic radiotherapy (FSRT).

Material and Methods: 2009-2018, treatment outcomes were evaluated retrospectively in 26 patients with local recurrent NPC were cured applying FSRT with Cyberknife. Five patients had metastatic disease and one had second recurrence was excluded from the research, remaining 20 patients were analyzed. Median agewas 52 years (range,28-80 years), re-treatment T stagewas; 6 (30%) T2, 5 (25%) T3, 9 (45%) T4.Median time from initial RT to recurrence was 22 months (range,8-159 mo.). The median re-irradiation FSRT dose was 30Gy in 5 fractions.

Results: Median follow-up was44 (22-179)months, the overall survival(OS) rate, local failure-free survival (LFFS) and disease progression-free survival(DPFS) rate at 3 years were 89%,73% and 53%, respectively. All patients were evaluated for response after treatment; 9 (45%) had complete, 3 (15%) partial, 6 (%30) had no response.Univariate analysis demonstrated that; higher cumulative total radiotherapy dose, gross tumor volume and recurrent time interval were prognostic factors for LFFS. Recurrent time interval was also independent factor for DPFS and OS. The incidence of temporal lobe necrosis and trismus were 10% and 20%,respectively. One patient had grade 5 toxicity to treatment related bleeding.

Conclusion: Tumor dose coverage is critical for treating recurrent NPC and treatment linked death rate was vascular in nature. Fractionated stereotactic radiotherapy is promising treatment modality for recurrent NPC.

Keywords: Fractionated stereotactic radiotherapy; recurrent nasopharyngeal carcinoma; re-irradiation

INTRODUCTION

The principal treatment for definitive nasopharyngeal carcinoma (NPC) is radiation therapy. Recent developments in radiotherapy techniques have shown that excellent local control has been provided by intensity-modulated radiotherapy (IMRT) (1-3) and combined chemotherapy has markedly decreased the local failure rate in NPC. Despite the progress in these treatments, salvage therapy have a crucial role in the local recurrence of NPC. While about only 20-30% of patients are eligible for salvage surgery, it is only considered appropriate in the early stage of recurrence; therefore, salvage surgery is not suitable for rT3 to rT4 diseases. Re-irradiation is the primary treatment for advanced-stage local recurrence (2,3). Chemotherapy remains the first-line treatment for those who are not eligible for re-irradiation, providing a middleviability time of 6-10 months.

Because of being very close to vital structures, it may be challenging to administer conventional radiotherapy, which has a over frequency of late complications and poor 5-year total viability rate, ranging between 8-36% (4). IMRT on the other hand, may be a better treatment technique and preserves the surrounding organs. Some studies have reported survival with a low level frequency of late complications and better control of the disease (5-7). Another treatment option for recurrent NPC may include charged-particle radiation therapies, like proton and carbon ion radiotherapy. These treatment modalities have an enormous energy discharge compared to photon beams and deliver a max radiation dose at an exact depth, generating Braggpeak. Various studies have shown that particle therapy provides improved dose distributions in recurrent cancers of the head and neck (8-10). In these studies, the oropharynx was the most common tumor site

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and the sample size of recurrent NPC patients was small. Moreover, no consensus has been reached on the fraction size and optimal dose of re-irradiation using charged particles in recurrent NPC patients.

The Cyber-Knife system (Accuray, Sunnyvale, CA) was designed for stereotactic radiotherapy and has software of inverse treatment planning with a 6-MV linear accelerator settled on a computer-controlled, frameless and image-guided system. The system can offer high dose RT with irregularly shaped lesions with good dose distribution homogeneity and conformity indexes .In the literature, the data on the toxicity and efficacy of FRST in the recurrence NPC treatment is limited (7).

In this study, we aimed to evaluate the long-term survival benefits and late toxicities in patients with locally recurrent rT3-rT4 NPCs who were re-irradiated with FRST using Cyberknife.

MATERIAL and METHODS

Patient selection and pretreatment evaluation

We retrospectively analyzed that 26 cases with NPCs that locally recurred between 2009 and 2018 were treated with FSRT in our institution (SBU,KartalDrLutfiKırdar Training and Research Hospital).Ethics committee approval was obtained for this study (2019/514/156/2). The data of the cases were collected from hospital data base and patient files. Pretreatment assessment comprised a comprehensive history and physical examination, flexible fiberoptic nasopharygoscopy with biopsy, serum electrolytes, complete blood counts, liver enzymes, magnetic resonance imaging (MRI) of the head – neck and fluorodeoxyglucose-positron emission tomography(FDG-PET). Expulsion criteria were as below; presence of distant metastases during recurrence, involvement of regional lymph nodes in MRI or PET-CT and palliative intent re-irradiation. Appropriate patients had locally recurrent singe lesion. Five patients had metastatic disease and one had second recurrence was excluded from the study, remaining 20 patients were analyzed. In the definition of persistent disease, it is called local recurrence that occurs within 6 months. Local recurrences were histological confirmed though biopsy. All recurrent tumors were re-staged according to the 8th edition of the American Joint Committee staging classification

Sterotactic radiosurgery

The delivery of FRST were performed with CyberKnife in our department. The CyberKnife SRS system used a 6 MV X-band linear accelerator mounted on a robotic arm.Two x-ray detectors placed orthogonally during the treatment provide real-time visualization of the bone anatomy and provide correction of the intra-fraction movement. Treatment was generally performed on a patient basis, and each treatment lasted about 60-90 minutes. All patients were immobilized with a thermoplastic mask and a CT scan with a thickness of 1.5 mm was performed from the superior area of the skulls to the thoracic entrance. Diagnostic MRIs and PET-CTs fused with planning CT images for gross tumor volume (GTV) delineation and adjacent critical structures were contouring in each successive slice. The planning target volume (PTV) was produced by expanding the GTV by a margin of 5 mm for all patients. GTV uses a tighter margin in case of closed contact with critical neurological structures. Organs at risk (OAR), including the brain stream, temporal lobe, spinal cord, lens, optic chiasm and nerve were also contoured. Radiotherapy doses were prescribed to cover at least 97% of PTV in the isodose line (70-89% of the maximum dose; median 82%). Treatment plans consisted of hundreds of pencil beams shaped using a single 12.5, 15.0 or 20.0 mm diameter circular collimator. FRST was applied with a fraction at one-day intervals. The Standard dosage and fractionations were 30Gy in 5 fractions; but this was individualized by the treating physician. Biologically effective dosage (BED) was counted for each cure according to the Linear Quadratic (LQ) model. The Standard treatment dosage was 30 Gy in 5 fractions twice a week (Figure1).

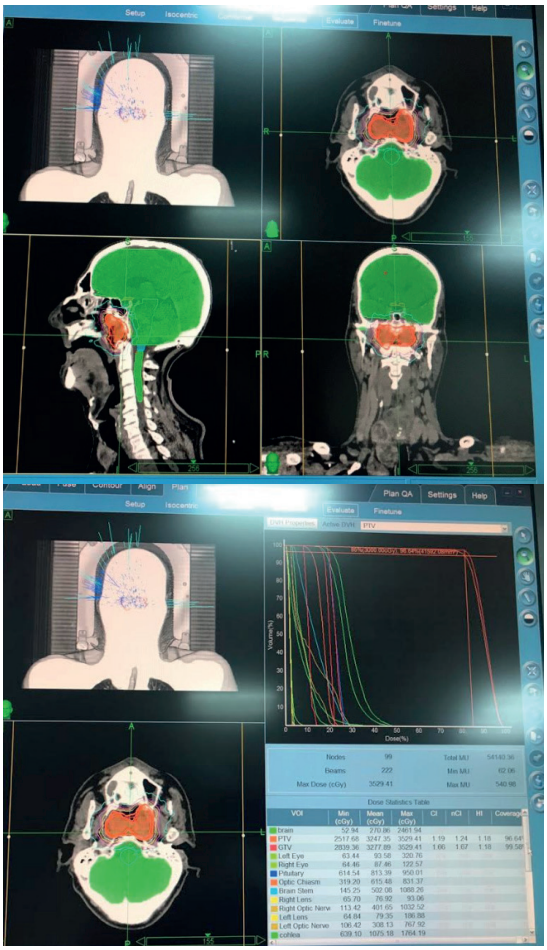

Figure 1. A typical fractionated sterotactic radiotherapy (FSRT) treatment plan with CyberKnife for a patient with rT3N0M0 locally recurrentnasopharyngeal carcinoma

Follow-up and response assessment

Tumor response was evaluated by fiberoptic nasopharyngoscopy and MRI 8 weeks after radiotherapy treatment.The follow-up period was every 3 months in the first year and then every 3-4 months thereafter. The

controls were performed every 4 to 6 months in the first 3 years after treatment with MRI imaging method. In suspicious cases, PET scans were performed to exclude distant metastasis or loco-regional. Nasopharyngeal biopsies were performed to rule out local recurrence in all suspected cases. Common Terminology Criteria for Adverse Events v3.0 (CTCAE) were applied for toxicity scoring (11).

For a complete response, it was defined as a complete tumor regression after FSRT when evaluated by imaging and nasopharyngoscopy. No response was defined as no significant change or increase in the treated lesion.Thepartialresponsewasdefined as not meeting ormeetingthecriteriafor a fullresponse.

Statistical analysis

To determine the effectiveness of FSRT, we analyzed the following end points: overall survival rate, local non-failure survival rate, disease non-progression survival rate, and response rate. All events were assessed from the time of disease diagnosis to loco-regional or distant failure, death or last follow up. The end points were analyzed applying the Kaplan-Meier method and the median values were reported. Log-rank analysis was applied to compare prognostic factors, and factors found to influence prognosis on univariate analysis were subjected to multivariate analysis using Cox's proportional hazard regression model. All calculations were performing SPSS, version 17.0 statistical software package (SPSS,Chicago,IL) and p values≤ 0.05 were considered significant.

RESULTS

The duration of the follow-up for surviving patients was 34(24-130) months. Nine out of 20 patients (45%) were found healthy with no symptom of illness as of reporting date and 10% of the patients (1 patient) stayed alive with disease of distant metastasis. 40% of the patients (8 patients) lost their lives since they were at advanced stage of the disease while one person (10%) died because of radiotherapy complication and one patient died of co-morbid disease.

The patients' median age during the re-irradiation was 52(28-80). The number of male patients was 18, making up majority with 90% of the all patients while the number of female patients was only 2. The histology of the all the tumors was cell carcinoma. During the initial treatment, 14 (70%) patients received chemoradiotherapy and 3 (15%) patients received neoadjuvant chemotherapy.

Ranging from 66 Gy to 74 Gy, the median dose of the first radiation dose was 70Gy. The details of the main patient and medication features are given in Table 1. On the other hand, the median dose for SRS re-irradiation was 30Gy, varying between 24Gy-35 Gy while average dose for each fractions was 6Gy ranging from 5 Gy to 7 Gy, and the median of the fraction was 5, varying from 4 to 5 fractions. The median cumulative dose for nasopharyngeal radiation which was consisting of primary radiotherapy dose and aggregate re-irradiation dose was 132Gy, ranging from 121 Gy to 143 Gy. Assuming α/β ratio as 3 for late-responsive ordinary tissues, the cumulative median BED_3 (Biological Effective Dose)of the initial radiation course and the SRS treatment was 206,7 Gy varying between 179,3-233Gy. The median maximum SRS doses for brainstream, optic chiasm, right-left optic nerves were 17Gy, 11Gy, 10Gy and 9Gy, respectively (Table 2).

Table 1. Characteristics of the locally recurrent NPC patients and their initial treatment

Characteristics	No (%)
Gender	
Male	18 (90%)
Female	2 (10%)
Age at local recuurence	
Median(range)	52 yr (28-80)
Initial treatment	
IMRT	6 (30%)
3D	11 (55%)
2D	4 (15%)
Initial T stage	
T1	1 (5%)
T2	5 (25%)
T3	8 (40%)
T4	6 (30%)
Initial N stage	
N0	7 (35%)
N1	4 (4%)
N2	8 (40%)
N3	1 (5%)
Chemotherapy Schedule	
Induction+concurrent	1 (5%)
Concurrent only	10(50%)
Concurrent+adjuvant	3 (15%)
Adjuvant only	3 (15%)
Induction+concurrent+adjuvant	1 (5%)
None	2 (10%)
Initial Radiotherapy dose	
Median (range)	70 Gy(66-74Gy)
Time to recurrence	
Median (range)	10 mon. (2-20mon.)
Recurrence T clasification	
r-T2	6 (30%)
r-T3	5 (25%)
r-T4	9 (45%)

IMRT; Intensity Modified Radiotherapy, 2D; 2 Dimension, 3D; 3 Dimension

Table 2. Treatment characteristics of 20 patients receiving fractionated stereotactic radiotherapy

	Median	Range
Maximum dose with in*PTV (Gy)	36	31-42
Prescription isodose	82%	70%-89%
Number of beams	187	127-227
Conformity index	1.26	1.06-1.61
Homogenety index	1.20	1.12-1.61
Tumor volume	47.5cc	30.1cc-135.6cc
Maximum dose to critical stuructures		
Brainstream, Gy	17	6-28
Optic chiazma, Gy	11	6-24
R optic nerve, Gy	10	4-23
L optic nerve, Gy	9	2-24

R;Right , L;Left, Gy;Gray, PTV; Planning Target Volume

The median of the OS for the whole group was 44 months while the median LFFS was 34 months, and DPFS was 32 months. The LFFS, DPFS and OS rates during the 3 year period were measured as 73%, 53% and 89%, respectively. 45% (9 out of 20) of the all patients were fully-responsive to the treatment while 3 of them (15%) had partially responsive and 6 patients (30%) were found on-responsive. For the definitive FSRT treatment, 2 patients experienced an isolated local failure while 4 patients having an isolated distant failure, and 3 patients with both local and distant metastasis as of reporting date. As mentioned above, 9 (out of 20) patients stayed alive with no symptom of the disease and one survived with distant metastasis disease as of the reporting date. Nine patients died due to advanced level of disease (n:8) and toxicity (n:1). One patient was lost because of Alzheimer disease with in one year following the re-irradiation (Table 3).

Table 3. Cause of deaths after salvage FSRT

Cause	Number	Percentage (%)
Disease progression	8	40
RT toxicity	1	5
Other disease	1	5
Total	10	50

RT; Radiotherapy, FSRT;Fractionated Stereotactic Radiotherapy

Univariate analysis revealed that higher aggregate dose of nasopharengeal radiation (>132Gy) was associated with improved LFFS (p:0:03). Additionally, gross tumor volume (GTV) >60cc was an independent variable for LFFS (p:0.06) and DPFS (p:0,08) but this was not statistically significant. Recurrence time intervalwas>12 monthswasbetterOS (p: 0.01), LFFS (p:0.06) and DPFS (p:0.04) than<12 months, thiswasstatisticallysignificantforOSand DPFS. No other variables were found to be prognostic factor for univariate analysis. In multivariate analysis we couldn't find any prognostic factor for survival (Table 4).

Fifteen patients were experiencing RTOG (Radiation Therapy Oncology Group) Grade 1-3 acute toxicity together with the mucositis, dermatitis and nausea and all of these problems were solved with a conservative approach so that any of them had did not experience RTOG Grade-4 acutetoxicity. Nine patients had Grade 1 to 3 late long-term toxicity after irradiation. Four patients had hearing loss, 3 patients had trismus, 3 patients had temporal lobe necrosis. Severe late radiation-induced RTOG Grade 4-5 toxicity was found in 2 patients out 20 (10%). One of the patients were having side effects including soft-tissue necrosis, aspiration problems and dysphasia needing hospitalization. One patient died because of carotid blow out syndrome 1 year after completion of re-irradiation.

Table 4. Univariate analysis of potential prognostic factors

Factors		OS	DPFS	LFFS
Cumulative RT dose (primaryradiotherapy+re-irradiationdose)	<132Gy &>132Gy	0.6	0.9	**0.03**
GTV	<60 cc &>60cc	0.3	0.08	0.06
Time torecurrenceafterinitial RT	<12 mon. &>12mon	**0.01**	**0.04**	0.06

RT;Radiotherapy, GTV; Gross Tumor Volume

DISCUSSION

In the present study, 20 locally recurrent nasopharengeal cancer patients were treated with FSRT by Cyberkine. The OS, LFFS and DPFS rate, at 3 years were 89%,73% and 53%, respectively. All patients were evaluated for response after treatment; 9 (45%) had complete, 3 (15%) partial, 6 (%30) had no response. Univariate analysis demonstrated that; higher cumulative total radiotherapy dose, gross tumor volume and recurrent time interval was prognostic factor for LFFS. Recurrent time interval was also independent factor for DPFS and OS.

External radiationtherapy is required for the majority of patients with local NPC failure; however, the treatment results following re-irradiation with the conventional technique are poor. External re-irradiation has yielded a 5-year survival rate ranging from 8% to 36%, a complication rate of 20-57% and a local control rate of 19-38% in the local recurrence of NPC (12,13). The highest rate for long-term survival after there currence of the disease has been produced by brachytherapy and salvage surgery with survival rate of 40% at 5 years (14), but the most of the patients are not eligible because of the extension of the disease (15). On the other hand, IMRT has yielded promising results with a survival rate of 60-62% at 5 years. (6,7,19). Alternatively adding chemotherapy with radiotherapy for recurrent nasopharengeal cancer was also used as a standard treatment with a median of 5-9 month-survival time (16-18).

During the initial NPC treatments, higher dose increases has demonstrated significantly higher local control rates (20) and several studies on re-irradiation have also shown a strong correlation between the outcome and the re-irradiation dose. The studies by Wang and Oksuz et al. also found a better outcome with a dose of > 60 Gy than a dose of < 60 Gy (21,22). On the other hand, the study by Teo et al. gave a poorer survival rate and a highe rcomplication after the high-dose re-irradiation of NPC with>60 Gy; however, the survival rate was higher than those treated with low-dose re-irradiation with 40-50 Gy (4). There treatment was performed using conventional two-dimensional radiation therapy in all these series. Chang et al. found that 186 patients were re-irradiated using either conventional or conformal radiotherapy, a re-irradiation dose of >50 Gy produced a higher survival rate (23). In other series of re-irradiation of NPC, which uses IMRT-intensity-modulated radiotherapy, a dose range of 50-60 Gy provided a good control of tumor for rT1-3 disease, while tumor control was poor for rT4 disease (24). Given these results, at least a dose of 50Gy should be delivered using IMRT or conformal radiotherapy, though the optimal fractionation schedule is still unclear.

Robotic stereotactic radiosurgery is considered as an effective treatment technique that offers delivery of high-dose, but the toxicity risk continues to be a critical problem (21-23, 25-27). The SRS technique provides the advantage that the rapid dose reduction in the perimeter of the target allows the protection of critical adjacent structures. However, single-fraction radiation therapy results in increased late toxicity since FRST is a modification of SRS. FRST is especially beneficial if the tumor is too big or adjacent to a critical part. In the literature, there is a small number of studies defining the treatment of recurrent NPC using FRST. Wu et al. carried out a large of studies on FRST with 90 locally recurrent or persistent NPC and the median dose for the fractionated stereotactic radiotherapy was 48 Gy in six fractions. The 3-year disease-specific survival rate was 46%, while the local failure-free survival rate was 75%. The rate of severe late side effects was 25% (14 out of 56 patients). This study has found that FRST might be an useful method to treat recurrent NPC (27). There was also a small series of FRST for recurrent NPC, the majority of which had retrospective and heterogeneous patient population and treatment profile. The only research on the re-irradiation of recurrent NPC is a stage II trial carried out by Chua et al. Who used median IMRT dose of 54 Gy with FRST increase in 22% of cases with a single dose 8.5 Gy to 12.5 Gy. It was reported that 31 patients achieved a 1-year survival rate of 63% and a local control rate of 56% (24).

Another different treatment modality in recurrent NPC is carbon-ion therapy. The use of high-LET irradiation found to be safe and effective treatment for resistant tumor cells. Compared with proton-beam therapy with IMRT for re-irradiation has been shown to improve treatment outcomes for several disease (28). Locally recurrent 75 NPC patients who received using intensity-modulated carbon-ion RT up to 57,5GyE in 25 fractions tolerated well in recent study (29), In this study with a median follow-up of 15.4 months, the 1-year OS, DSS, PFS, LRFS, RRFS, and DMFS rates were 98.1%, 98.1%, 82.2%, 86.6%, 97.9%, and 96.2%, respectively. (29) but this study needs longer fallow up results.Dionisi et al 17 recurrent NPC patients were treated with proton therapy. Median follow-up was 10 months (range 2–41). Median proton therapy re-irradiation dose was 60 Gy RBE (range 30.6–66). The OS and local control rates were 54.4% and 66.6%,respectively. The majority of patients (53%) underwent concomitant chemotherapy. Grade 3 late event occured in 23.5% and most frequent late toxicity was hearing impairment (17.6%) , fatal bleeding was seen in one patient (30).

In the present study, all patients were cured with FSRT which uses Cyberknife and the average dose of FSRT in 5 fractionswas 30Gy. This study also had a retrospective design, but all patients had a homogenous profile, all recurrent NPC patients had squamous histology and the most common recurrence T stage of the patients was rT3-T4, while the study did not include persistent or metastatic disease. The previous studies have reported that patients with recurrence were having poorer outcomes as compared to patients with persistent disease (21,31-33). Yet, only patients with NPC recurrence were studied in this analysis. The 3-year rates for OS, LFFS and DPFS were 89%,73%, and 53% respectively. Of the patients, 10% (2/20patients) developed severe late toxicity induced by radiation. In our study, the local control and survival rates were favorable, while the severe late complication rates were within tolerable limits. Although severe-level rT 3-4 disease was present in 70% of our patients, the outcomes of our study for the survival rates, local control and late toxicity rates are promising as compared to results of prior study reports.

In our analysis, it has been concluded that recurrent time interval (>12 months), recurrence tumor volume (>60cc) and cumulative radiation dose (> 132 Gy) were the most significant indicative variables for the patients with local NPC recurrency. The basic biological features like the capability for damage repairment, radio-sensitivity, reflected by these prognostic factors may make contributions to alterations in survival rates of the patients (33). Tumor volume was an independent indicative variable in newly diagnosed NPC patients (12). Because of reduced radiation sensitivity due to hypoxia and inadequate supply of blood, a substandard distribution of dose as a result of critical structure protection, recurrence tumor volume is of significant importance (34). It was concluded by Yue. et al (35) that the recurrency in tumor may vary depending on primary tumor and it is also susceptible to hypoxia. In the present study, a recurrent tumor volume of > 60cc produced a poor outcome in DPFS and LFFS. In clinical practice, no consensus has been reached on the fraction size and optimal dose of re-irradiation in recurrent NPC patients. As a result, the median cumulative dose for re-radiation in our series was 132Gy. Although a much higher cumulative re-radiation dose than the previous irradiation dose was used in FSRT, a correlation was found

with >132Gy in LFFS. Accordingly, in a recently published meta-analysis, tumor volume and recurrent T stage were reported to be the prognostic variables for OS in patients receiving salvage IMRT (36).

In general, therates of severe latecomplicationsafterthe re-irradiation of recurrent NPC werefoundto be highwith 15%-45% (24 ,37,38). Koutcher et al. reportedthatthelatetoxicity rate was reduced to 8% by combining IMRT and brachytherapy (BRT) (18,19). Although patients treated using this treatment technique usually exhibited a smaller tumor volume, gold grain implantation (GGI) and BRT treatment were effective salvage treatments for locally recurrent NPC. However, instead of GGI and BRT, SRS or IMRT was used for bulky disease, advanced-stage recurrence and tumor encasement in carotid artery. A significant factor for the fatal toxicity and mortality was carotid blow out syndrome (CBS). Therefore, the rate of fetal hemorrhage was high, possibly because of the delivery of relatively higher cumulative dose. In the largest SRS series of Xiao et al., 16% of patients were reported to develop fatal hemorrhage (39). In the present study, it was found that only a patient with tumors around the carotid artery developed fatal hemorrhage.

All recurrent NPC patients in our study were given treatment under the control of qualified physicians. All of the patients were observed with MRI at 3-month intervals in our hospital. There were no level I clinical findings suggesting the re-irradiation of recurrent NPC as recovery treatment. In this study, we can speculate that FSRT is an optional salvage treatment for r-T3-T4 disease; however, patients should be attentively assessed before the treatment. The retrospective design and small sample size were the constraints of our study. This study did not include persistent disease or metastatic patients and included recurrent disease only. Various prior studies included persistent disease but excluded metastatic disease. However, this study was designed homogeneously, which may be the positive power of the study.

CONCLUSION

Our study provided favorable OS and LFFS rates and the cases of late toxicity was within tolerable limits. So, fractionated stereotactic radiotherapy-FSRT can be an alternative treatment option for the re-irradiation of locally recurrent NPC, especially for rT3-rT+ stage. However, sample population of patients should be increased by the new researchers to validate the efficacy and feasibility of FSRT. Thus, random based studies should be carried out to work out the combinatorial radio-immunotherapy with FSRT may benefit in radio resistant recurrent NPC to strengthen local control with tolerable toxicities.

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