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Nasopharyngeal Carcinoma- Role of External Beam Radiotherapy (EBRT) and Chemotherapy Vs EBRT, Chemotherapy and Intraluminal Brachytherapy

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ABSTRACT

Purpose: *We analyzed treatment out in patients with nasopharyngeal carcinoma who received External Beam Radiotherapy and Chemotherapy with those with EBRT+chemotherapy + Intra Luminal High Dose Rate Brachytherapy.*

Materials and Methods: *Total 70 non metastic nasopharyngeal carcinomas patients treated between 2004-09 were retrospectively analyzed.*

The group A consists of 48 patients who received External Beam Radiotherapy and Chemotherapy and the group B patients had EBRT+chemotherapy + Intra Luminal High Dose Rate Brachytherapy.

The EBRT dose ranged between 66-70Gy. Patients had concurrent chemotherapy with Inj.Cisplatin+5fu and adjuvant chemo. Intra Luminal High Dose Rate Brachytherapy total 3-4 fractions were delivered with minimum 6 hours gap between the two fractions, with 2 -3 Gy per fraction based on the dosage to critical normal structures.

Results: *Both groups were compared in terms of Local recurrence rates were 8.34% Vs 4.5% (p value 0.4874336) , Local and regional recurrence 2.08% vs 4.5% (p value 0.131522), Regional recurrence 4.16% vs4.5% (p value 0.7547963), Distant metastasis 25% vs 41 % (p value 0.2994465) for group 1 and 2 respectively. Advanced nodal status and male gender were bad prognostic factors as per multivarient analysis. Administration of HDR ILRT was not significant prognostic factor in our study but none developed severe complications with brachytherapy.*

Conclusion: *Both acute and delayed complications in HDR ILRT group were acceptable. Despite limitations of our study being a retrospective analytical study and non uniform distribution of treatment groups, we made an attempt to treat all the patients with uniform brachytherapy protocol. This study will help to design a prospective randomized studies in centers where advanced radiotherapy technologies were not available*

Key Words: *Non metastatic Nasopharyngeal carcinoma, Radiotherapy, chemotherapy and Intra Luminal High Dose Rate Brachytherapy.*

Introduction

Definitive Radiotherapy is the standard treatment e for patients with nasopharyngeal carcinoma. Combined chemotherapy and External Beam Radiotherapy (EBRT) used for advanced nasopharyngeal carcinomas[1,2.] For T1 and T2 lesion local tumor control rates between 70-90% with concurrent chemo radiotherapy or with EBRT alone[3,4], as compared to T3 and T4 lesions, which is between 44-68%[4,5,6.]Local control rates is an important prognostic factor[7]and it improves with enhanced radiation dose was well documented[3,8]. Advanced nasopharyngeal carcinomas carry a significant proportion of local and regional recurrence rates of failure in treatment in addition to higher distant metastatic potential of these nasopharyngeal carcinomas as compared to other head and neck carcinomas[9,10,11.] Combined modalities of chemo radiotherapy have shown to improve local control rates and distant metastases, which were promising[12,13.]

It is a challenging task for radiation oncologist to deliver a curative dose due to the situation of critical structures around the nasopharynx , so as to minimize the complications. Interstitial or intracavitary brachytherapy as a boost to EBRT is one of the promising option to administer additional dose of radiotherapy to nasopharyngeal tumors ,so as to achieve the better local control rate without much toxicities. This can be achieved by utilizing the principle of brachytherapy, as there is more dose rate near the source and rapid fall off of dose as we go away from tumor towards normal structures, per inverse square law. The local control rates which can be achieved were between 83-93% by some authors[14,15,16,and 17].

At M.N.J. Institute of Oncology and RCC, Hyderabad, India, we treated total number of 70 consecutive patients with non metastatic nasopharyngeal carcinoma between 2004-2008 with concurrent EBRT and chemotherapy. After acquiring High Dose Rate (HDR) brachytherapy machine with nasopharyngeal applicators, we treated the patients with concurrent EBRT and chemotherapy with boost to primary with fractionated high dose brachytherapy. The follow up of the patients were done up to September 2012. Now the results were analyzed in retrospective manner.

Materials and Methods

Patients and Metastatic work up and staging evaluation

Total number of seventy (70) patients with Non metastatic Nasopharyngeal Carcinoma was taken up for treatment at the Department of Radiation Oncology between 2004-08. Out of which fourty eight (48) patients were treated with EBRT (Group I) and twenty two (22) Patients were treated with EBRT and HDR intraluminal brachytherapy (Group II). The patients with stage III and stage IV were treated with concurrent chemotherapy. Patients who were 70 years and above, who were not willing for chemotherapy were not considered for chemotherapy.

Before starting treatment, all the patients under went pre treatment evaluation, which consist of detail history and physical examination, complete ENT evaluation including nasopharyngoscopy and biopsy. Patients underwent pre treatment base line complete blood picture, renal function tests, and liver function tests including serum alkaline phosphatase examination, chest X ray, ultrasound abdomen and pelvis. All the patients underwent CECT head and neck and if any suspicious lesions were found on chest x ray and ultra sound abdomen, CECT of chest, abdomen was done. All the patients underwent base line bone scan as the part of metastatic work up. Pre treatment dental evaluation, including pre radiotherapy dental prophylaxis and extractions were done. Mandatory rest period was given before starting EBRT in patients who underwent pre EBRT dental extraction. All the patients were staged according to American Joint Committee on Cancer Staging Classification 1992[18]. All the patients with metastatic disease were excluded from this retrospective analysis.

Treatment and Technical Details

External Beam Radiotherapy (EBRT)

The patients received External Beam Radiotherapy (EBRT) as primary modality of treatment. The irradiation was carried out with megavoltage equipment with Cobalt 60 equipment. Once Multi energy Linac was available, the patients were treated with appropriate energy. For residual neck nodes, electron boost was administered.

Immobilization was done for all patients (both groups of patients) with head and neck thermoplastic masks in supine position and all patients were simulated with immobilization mask. Two lateral parallel opposed fields were used to cover the primary Nasopharyngeal tumor and upper neck nodes. A lower anterior field was added to cover lower neck up to supraclavicular area. When there is tumor extension to the ethamoids or to nasal cavity, an anterior field was added to the lateral parallel opposed fields. Laryngeal shielding was done in all patients. The treatment was carried out up to 44-46 Gy in this 1st phase. In the second phase, spinal cord sparing was done and EBRT was extended up to 66-70 Gy. Patients with residual neck nodes received electron boost to neck nodes.

All the patients in both groups received conventional Radiotherapy 66-70 Gy of EBRT, 200cGy per fraction, 5 fractions per week. Stage III and Stage IV disease patients received concurrent chemotherapy with Inj. Cisplatin 40 mg/m2 weekly during EBRT, then adjuvant chemo after completion of EBRT and Intra Luminal High Dose Rate Brachytherapy (ILHDRBT) with Inj. Cisplatin 75 mg/m2 on day 1 and 5 Fu 750 mg/m2 day 1-4 for 6 cycles with adequate premedication and hydration.

Intra Luminal High Dose Rate Brachytherapy (ILHDRBT)

After acquiring Intra Luminal High Dose Rate Brachytherapy flexible nasopharyngeal balloon applicators, the patients without residual lymph nodes after EBRT were planned with Intraluminal High Dose Rate Brachytherapy. There was 2 weeks gap after EBRT was allowed for brachytherapy so as to allow some of the acute radiation reactions were to be subsided. Patients >70 years and not willing for chemo were not considered for chemotherapy.

Before brachytherapy, review of history and physical examination, Nasopharyngoscopy and ENT re evaluations were carried out. In all patients flexible nasopharyngeal balloon applicators were used (Fig 1). Informed consent was taken and the procedure was explained to the patient.

Patients were asked to be on Six hours fasting before the procedure. Lidocaine was applied with nasal swabs and sprayed in to nasal cavity and to the soft palate region with nebulizer. Nasopharyngeal Intra Luminal High Dose Rate Brachytherapy applicators were introduced into nasopharyngeal space directly through nasal cavity or through oral cavity under guidance of pediatric nasal feeding tubes, on the surface of tubes Lidocaine jelly was applied to avoid discomfort for the patient. After inserting the applicator in to both nostrils, the applicator is fixed in the nasopharyngeal cavity by inflating the nasopharyngeal balloon.

Once the applicators in place, their position is verified on simulator with check films with dummy sources in the applicator (Fig 2). The exact location of tubes was verified with Orthogonal localization simulator check films. The data was transferred to Plato Treatment planning system. The dose prescription is made to the Nasopharyngeal Point (NP), and definite set of normal tissue structure points(NS) as per Peter C. Levendag, Rob Peters et al[19]. The Target points include the nasopharynx (NP), the node of Rouviere, and the base of the skull. The normal tissue dose points include the retina, the optic chiasma, the anterior clenoid, the pituitary, the spinal cord and the junction between hard and the soft palate (Fig 3,4). Computer optimization was done with Treatment planning system, so as to deliver prescribed dose delivered to NP and to

optimize the minimal dose delivery to NT points (Fig 5,6). The data was transferred to nucletron brachytherapy machine and the treatment was executed. Total 3-4 fractions were delivered with minimum 6 hours gap between the two fractions, with 2 -3 Gy per fraction based on the dosage to critical normal structures. The nasopharyngeal applicators were retained by the patient for 2 days without much problem with single application.

Follow up:

All the patients were review every week, evaluated with weekly to asses radiation reactions, objective response, nutritional status during EBRT. Radiation reactions were graded as per RTOG scoring system (20). Before each chemo cycles, routine pre chemotherapy evaluations were carried out. After completion of entire treatment, patients were kept on follow up. Once in every month in the first year, every two months in the second year, every three months in third year, every six months in forth year and every year thereafter. At each visit, asked regarding appetite, weight gain or weight loss, disease related symptomatology. Physical examination including weight, palpation of neck, nasopharyngeal examination ,was carried out. Post treatment CT scans were done, when indicated due to financial constraints.

Statistical Analysis

There are four different kinds of events defined in this study, which consist of "Local Recurrence", "Loco regional recurrence", "Regional Recurrence" and "Mets". There are 7 categorical variables, which are sex, WHO grade, T status, N status, Stage, Cranial Nerve Palsy, and chemotherapy. Two tables 1,2 were combined together. The association between the 8 categorical variables (including the group variable) and each of the recurrence events were investigated by using log-Rank test with Kaplan–Meier survival curves [21].

There are also two continuous variables in the excel table, age and "EBRT Dose in Gy". The COX proportional hazard models were applied on these two variables [22.]Potentially significant patient's prognostic factors like, patient 's age, gender, T and N stage status, stage of the disease, cranial nerve involvement, administration of Intra Luminal High Dose Rate Brachytherapy and administration of chemotherapy were analyzed using Cox regression multivariate analysis[22.]

All the statistical analysis was carried out with R (R Core Team (2013). R: A language and environment for statistical computing) and statistical significance was determined at $P < 0.05$

Results

The prognostic characters between group I and II , patient 's gender, WHO 's grade of histopatho-logic sub type, T,N status were summarized in the table. The T status and cranial nerve involvement at diagnosis were equally distributed between both groups. There were more number of patients who belong to stage II in group II. There were more number of N2 and stage III, which will fall under advanced stage disease patients in group II, hence, chemotherapy administration rates were more in group II patients.

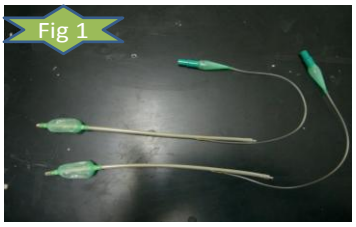
The T stage distribution in group I is 20,14,6 and 8 for T1,T2,T3 and T4 respectively and for group II, 7,5,4 and 6 for T1-4 respectively. As far as N status is concerned, in group I, 11,17,7,13 patients belong to N0,N1,N2 and N3, where as 4,7,8,3 patients respectively. There were 4, 14,10 and 20 patients in group I in stage I,II,III and IV respectively. While 1,3,10 and 8 patients in group II in stage I,II,III and IV respectively. All the patients were under regular follow up. The mean follow up period was 38.5 months and median follow up was 40 months.

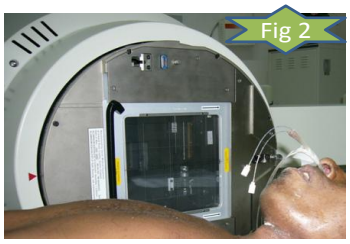
The failure rates in terms of local recurrence, loco regional recurrence, regional recurrence rates as well as distant metastasis rates were summarized in table 2and 3 with p values.

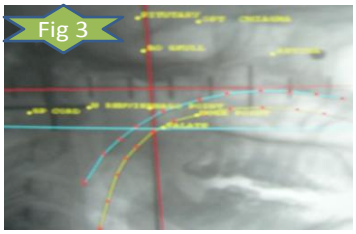
The delayed complication rates between two groups were summarized in table 3. Out of seventy patients only four patients in both groups experienced hearing loss. Two patients developed

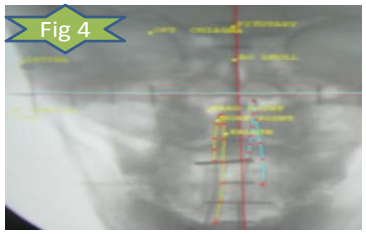
trismus, one each in both groups developed Soft tissue Necrosis of Nasopharynx, Temporal Lobe Necrosis. Five patients had Cranial neuropathy and neck fibrosis in three patients. None of the patients in Brachytherapy group(II) experienced, complications like severe epistaxis, ulceration, necrosis, foul smell, soft palate fistulae and cranial nerve palsies.

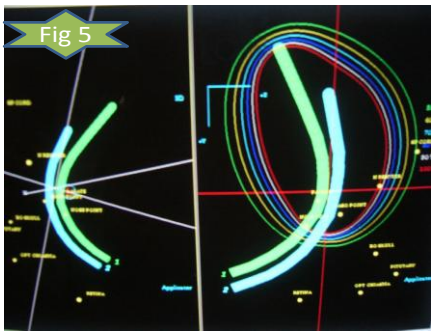
Nasopharyngeal brachytherapy Procedure











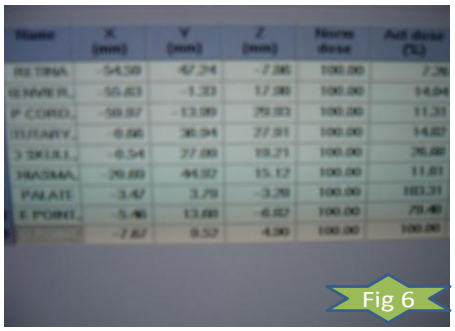


Fig 1. Nasopharyngeal brachytherapy balloon applicators
Fig 2. Patient with applicator insitu with dummy sources on simulator for verification of source position.
Fig 3.Simulator check film lateral view with dose prescription (NP) and Normal Tissue(NT) points.
Fig 4. Simulator check film AP view with dose prescription (NP) and Normal Tissue(NT) points.
Fig 5. Nasopharyngeal applicator with isodose charts. Computerized Treatment Planning System Details.
Fig 6. Dose received by Nasopharygeal point(NP), by normal tissues(NT) points.

Table 1. Patient Characteristics

Prognostic Factor	GROUP I(n=48)	GROUP II (n=22)
1.Age		
<20	3	1
20-40	19	12
>40	26	9
2. Gender		
Male	38	14
Female	10	8
3. HISTOPATHOLOGY		
WHO GRADE 1	5	3
WHO GRADE 2	15	4
WHO GRADE 3	28	15
4.T status		
T1	20	7
T2	14	5
T3	6	4
T4	8	6
5.N status		
N0	11	4
N1	17	7
N2	7	8
N3	13	3
6.Stage AJCC 1992		
I	4	1
II	14	3
III	10	10
IV	20	8
7.Cranial Nerve Palsy at Diagnosis		
Present	7	4
Absent	41	18
8.CHEMOTHERAPY		
Not given	3	2
Given	45	20
9.EBRT dose(Gy)		
Range	66-70	66-70
10.Follow up(months)		
Mean	33.958	37.2
Median	43.5	35.2

Table 2 Local, Loco regional, Regional and distant mets comparison in two groups .COXPH p-values.

	Group I(n=48)	Group II(n=22)	P value
Local recurrence	4	1	0.4874336
Local and regional recurrence	1	1	0.131522
Regional recurrence	2	1	0.7547963
Distant metastasis	12	9	0.2994465

Table 3 . The association between the 8 categorical variables (including the group variable) and each of the recurrence events investigated by using log-Rank test with Kaplan–Meier survival curves. The p-values are listed in the following table.

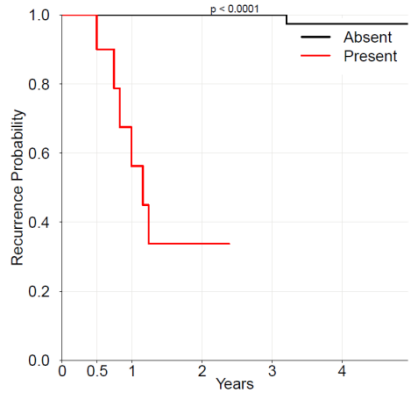
	Local Recurr	Loco regional	Regional Recurr	Mets
T status	<0.0001	< 0.0001	< 0.0001	< 0.0001
Stage	0.00731	0.0114	< 0.0001	< 0.0001
N status	0.00883	0.0233	< 0.0001	< 0.0001
Group	0.351	0.447	0.0638	0.142
Grade	0.0433	0.102	0.000848	0.000494
Gender	0.161	0.229	0.0153	0.0634
Cranial	< 0.0001	< 0.0001	0.000573	< 0.0001
chemotherapy	0.439	0.479	0.711	0.196

Table 4: Two continuous variables-COX proportional hazard models. The log test p-values are listed in the following table.

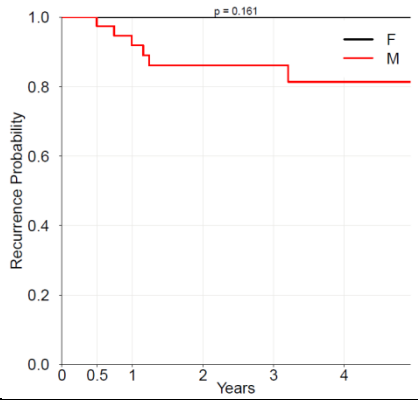
	Local Recurrence	Local Regional Recurrence	Regional Recurrence	Mets
Age	0.4874336	0.131522	0.7547963	0.2994465
EBRT Dose in Gy	0.002395778	0.02617464	3.313693e-09	2.815214e-08

Local Recurrence Plots

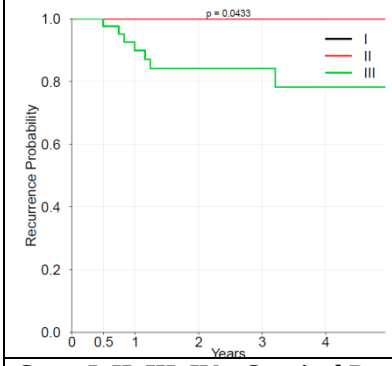
Cranial Nerve Involvement - Survival Pattern



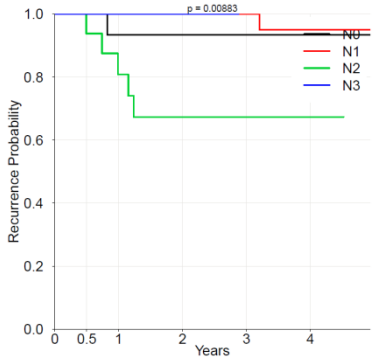
Gender – Survival Pattern



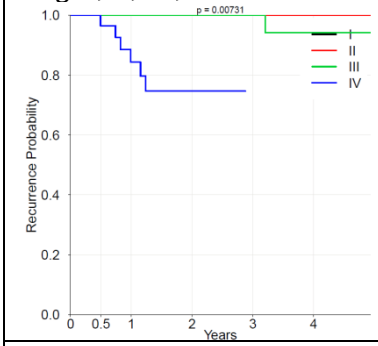
Histopathological Grade – I, II, III – Survival Pattern



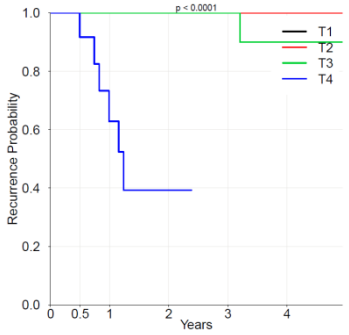
Nodal Status – Survival Pattern



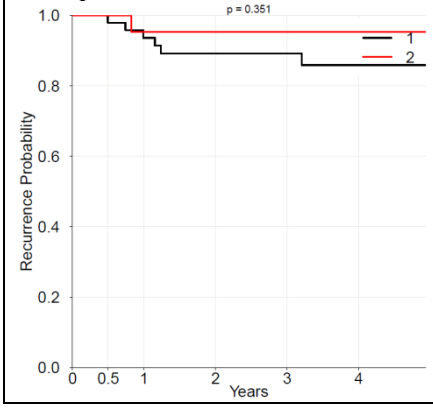
Stage I, II, III, IV – Survival Pattern



Tumor Status (T) – Survival Pattern

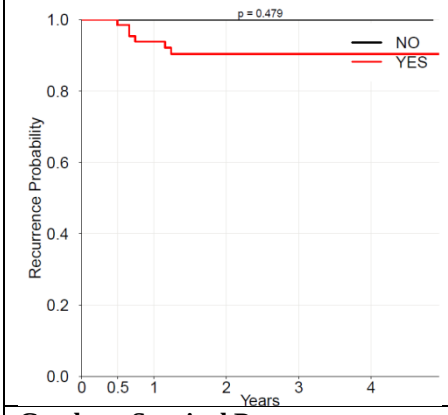


Group I, II – Survival Pattern

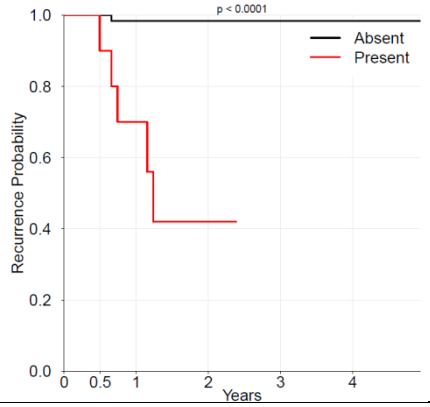


Local Regional Recurrences – Survival Curves

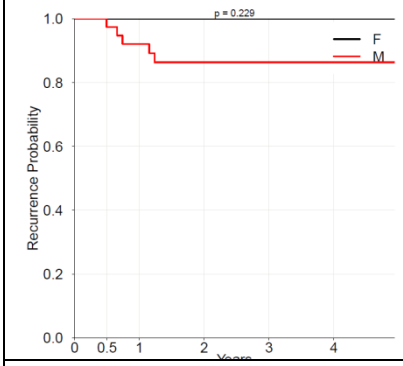
Chemotherapy - Survival Patterns



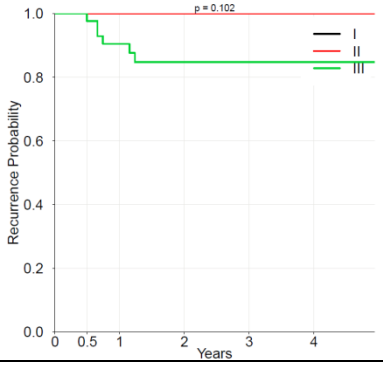
Cranial Nerves – Survival Pattern



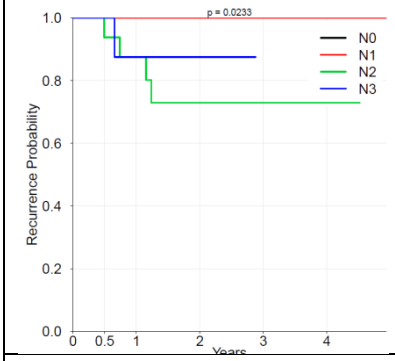
Gender – Survival Patterns



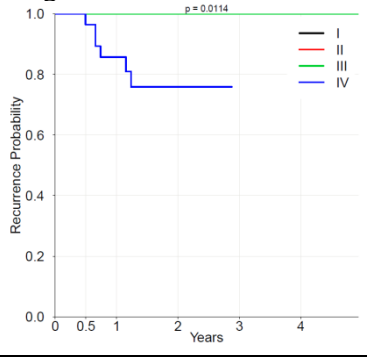
Histological Grade I, II, III – Survival Pattern



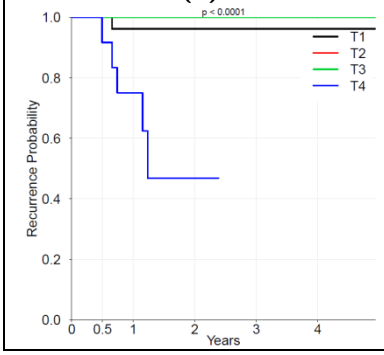
Nodal Status – Survival Patterns



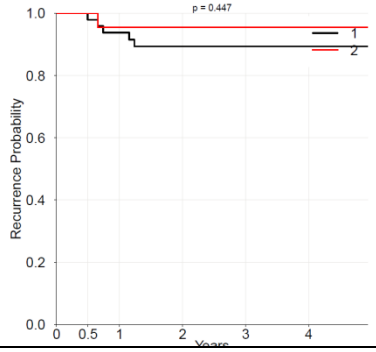
Stage I, II, III, IV – Survival Pattern



Tumor Status (T) – Survival Pattern

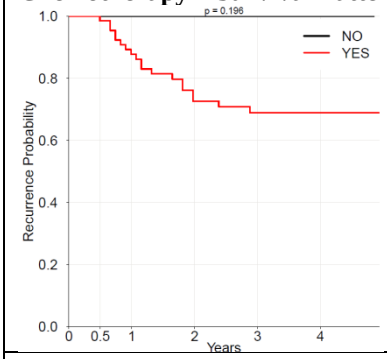


Group I & II – Survival Patterns

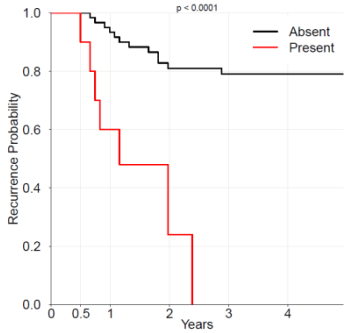


Distant Metastasis – Survival Patterns

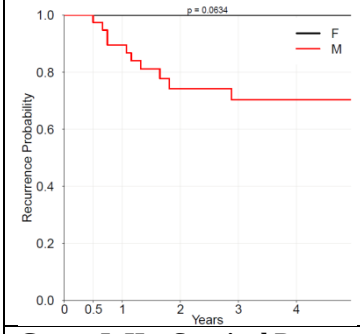
Chemotherapy – Survival Pattern



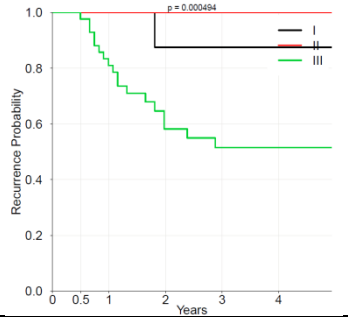
Cranial Nerve Involvement – Survival Pattern



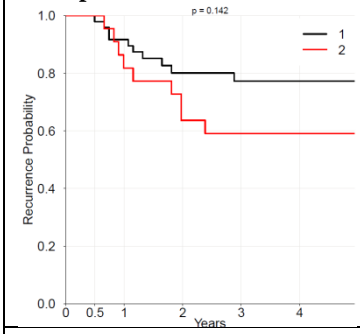
Gender – Survival Pattern



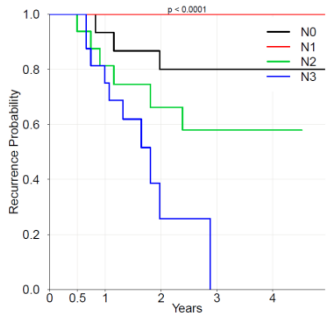
Histopathological Grade I, II, III – Survival Pattern



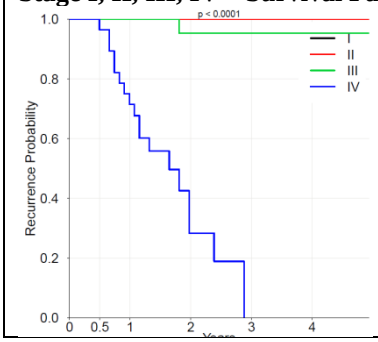
Group I, II – Survival Pattern



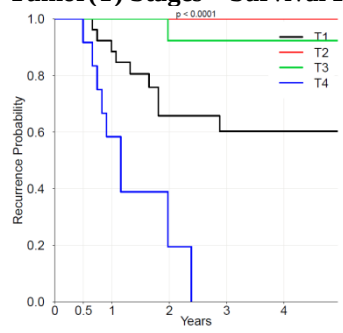
Nodal Status – Survival Pattern



Stage I, II, III, IV – Survival Pattern

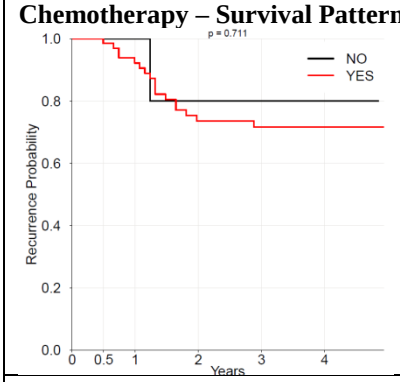


Tumor(T) Stages – Survival Pattern

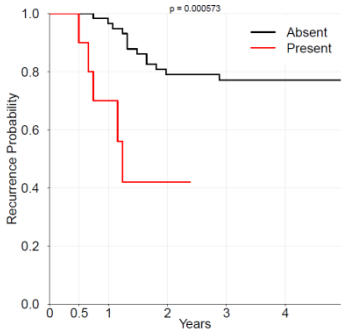


Regional Recurrence – Survival Patterns

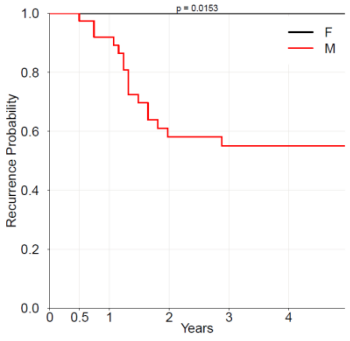
Chemotherapy – Survival Pattern



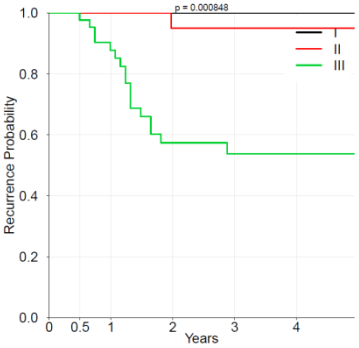
Cranial Nerve Involvement – Survival Pattern



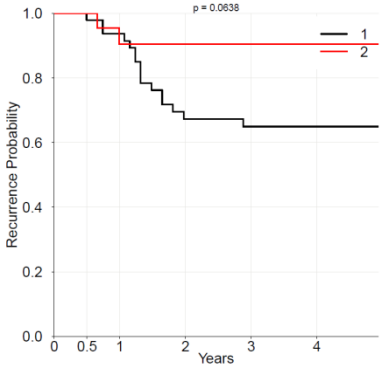
Gender – Survival Pattern



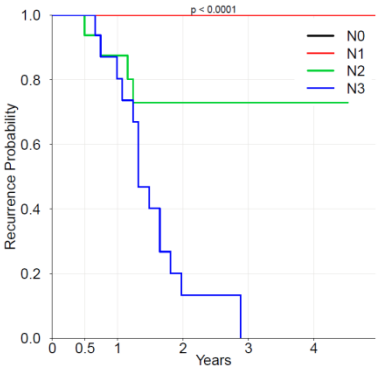
Histopathological Grade I, II, III – Survival Pattern



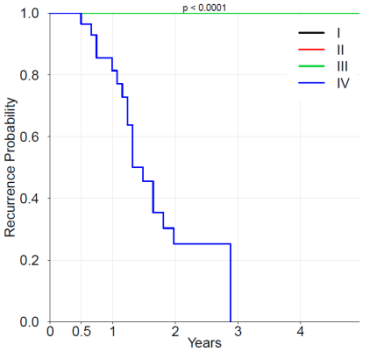
Group I, II – Survival Pattern



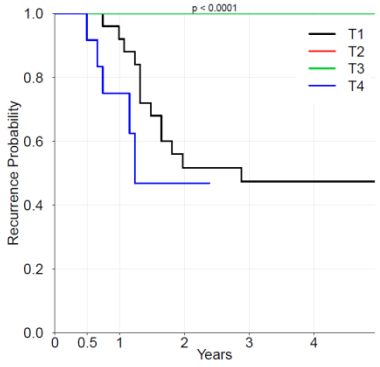
Nodal Status – Survival Pattern



Stage I, II, III, IV – Survival Pattern



Tumor(T) Stages – Survival Pattern



Discussion

Nasopharyngeal carcinomas carry a substantial risk of distant metastases. The survival rates come down with failure to control the primary tumor there by increases the risk of distant metastases. Better local control rates can be achieved by higher radiation dose[3,23]. It is very difficult to deliver higher dose of radiation to nasopharynx in view of location of critical dose limiting normal structures, which may lead to excessive

complication rates. Various other methods like Stereotactic Radio Surgery, 3-D Conformal Radiotherapy, IMRT, altered fractionation were tried for this purpose. Various methods of dose escalation were tried using combination of EBRT and brachytherapy. Brachytherapy is advantageous in this area in view of delivery of high tumor dose and minimal dose to surrounding healthy critical structures , by rapid dose fall off.

Various authors reported better local control rates for early stage disease by applying various brachytherapy techniques[24,25,26]. Study done by Chang et al between 1979-91, stage I and II patients of 133, received EBRT and Brachythrerapy. Total dose delivered was 72.5-75 Gy. The 5 year local control rate was 94%. Dose escalation beyond 75 Gy did not have local control benefit. In this series, when patient who received dose beyond 75 Gy experienced severe complications like nasopharynx necrosis, palate perforation and sphenoid floor perforation (<75 Gy Vs >75 Gy :: 4.2%Vs 13.8%). They concluded that the dose and fraction size must be reduced to decrease the complication rate from 10Gy per fraction to 2 to 2.5 Gy per fraction and limited total dose to 70.2 Gy followed by one or 2 fractions of brachyther-apy with 2 to2.5 Gy per fraction.

Syed et al[14] published their 20 years experience for treatment of primary and recurrent nasopharyngeal carcinomas between 1978 and 1997. Fifty six patients underwent interstitial and intracavitary after loading brachytherapy The study consists of three groups of patients. Patients with primary , second with recurrent or persistent disease after EBRT and the third group of patients, who were already treated for head and neck carcinoma and later had Ca.Nasoharynx. For primary tumor group, the2 and 5 year local control rate was 93% , and those with previous EBRT to nasopharynx and then recurrent tumors was 81% and 59%. The complications experienced in this series were soft tissue necrosis, chronic dysphagia, soft palate atrophy, facial numbness, persistent nasal regurgitation were experienced in seventy five percent of previously irradiated patients. The complications were seen in only 45% of the patients.

In our series, we treated total number of 70 patients with primary non metastatic nasopharyngeal carcinoma between 2004-08 in two groups. In both groups, all the patients had EBRT 66-70Gy. All the patients with T3 and T4 and N2,N3 disease, had chemotherapy. After acquiring nasopharyngeal intracavitory balloon applicators, we did brachytherapy for 22 patients, who were eligible for brachytherapy. The follow up of the patients were done up to 2012. Now we retrospectively analyzed the results. The median follow up period was38.5months. The numbers were comparable to the other reported series. There were no major complications were noted in our series as compared to other reported series [(14)]. This may be because the patients in our series did not have prior radiotherapy and due to the balloon applicator design which will cause less trauma during procedure as compared to interstitial and other applicator design. One more reason for fewer complications may be due to less number of patients in our series.

A new brachytherapy applicator design, which is easy to apply and well tolerated by the patients for treatment of nasopharyngeal carcinoma was published by Peter C Levendag et al[19] . In their series they used 200cGy per fraction, total 60Gy of EBRT followed by brachytherapy boost of 3Gy per fraction, two fractions per day for 6 fractions in T1-T3 patients without parapharyngeal extension. The patients with parapharyngeal extension received 12Gy in 4 fractions over 2 days. The reported local control rate was 96% for five years. The 3 year actuarial control rate of 86% patients treated with adjuvant Brachytherapy, as compared to 6o% in patients who had EBRT alone. Our 3 year actuarial local control rates were similar to the results with EBRT and EBRT+ Brachytherapy group. Similar patient characters were noted in both studies. Similar results were observed in a study by E.ozYAR et al.[27]

Patients with Larger tumor size and advanced T stage were not right candidates for brachytherapy, as compared to early T stage tumors. But as results were observed in a study by E.ozYAR et al[27], there will be a drastic regression of tumor after EBRT, in patients with T3,T4 lesions , these patients can be taken up for brachytherapy after EBRT as there will be regression of the tumor after EBRT.

Nasopharynx being immobile and due to central location in head and neck region and location of critical normal structures surrounding the location, Which makes an idea site for 3-D Conformal Radiotherapy(3D CRT) and Intensity Modulated Radiotherapy(IMRT) or Fractionated Steriotactic Radiosurgery even in T3,T4 lesions with better tumor control with acceptable complication rate[28,29]. When such advanced technologies were not available, and most of the patients with advanced T stage disease as in countries like India, where the advantage of additional brachytherapy should not be denied to such patients, which is a type of 3D CRT.

Conclusion

Both acute and delayed complications in HDR ILRT group were acceptable. Despite limitations of our study being a retrospective analytical study and non uniform distribution of treatment groups, we made an attempt to treat all the patients with uniform brachytherapy protocol. This study will help to design prospective randomized studies in centers where advanced radiotherapy technologies were not available.

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References

1. Cooper JS, Lee H, Torrery M et al. Improved outcome secondary to concurrent chemo radiotherapy for advanced carcinoma of the nasopharynx: Preliminary corroboration of the intergroup experience. International Journal of Radiation Oncology Biology and Physics 2000;47:861-866.
2. Al-Sara M, LeBlanc M, Giri S, et al Chemotherapy versusradiation in patients with advanced carcinoma of the nasopharynx: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310-1317.
3. Vikram B, Mishra UB, Strong EW,et al. Patterns of failure in carcinoma of the nasopharynx:I. failure at primary site. International Journal of Radiation Oncology Biology and Physics 1985;11:1455-1459.
4. Sanguineti G, Geara F, Garden A et al, Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. International Journal of Radiation Oncology Biology and Physics 1997;37:985-996.
5. Wang CC. Carcinoma of the nasopharynx. In: Wang CC,editor, Radiationtherapy for head and neck neoplasms: Indications, techniques and results. 2Nd ed. Chicago: Year book Medical publishers. Inc: 1990,p 261-283.
6. Bailet JW, Mark RJ, Abemayor E , etal. Nasopharyngeal carcinoma Treatment results with primary radiation therapy, Laryngoscope 1992;102:965-972.
7. Yang TS,Ng KT, Wang HM, et al, Prognostic factors of loco regionally recurrent nasopharyngeal carcinoma- a retrospective review of 182 cases. Am J Clin Oncol 1996;19:337-343
8. Mark JW,Bedwinek JM,Lee F, et al. Dose response analysis for nasopharyngeal carcinoma. Cancer 1982;50:1042-1050.

9. Perez CA, Devineni VR, Marcial-Vega V, et al. Carcinoma of nasopharynx: Factors affecting prognosis. . International Journal of Radiation Oncology Biology and Physics 1992:22:941-947.
10. Russel JD, Bleach NR, Glaser M, et al . Brachytherapy for recurrent nasopharyngeal nasoethamoidal tumors. J Laryngol Otol 1993;107:115-120.
11. Lee AWM, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: Overall survival and patterns of failure. International Journal of Radiation Oncology Biology and Physics 1992;23:261-270.
12. International Nasopharynx Cancer Study Group: VMCA I Trail. Preliminary results of a randomized trail comparing neoadjuvant chemotherapy(cisplatin, epirubicin, and bleomycin) plus radiotherapy vs radiotherapy alone in stage IV(>N2 Mo) undifferentiated nasopharyngeal carcinoma-ma: A positive effect on progression free survival. International Journal of Radiation Oncology Biology and Physics 1996;35;463-469.
13. Garden AS, Lippman SM, Morrison WH, et al. Dose induction chemotherapy have a role in the management of nasopharyngeal carcinoma? ?Result of treatment in the era of computerized tomography. International Journal of Radiation Oncology Biology and Physics 1996;36:1005-1012.
14. Syed AM, Puthawala AA ,et al. Brachytherapy for primary and recurrent nasopharyngeal carcinoma: 20 years experience at Long Beach Memorial. International Journal of Radiation Oncology Biology and Physic 2000 Jul 15;47(5):1311-21.
15. Chang JT, See LC, Tang SG, et al. The role of brachytherapy in early stage nasopharyngeal carcinoma. . International Journal of Radiation Oncology Biology and Physics 1996;36:1019-1024.
16. Lu JJ, Shakespeare TP ,Tan LK, et al. Adjuvant fractionated HDR intracavitary brachytherapy after external beam radiotherapy in T1 and T2 nasopharyngeal carcinoma. Head and Neck 2004 May;26(5):389-95.
17. Lee N, Hoffman R, Phillips TL, et al. Managing nasopharyngeal carcinoma with intracavitary brachytherapy: one institutions' 45-year experience. Brachytherapy 2002;1(2):74-82.
18. Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer Staging Manual. 5th edition. Philadelphia: JB Lippincott :1997.p 31-39.
19. Peter C. Levendag, Rob Peters et al. A new applicator design for endocavitary brachytherapy of cancer in cancer in nasopharynx; Radiotherapy and Oncology 1997;45:95-98.
20. Cox JD, Stetz J, et al. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)[Editorial]. International Journal of Radiation Oncology Biology and Physics 1995;31:1341-1346.
21. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
22. Cox DR. Regression model and life tables. J R Stat Soc B 1972;34:187-220.
23. Marks JE, Bedwinek JM, Lee F ,et al. Dose –response analysis for nasopharyngeal carcinoma. Cancer 1982; 50:1042-1050.
24. Wang CC. Improved local control of nasopharyngeal carcinoma after intracavitary boost. Am J Clin Oncol 1991;14:5-8.
25. wang CC, Busse J, Gitterman M. A simple after loading applicator for intracavitary irradiation for carcinoma of the nasopharynx. Radiology 1975;15:737-738.

26. Zang EP, Lian PG, Cai KL, et al. Radiation therapy of nasopharyngeal carcinoma: Prognostic factors based on a 10-year follow up of 1302 patients. International Journal of Radiation Oncology Biology and Physics 1989;16:301-305.
27. Enis Ozyer, Ferah Yildz, Fadil H. Akyol et al. Adjuvant high dose rate brachytherapy after external beam radiotherapy in nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology and Physics 2002;52(1),101-108.
28. Xia P, Fu KK, Wong GW, et al . Comparison of treatment plans involving intensity modulated radiotherapy for nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology and Physics 2000;48:329-337.
29. Sultanem K, Shu H.K, Xia P ,et al. 3D intensity modulated radiotherapy for nasopharyngeal carcinoma.The university of California-San Francisco experience. International Journal of Radiation Oncology Biology and Physics 2000;48:711-722.
30. The American Brachytherapy Society Recommendations for HDR brachytherapy for Head –And-Neck carcinoma. . Int J Radiation oncology Biol Phys vol 50:2001;1190-98