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"Recurrence Following Chemoradiation in Locally Advanced Head and Neck Carcinoma – An Institutional Experience"

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Abstract: *The main objective of our study is to describe the pattern of recurrence in locally advanced head and neck cancer patients treated with chemoradiationat Father Muller Medical College Hospital, Mangalore, India. Thirty patients treated with Loco-regional recurrence chemoradiation were included. Loco-regional failure volume was defined on the planning at relapse, and dose received was analyzed by use of dose–volume histograms. Loco-regional failure was classified as In-field, Marginal or Out-fields.Median interval time from end of treatment to Loco-regional failure was 29months. There were 19 patients with local failure, 8 with a regional failure, and the remaining 3 patients failed simultaneously at both local and regional sites. 26 patients (86.7%) had In-field recurrence, 2(6.7%) patients with Marginal recurrence and 2 (6.7%) patient with Out-field recurrence. Considering primary target volumes, 18 (69.2%) Loco-regional failure occurred inside Gross Tumor Volume (GTV), 5 (19.2%) in Clinical Target Volume (CTV) region and 3 (11.6%) in GTV + CTV region. The majority of Loco-regional failures occurred In-field and precisely within GTV (High dose region). Given the low incidence of geographical misses, future studies should be directed towards additional efforts aimed at improving loco-regional tumour control with radiotherapy.*

Keywords:*Chemoradiation,Head and neck cancers,In-field, Loco-regional, Marginal, Outfield, Recurrence.*

I. Introduction

Head and neck squamous cell cancer (HNSCC) is the sixth most common malignancy worldwide and most common malignancy in male and third most common in females in India.[1]The main treatment modalities for head and neck malignancies are surgery, radiotherapy and chemotherapy. Radiotherapy is the integral component for the loco-regional control. A better loco-regional control is responsible for a better disease free survival and a better quality of life. Novel radiotherapy techniques, such as 3 dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), enable escalating the radiotherapy doses given to advanced tumours and simultaneously reducing the doses to healthy normal tissues, thus significantly improving the therapeutic ratio of radiotherapy. In patients with locally advanced disease, concurrent chemoradiation has led to improved local and regional control.

Loco-regional failure (LRF) however remains a significant cause of mortality and morbidity despite significant progress in therapeutic modalities. Most of the patients develop Loco-regional failure within 2 years from the end of treatment, and prognosis following LRF is often described as worst event, with 85% of deaths attributable to disease progression.[2,3]

Aims and Objectives

To describe the patterns of failure in patients treated with chemoradiation for head and neck cancers and to correlate the recurrences with the treated volumes.

II. Materials And Methods

All the patients diagnosed with HNSCC recurrence between September 2014 to August 2016 previously treated with concurrent chemoradiation at the department of Radiotherapy in Father Muller's Medical College, Mangalore, were taken up for this study.

- Study type- A Descriptive study
- Sample size- 30 patients satisfying inclusion and exclusion criteria given below were selected by purposive sampling.

Inclusion Criteria:
- Patients with HNSCC recurrence previously treated with concurrent chemoradiation.

Exclusion criteria:
- Patients who underwent surgery as a primary therapeutic modality.
- Patients who had inadequate clinical follow-up.

Recurrence is defined as re-emergence of tumor after initial complete regression. Recurrences are divided into local and regional recurrences. **Local recurrence** is defined as if the tumour recurs within the zone of the primary tumor. **Regional recurrence** is defined as if the tumor recurs in neck lymphnodes.

Failure is described as
- **"In-field failure"** if the 95% or more of the recurred tumor volume was covered by the 95% of prescription isodose.
- **"Marginal failure"** in which 20% to 94% of recurred tumor volume was covered within the 95% isodose.
- **"Out-of-field failure"** in which less than 20% of recurred tumor volume was within the 95% isodose line.

After taking informed consent, patients with HNSCC recurrence fulfilling the inclusion criteria were evaluated and assessed clinically, radiologically. Data was analysed by frequency, Standard deviation, t test and ANOVA using SPSS version 16.

III. Results

Of the 244 patients of HNSCC were treated with chemoradiation at Father Muller Medical College Hospital, 145 patients had complete response at 3 months. With a median follow up time of 29 months for all patients with complete response at 3months, 30 patients recurred during this period. The mean time to failure for these 30 patients with recurrent disease was 9.6 months (range:2-24 months). The patient characteristics has been depicted in the Table 1.

Table 1: Characteristics of patients with HNSCC recurrence

		Number(N=30)	%
Sex	Female	3	10.0%
	Male	27	90.0%
Primary Site	Ca Hypopharynx	8	26.7%
	Ca Oral cavity	8	26.7%
	Ca Oropharynx	11	36.7%
	Ca Larynx	3	10.0%
STAGE	STAGE II	2	6.7%
	STAGE III	4	13.3%
	STAGE IV	24	80.0%
T stage	2	6	20.0%
	3	10	33.3%
	4	14	46.7%
N stage	0	3	10.0%
	1	5	16.7%
	2	21	70.0%
	3	1	3.3%
DIFFERENTIATION	WDSCC	9	30.0%
	MDSCC	18	60.0%
	PDSCC	3	10.0%
Treatment Delivery	3DCRT	21	70.0%
	IMRT	9	30.0%
Continous/interrupted Treatment	Continuous	25	83.3%
	Interrupted	5	16.7%
Chemotherapy Drug	Carboplatin + Nimotuzumab	1	3.3%
	Cetuximab + Cisplatin	1	3.3%
	Cisplatin	28	93.3%
Site of Recurrence	LOCAL	19	63.3%
	LOCOREGIONAL	3	10.0%

	REGIONAL	8	26.7%

The time to recurrence varied between the patients. The mean time to Local failure was 10.1 months. Regional failure had a mean time to failure of 9 months. Patients with simultaneous local and regional failures tended had a mean time to recurrence of 12.8 months. There was no significant difference between the site of recurrence and time to recurrence (p=0.615). The subset of patients with N2-N3 showed a statistically significant (p = 0.003) time to relapse as compared with N0-N1 stages.

It appears to suggest earlier recurrence among patients with higher stages of the disease with a statistically significant difference (p=0.027). There was no significance with time to recurrence with respect to the primary T staging, site and histological differentiation.

Majority of the patients had recurrent disease, either primary of nodal, within the prior radiation field. There were 26 patients (86.7%) with In-field recurrence of which 18 patients were treated with 3DCRT and 8 Patients with IMRT. 2(6.7%) patients with Marginal recurrence, 1 was treated with 3DCRT and 1 with IMRT. 2(6.7%) patient with Out-field recurrence, both were treated with 3DCRT.

Considering the infield failures, 18 (69.2%) LRF occurred inside GTV, 5 (19.2%) in CTV region and 3 (11.6%) in GTV + CTV region.The statistical analysis revealed no association between the site of recurrence and the mean dose delivered to the tumour volume.

IV. Discussion

Loco-regional failures continue to be a major problem in patients with locally advanced head and neck cancers, even with combined modality treatment. While this is in part due to inherent radio-resistance of the tumours, combined with larger disease loads, the treatment technique and margins are also likely to affect the local control. The 3 month time point used here is intended to allow adequate time for the response to radiotherapy as demonstrated by Pacagnella et al. in their study on 101 patients in Italy showed that an 8 week response assessment is too early, with more complete responses 8 weeks post-treatment.[4]

The predominant pattern of relapse in this study following concurrent chemoradiation with 3DCRT or IMRT was in-field, in areas at highest risk of recurrence, including gross disease, and first echelon nodes. Pigott et al. previously demonstrated that the majority of local-regional relapses after standard two-dimensional RT as the primary treatment for head and neck cancer were in-field.[5]

Studer et al in their Locoregional failure analysis in Head-and-Neck Cancer patients treated with IMRT in 2007 have observed that in 280 treated patients, 46 local (16%) and 31 nodal (11%) failures have been observed. One marginal local failure developed in a patient referred for a recurred oral cavity tumor. Three nodal failures developed outside the PTVs at unexpected locations. All other failures have been confirmed "in field".[6]

In the present study among the 26 infield failures, 18 (69.2%) patients had recurrence inside GTV, 5(19.2%) patients had recurrence in CTV region and 3 (11%) patients had recurrence in GTV +CTV region.

In-field failure is more suggestive of radio-resistance and consequent incurability of the tumour by radiotherapy, rather than failure due to marginal miss. Large tumours are known to fail locally, likely due to the large malignant cellular population to start with, other than a host of factors like hypoxia and poor nutrition. The predominance of In-field recurrence in our study is most likely due to this reason.

The results of our analysis that local failure occurred predominantly within the high-dose region suggests the need to discern a radiation/chemotherapy-resistant subpopulation of tumours. This data, demonstrating that LRF are predominantly occurring in-field, is at least reassuring in terms of the quality of target volume definition and elective nodal targets. A search for the clinical factors that can significantly predict Loco-regional failure is warranted to identify the patients who are likely to have failure and to spare the rest of the patients from the risks of treatment intensification.

V. Conclusion

Loco- regional recurrence is a major problem in HNSCC patients and majority of them have In- field recurrences. Most of these recurrences occurred in the High dose regions. Further larger trials should be aimed in prediction of recurrence and improving the loco regional control with radiotherapy.

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