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Re-irradiation in Head and Neck Squamous Cell Carcinoma – A Single Institute Experience

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: In head and neck squamous cell carcinomas (HNSCC), residual disease, loco regional recurrence or development of second primary are causes of treatment failure. A combination of either surgery or chemotherapy or radiotherapy is used. The aim of this study was to evaluate recurrent/ relapsed HNSCC who were treated with re-irradiation, its toxicities and survival analysis.
Materials and Methods: 72 patients were analysed retrospectively who had undergone re-irradiation at our institute. All patients were histologically proven cases of recurrent/relapsed HNSCC. Treatment was done using conformal radiotherapy techniques like IMRT or IGRT technique.
Results: Patients who had recurrent disease and second primary were 38 (52.8%) and 34 (47.2%) respectively. The time interval between radiotherapy treatments ranged from 7 months to 25 years. Salvage surgery preceded radiotherapy in 16 (22.2%) patients and 56 patients (78.8%) underwent radical radiotherapy. The PTV volume ranged from 15.6 to 672.2 cc (median: 117 cc) and median

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dose was 54Gy. Mucositis and skin reactions were associated in patients with larger PTV volumes and lower time interval between the radiation treatments. The median DFS and OS was 13 months and 29 months respectively. OS at 1 year and 2 years was 58.3% and 36.1%. Patients who received radiation dose of >54Gy and who had >24 months interval between the radiation treatments fared better.

Conclusions: Treatment approaches have to be personalized in cases of recurrent HNSCC. For re-irradiation in HNSCC we found better outcomes when there is adequate time period (> 24 months) between the radiation treatments and with dose > 54Gy.

Keywords: Re-irradiation; survival analysis; head and neck squamous cell carcinomas.

1. INTRODUCTION

"Head and Neck Squamous Cell Carcinomas (HNSCC) are the 2nd most common cancer in India" [1]. Radiation therapy with Intensity Modulated Radiotherapy (IMRT)/ Volumetric Arc Radiotherapy (VMAT)/ Image Guided Radiotherapy (IGRT) with chemotherapy/ surgery have led to an improved Loco Regional Control (LRC) and Overall Survival (OS) of such patients. However one of the most challenging and complicated situations in head and neck oncology is the development of locoregional failure/ recurrence or development of a second primary malignancy in the head and neck region. It has been observed that there is 16% to 25% chance of locoregional recurrence in patients treated with postoperative chemo radiation for high-risk HNSCC [2] and 17% to 52% (depending on stage) of patients treated with definitive chemo radiation as definitive treatment for HNSCC [3]. In elective irradiation of neck there is a recurrence rate of 4–11% [4].

For patients with recurrent/ relapsed tumours the combinations of either surgery, chemotherapy or radiotherapy are usually used. Most of the times these locoregional recurrent cases are usually unresectable. In a meta-analysis done by Goodwin et al, "efficacy for salvage surgery in patients with recurrent head and neck cancer was good however they found that success was limited and costs were great in stage III and stage IV recurrences" [5]. In addition to disease-related factors, patient's comorbidities and pre-existing organ dysfunction must be considered when selecting patients for a particular treatment" [6].

"Re-irradiation or repeating radiotherapy treatment is a potentially curative treatment option in patients with unresectable disease. However these patients pose a tough clinical scenario for the treating clinician due to high morbidity associated with the treatment. But with the availability of advanced radiation techniques like Intensity Modulated Radiotherapy (IMRT) and Image Guided Radiotherapy (IGRT), Volumetric Arc Radiotherapy (VMAT) and Stereotactic Body Radiotherapy (SBRT), re-irradiation is feasible and gives encouraging results in recurrent/ relapsed HNSCC" [7,8], however at the expense of high morbidity along with an increased risk of severe or life-threatening treatment related toxicity [9]. Hence the benefits and risks should be weighed before proceeding to treatment.

Various factors determine the outcome in re-irradiation of HNSCC. Some of the factors are the volume of disease (Gross Tumour Volume - GTV), time interval between two radiation treatments, general condition of the patient, pre-treatment imaging and the functional status of Organ at Risk (OAR) in the treated area. Out of all these factors, time interval between the primary and re-irradiation is the most important factor in determining the results and morbidity associated with the treatment [10].

The aim of this study was to evaluate the behaviour of recurrent/ relapsed HNSCC with re-irradiation and its associated toxicities. Disease Free Survival (DFS) and Overall Survival (OS) were also calculated as primary end points of the study.

2. MATERIALS AND METHODS

A total of 72 patients from 2012 to 2018 who underwent re-irradiation with curative intent at our institute were retrospectively analysed after ethical committee clearance. All the patients had received their first course of definitive radiotherapy using 6MV linear accelerator and the previous treatment records were available for review. Inclusion criteria included those patients who had histologic evidence of recurrent disease or second primary after previous radiation to the head and neck region and those with ECOG

performance status of 0-1. Patients with metastatic disease were excluded. The diagnostic evaluation included physical examination, radiologic evaluation of the head and neck by Computed tomography (CT) and Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET-CT). Metastatic work up was done for each patient. Patients with poor nutritional status or significant dysphagia were taken up for feeding procedure like Nasogastric tube insertion or Feeding Jejunostomy.

Patients were evaluated for feasibility of salvage surgery before taking up for re-irradiation. Postoperative re-irradiation was considered only if the pathologic features of the surgical specimen indicated a high risk of subsequent recurrence: tumour size, positive margins, lymph node metastasis with extra capsular extension, and/or multiple lymph node metastases (>2 lymph nodes positive). However in cases of unresectable tumours primary re-irradiation (with or without concurrent chemotherapy) was considered as a therapeutic option. The decision regarding concurrent chemotherapy was solely under the discretion of medical oncologist taking into account patient factors like performance status, previous toxicities, comorbidities and choice. All patients were evaluated in multidisciplinary tumour board before proceeding with re-irradiation.

2.1 Radiotherapy Details

All patients were immobilized with a thermoplastic head and- neck cast up to the shoulders, to ensure reproducibility of re-irradiation. CT simulation with a 2.5 mm slice thickness was performed in all patients. Intravenous contrast was given to all patients at the time of simulation. Targets and organs at risk were delineated on axial CT scan sections. Gross Tumour Volume (GTV) encompassing tumour (with the help of MRI/ PET CT scan) and/or pathological lymph nodes was expanded with a margin of 0.5cm to 1cm (cropped from bone and air) to form the Clinical Target Volume (CTV). In case of post-operative patients, the CTV included the postoperative tumour bed. The CTV was expanded isotropically with a 5mm margin to form PTV as per departmental protocol. Patients were treated using 3 volume approach – high, intermediate and low risk (elective nodal) PTV depending on the volume of recurrent disease and its site. The spinal cord, brainstem, optic chiasm and nerves, eyes, carotid vessels and mandible were contoured as high priority avoidance structures.

Treatment planning and contouring was done on the ECLIPSE treatment planning system followed by evaluation of target coverage, dose uniformity, and dose to normal structures. Dose prescription ranged from 40 to 60Gy in conventional fractionation of 1.8-2Gy per fraction. Dose prescription was aimed to deliver at least 95% of the prescribed dose to at least 95% of the PTV and not more than 107% of the prescribed dose to not more than 5% of the PTV. Constraints to critical organs were tailored for each individual patient with an aim to reduce the dose to as low as achievable. Treatment was delivered using IMRT or IGRT technique. The treatment was delivered using 6 MV photons by a linear accelerator (CLINAC iX or TrueBeam STx @ Varian system). Setup verification was done using daily Cone Beam CT (CBCT).

“The patients were seen at least once a week by a radiation oncologist who assessed acute toxicity according to the (Radiation Therapy Oncology Group) RTOG criteria” [11]. Weekly blood investigations were performed which included a complete blood count and evaluation of renal parameters for patients receiving concurrent chemotherapy. Weekly assessment of grade of mucositis and skin reactions were also done. Response evaluation was done either by MRI neck or PETCT scan 3 months after treatment. Response assessment was done using Response Evaluation Criteria in Solid Tumours (RECIST) criteria” [12].

2.2 Statistical Analysis

For statistical analysis the data was entered into SPSS version 22 (Corp, Armonk, NY, USA). Descriptive statistics of all parameters under study were generated. Qualitative data were summarized as frequencies and percentages. Progression was considered when there was an increase in the locoregional size of the disease or with the presence of distant metastasis. DFS and OS was evaluated using Kaplan-Meier analysis. Univariate analysis was done to evaluate relationship between variables under study. A p value less than 0.05 was considered statistically significant.

3. RESULTS

A total number of 72 patients were analysed retrospectively. The baseline characteristics of

the patient cohort is described in Table 1. The mean and median age of the cohort was 57.6 and 58.5 years respectively. The range of age group was from 38 to 78 years. Majority of the patient population were men 62 patients (86.1%). Initial primary sites included 22 patients in oral cavity (30.5%), 38 patients in oropharynx (52.8%) and 12 patients in hypopharynx (16.7%). Patients who had recurrent disease and second primary in the head and neck region were 38 patients (52.8%) and 34 patients (47.2%) respectively.

The time interval between initial radiotherapy and re-irradiation ranged from 7 months to 25 years with mean and median duration being 42.3 months and 30.5 months respectively.

Salvage surgery preceded radiotherapy in 16 (22.2%) patients and 56 patients (78.8%) underwent definitive radiotherapy. Among these 16 patients who underwent upfront surgery, 8 patients (50%) received adjuvant concurrent chemo radiation while 8 patients were treated with adjuvant radiotherapy. Out of the patients who underwent definite radiotherapy, 40 patients (71.4%) received concurrent chemotherapy along with radiation therapy. Among these 36 patients (90%) received concurrent weekly cisplatin and 4 patients (10%) received concurrent carboplatin. The others did not receive concurrent chemotherapy either due to poor general condition, medical comorbidities or patient refusal as per discretion of medical oncologist.

The PTV volume of re-irradiation ranged from 15.6 to 672.2 cc (median: 117 cc). The PTV dose ranged from 40 to 60Gy with a median dose of 54Gy. The patients were treated using 1.8 to 2 Gy per fraction and the number of fractions ranged from 20 fractions to 35 fractions.

D_{max} to the spine ranged from 1.16Gy to 40.47Gy (median: 7.89Gy) and the D_{mean} to the spinal cord ranged from 0.54Gy to 30.57Gy (mean: 8.92Gy. D_{max} to the brainstem ranged from 0.11 to 47.3Gy (median: 4.98Gy) and the D_{mean} to the brain stem ranged from 0.46Gy to 31.45Gy (mean: 3.76Gy).

The median follow up time of the patient population was 24 months. At last follow-up, 12 (16.7%) patients have no evidence of disease, 20 (27.8%) patients were alive with disease either in the form of partial response or progressive disease after treatment and were being managed with palliative chemotherapy, 28 (38.8%) patients expired and 12 (16.7%) patients were lost to follow up.

The median DFS and OS of the total cohort was 13 months and 29 months respectively (Fig. 1a & b). At the end of 1 year and 2 years the OS was 58.3% and 36.1%.

The number of patients who were treated with a re-irradiation dose more or equal to 54Gy were 44 patients (61.1%). The median OS of patients receiving <54Gy compared to ≥ 54Gy were 15 months and 31 months respectively (p value for log rank test: 0.21) as seen in Fig. 2(a). The median DFS of patients receiving <54Gy compared to ≥ 54Gy were 3 months and 13 months respectively (p value for log rank test: 0.38) as seen in Fig. 2(b).

Table 1. Shows the baseline clinical and treatment characteristics of the cohort N=72

Characteristic	Value
Mean Age	57.6 years
Comorbidities (DM/HTN/Thyroid disease)	18 patients (25%)(total)
Initial Stage of disease (III/ IV)	19%/ 81%
Initial treatment – surgery	16 patients (22.2%)
Initial treatment – concurrent chemo radiotherapy	56 patients (77.8%)
Complete response to initial treatment	62 patients (86.1%)
Recurrent disease	38 patients (52.8%)
Second primary	34 patients (47.2%)
Stage of recurrent disease (II/ III/ IV)	19.5%/ 47.2%/ 33.3%
Range of time period between RT	7 months to 25 years
Salvage surgery	16 patients (22.2%)
Concurrent chemotherapy	40 out of 56 patients (71.4%)
PTV volume (Re-irradiation)	15.6 to 672.2 cc (median: 117 cc).
PTV dose (Re-irradiation)	40 to 60Gy (median: 54Gy)

The patients with a time period of >24 months between the two radiotherapy treatments fared better than those with <24 months both in terms of OS (29 months vs 21 months) (Fig. 3a) (p value: 0.478) and DFS (13 months vs 10 months (p value: 0.731) (Fig. 3b). However both these results were not statistically significant. In subgroup analysis elder age group (>60 years) had poorer DFS as compared to <60 year old 13 months vs 20 months (p value: 0.206).

The most common acute side effect was mucositis. Grade 3 mucositis was seen in 36 patients (50%). Toxicity was more in patients receiving concurrent chemo radiation, patients with lesser time interval between primary irradiation and re-irradiation and with greater PTV volumes. Grade 2 skin reactions were seen in 28 patients (38.9%).

Grade III laryngeal toxicity was observed in 6 patients (8.3%). Complete mouth dryness (xerostomia) was reported in 20 patients (27.7%), severe subcutaneous fibrosis was reported in 24 (33.3%), severe dysphagia in 6 patients (8.3%). Eight patients (11.1%) patients expired during the treatment. Osteoradionecrosis (ORN) and radiation myelopathy were seen in 1 patient each respectively. The patient who developed myelopathy had symptoms of lower limb weakness and numbness however there was improvement with the administration of steroids.

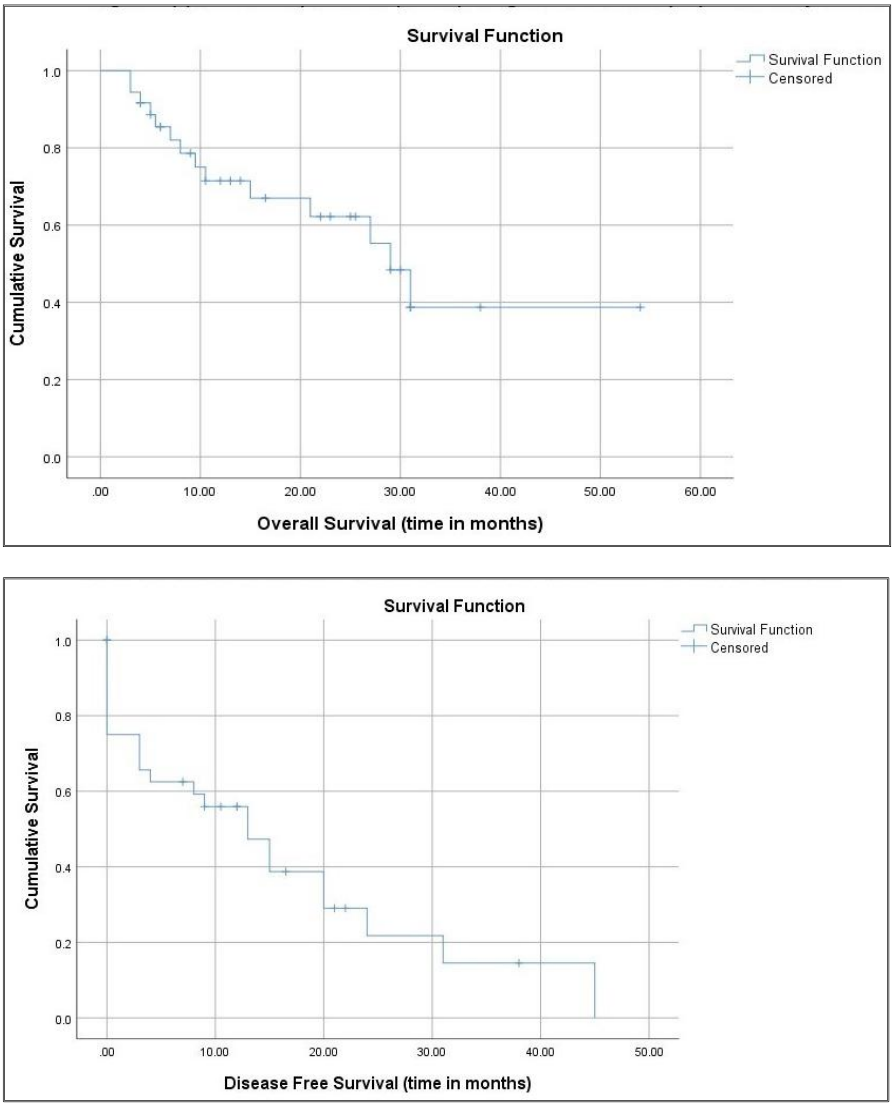


Fig. 1. Shows Kaplan Meier plot of the entire study cohort (a) overall survival (b) disease free survival

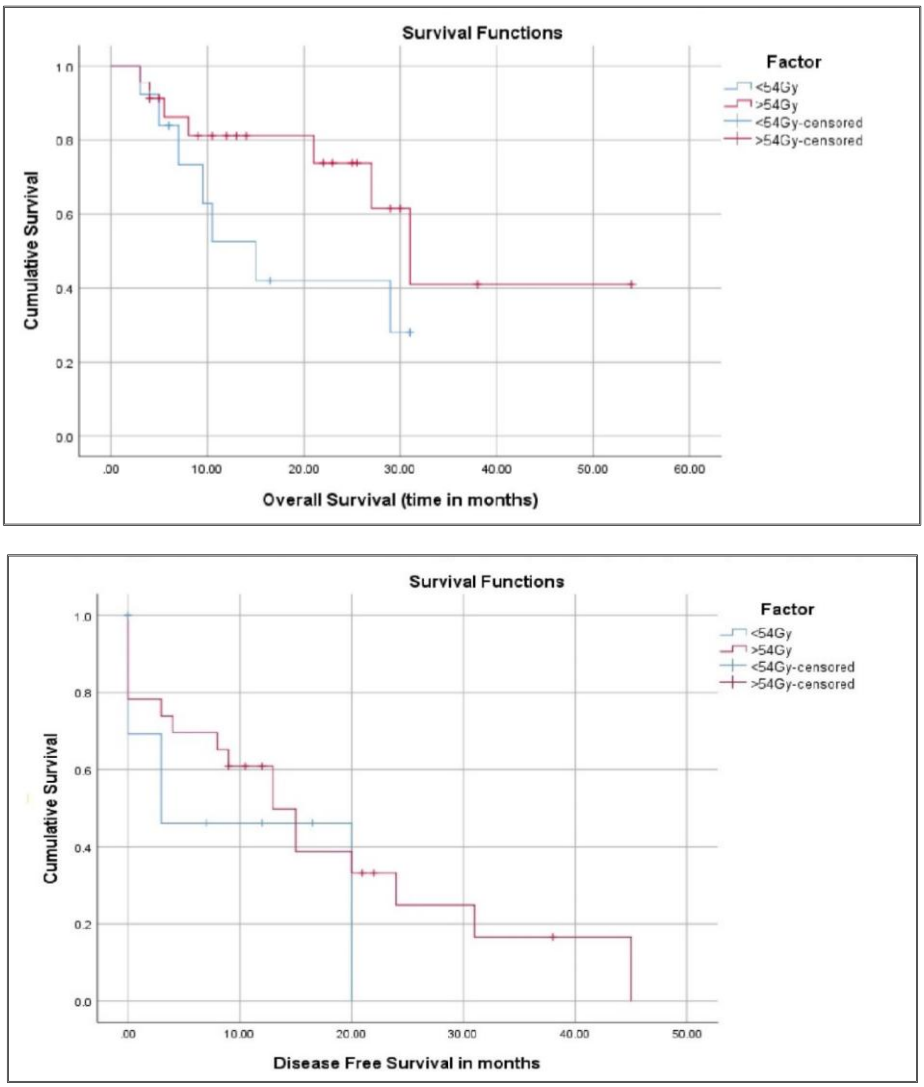
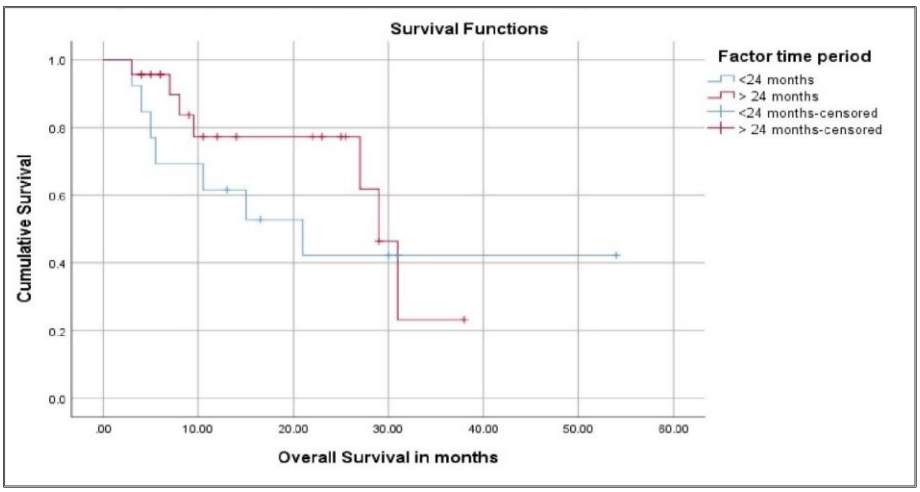


Fig. 2. Shows comparison of 2 groups (<54Gy – blue) (>54Gy – red) in terms of (a) overall survival (b) disease free survival



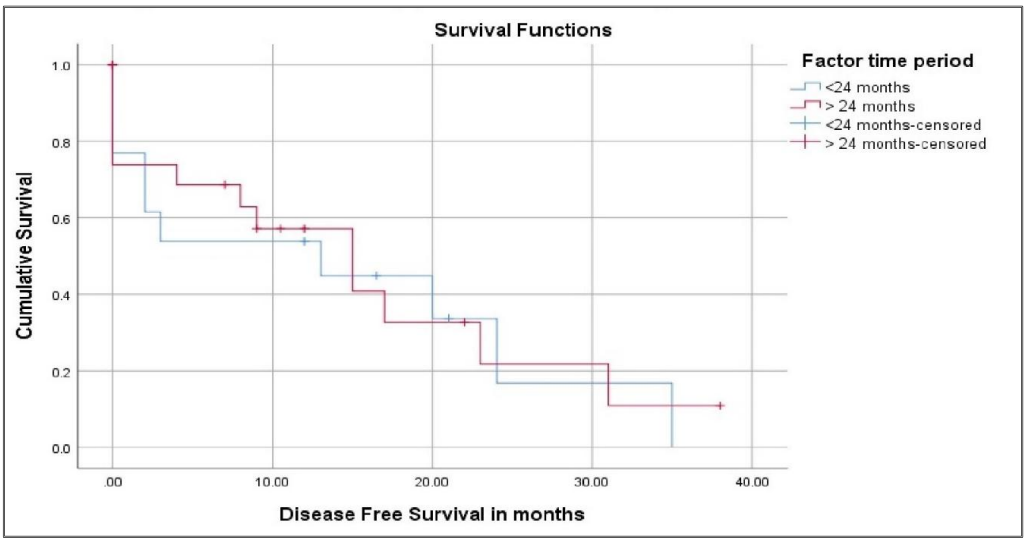


Fig. 3. Shows the comparison between 2 groups (< 24 months between radiation treatments – blue) (>24 months between radiation treatments – red) in terms of (a) Overall Survival (b) Disease Free Survival

4. DISCUSSION

Patients presenting with recurrent or second primary tumours should undergo careful restaging evaluation before the treatment with curative intent, that is, surgery or re-irradiation. "Patient selection is a key step in determining which patient should be offered re-irradiation. Evaluation should include detailed history, performance status, assessment of life expectancy and comorbidities, careful restaging imaging. Assessment to the prior radiotherapy details including dose received by critical structures such as the spinal cord, brain stem, optic apparatus, mandible etc. is very crucial. Previous treatment impairments in speech, swallowing, and hearing should be taken into consideration. The American College of Radiology (ACR) recommends that patients with a reasonable performance status who do not have a severe soft tissue or bone toxicities from prior therapy and do not have the distant metastatic disease are likely to be benefited by repeat radiotherapy treatment" [13].

One important factor is the interval of time from initial radiotherapy treatment. The longer the interval, the less likely the chances of development of severe morbidity and better chance of improved DFS and OS. This was also seen in our study and the patients with a time period of >24 months between the radiation treatments fared better however the difference was not statistically significant. "A time interval of more than 6 months from previous radiation is accepted by some as adequate for retreatment" [14] , but there is experimental data to suggest that a period of at least 2 years is required for cervical cord to recover from previous radiation dose" [15]. In our patient population this time period ranged from 7 months to 25 years with a median duration being 30.5 months. Patients who had a time interval of around 6 months between the two radiation treatments fared poorly in our study.

ACR expert panel recommends re-irradiation with a limited target volume encompassing known disease with a safety margin. A dose <50Gy was considered inadequate and 60Gy or higher was recommended [13]. Salama et al. reported "a 3-year overall survival and locoregional control of 30 and 56%, respectively for patients who received greater than 58Gy compared with only 6 and 33% among those who received less than 58Gy" [16]. Janssen et al recommended "re-irradiation with curative intent using a dose prescription of at least 46Gy" [17]. In our study majority of patients received a re-irradiation dose >54Gy and these patients fared better than the ones treated with re-irradiation dose of <54Gy. In our study 22 patients (30.5%) did receive elective nodal irradiation but these patients are the ones with adequate time between the two radiotherapy treatments and in these full recovery of OARs has been assumed.

"IMRT is known for its ability to deliver conformal treatment plans to complex target volumes, this technology is critically based on an inherent

assumption that the region of interest lies in the exact same position each day as at the time of simulation [18]. The advantage of IGRT is that it offers good quality three dimensional view of the region of interest with excellent soft-tissue contrast at the time of treatment, thereby reducing setup errors and better radiation delivery" [19]. Nowadays SBRT is also recommended for such patients and the aim is to deliver precise and focussed radiation in a small target volume [20].

In our study we found subgroups of patients who had a better outcome. These were the ones with younger age group, new primary cancers, higher time interval since previous irradiation, higher radiation dose at the time of re-irradiation and the use of concurrent chemotherapy.

In our study the median overall DFS and OS was 13 months and 29 months respectively. Higher OS was seen due to the fact that patients who recur or progress after re-irradiation do undergo some form of systemic treatment either in the form of palliative chemotherapy or immunotherapy. In a study done by Gupta et al the median OS was 33 months [21] which was similar to the results found in our study.

Dawson et al. showed "2-year actuarial survival of 32% with re-irradiation and treatment associated complications were seen in 18% of patients" [22]. Langendijk et al. reported "a 3-year locoregional control of 22% at 2 years in using dose prescription up to 60Gy" [23]. Chen at al. reported "results of using image guidance in IMRT for re-irradiation with 2-year rates of control of 65%. Grade 3 or more skin desquamation, dysphagia, and mucositis were reported by them in 57%, 42%, and 23% patients, respectively" [7].

Failures of re-irradiation are mainly within the treatment fields and are likely due to the fact that more resistant tumour clonogens are present at the site of recurrence [17]. In our study 18 patients (25%) developed local or regional recurrence after re-irradiation; 4 patients (5.5%) developed a third primary in the head and neck region and 12 patients developed metastatic disease (16.6%)

The present analysis has a small number of patients with a limited follow-up but it reaffirms the use of a re-irradiation dose of more than 54Gy in conventional fractionation for curative retreatment of head and neck cancer patients. The late toxicity profile continues to evolve in patients surviving longer and needs to be further evaluated. One of the main disadvantages of our study is that no patient received SBRT treatment.

5. CONCLUSION

Treatment approaches have to be personalized in cases of recurrent HNSCC. For re-irradiation in HNSCC we found better outcomes when there is adequate time period (> 24 months) between the radiation treatments and with dose > 54Gy.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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