www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i2.91

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Distant Metastases in Head Neck Cancer: An Impact of Reconstruction Modality

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Abstract
Background: *With an estimated yearly global burden of 550,000 incident cases and 300,000 deaths Head neck squamous carcinoma is the sixth most common malignancy reported worldwide, and the eighth most common cause of cancer-related mortality. Surgery is the mainstay of treatment and needs extensive morbid resections. Morbidity is partly compensated with use of microvascular free flaps and provides a more functional outcome. Recurrence after all possible initial treatment is the harbinger of failure and death in head and neck cancers, especially distant metastatic disease which occurs in 4-26% of patient with almost no reported significant 5-year survival.*
Study: *A series of surgically treated head neck cancer patients developing distant metastatic recurrent disease was reviewed to evaluate surgical and etio-pathological factors prognosticating the chance of having recurrence at distal sites with a special focus on the type of reconstruction used..*
Results: *Along with generally accepted factors like tobacco intake, higher T and N stage, extranodal spread and need for neoadjuvant and adjuvant treatment; use of microvascular free flap reconstruction was more conspicuous and statistically significant in the patients having distant metastatic disease compared to those who had locoregional reconstruction done.*
Conclusion: *Extensive local disease needing multimodality treatment predicts a higher incidence of distant metastatic recurrence. Patients getting a free flap reconstruction also showed a statistically significant chance of the same as compared to those treated with locoregional reconstruction. In the present scenario, where microvascular free flap reconstruction is universally accepted as a safe modality, further studies are needed to confirm its role in occurrence of distal metastases.*
Keywords: *distant metastasis, head neck cancer, hnscc, free flaps.*

Introduction

With an estimated global burden of approximately 550,000 incident cases and 300,000 deaths per year and a high case fatality rate, Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy reported worldwide, and the 8th most common cause of cancer-related mortality.[1] It is most common cancer in developing countries, especially in Southeast Asia.[2]

In India, it accounts for one fourth of male cancers and one tenth of female cancers. With annualized incidence rate of 30/100000 in males and 10/100000 in females there is occurrence of more than 120000 cases every year in India. According to incidence statistics, in India, there has been an 75% increase in cancer death burden in 2015 compared to 2000, mostly attributed to head neck cancers.

Recurrence is the harbinger of failure and death in head and neck cancers. Despite all possible site-specific multimodality therapy, up to 60% and 30% of patients will eventually develop local and distant recurrence.[3] Overall survival significantly reduces in patients developing any recurrence. Camisasca *et al* have reported that the 5-year survival rate was 92% in HNSCC patients without recurrence and only 30% in patients with recurrence.[4] Most of the studies done worldwide have shown a 30-35% disease recurrence rate. Amongst recurrences, local and locoregional diseases are commoner and often amenable to some form of surgical salvage, irradiation or re-irradiation. Chang JH recommends that regardless of recurrence stage or site, salvage surgery is the recommended treatment of choice for recurrent HNSCC[5]. Inspite of that, outcome of such patients is still dismal with less than 20-25% 5-year survival rate. Worse than locoregional recurrent disease, outcome seen in patients having distant metastatic recurrence is dismal with almost no reported 5 year survival. Lix reported that overall survival rates of patients with DMs were 56.8% at 1 year, 9.1% at 3 years, and 6.8% at 5 years, respectively[10].

Patterns of recurrence have been frequently evaluated by many authors along with the factors associated with overall recurrence. Very few times have the factors specifically associated with distal metastases been studied. We attempt to focus on this aspect of the disease pathology to gain insights on the chances of distal metastatic recurrence in primary hnscc patients.

Study

We assessed clinico-pathological and treatment data of hnscc patients who had distal recurrence of disease after standard treatment of the primary disease. The data was analyzed to evaluate the factors responsible for the recurrence of disease. The patterns of recurrence were assessed vis a vis the modalities of treatment and clinicopathologic factors. Specific focus was on the factors which influenced occurrence of distant metastatic disease.

Inclusion criteria

1. Pathologically confirmed hnscc
2. Patients confirmed to have no distant disease at time of primary treatment with at least clinical examination, x ray chest and liver ultrasound examination.
3. Underwent standard surgery by trained oncosurgeon.
4. Advised all standard neoadjuvant and adjuvant therapy as per present clinical norms.
5. Had a recurrence of disease at a distal site, evident clinically, radiologically or histologically, with or without presence of a local or locoregional recurrence.

Exclusion criteria

1. Patients unfit for standard disease specific treatment.
2. Patients with evidence of distal spread of disease upfront.

Data collection

All the patients having clinically, radiologically or pathologically proven distal metastatic recurrent

disease were taken into study. Duration between primary surgery and first occurrence of the new lesion was considered as the time of recurrence. Site of the initial recurrence was documented. Patient data was recorded and stratified on basis of type of received neoadjuvant treatment, clinical and pathological features of the primary disease, history of tobacco intake, type of surgery and reconstruction done, and need and type of adjuvant treatment advised and received.

All the patients were operated by qualified onco-surgeons and underwent all the treatment as per standard evidence based protocols. Surgery was done in standardised manner with appropriately required local and regional resections. Frozen section evaluation of margins was selectively done as deemed appropriate. Reconstructions were done in accordance to the type of defect, comorbidities and available resources and the procedures were stratified according to the type of reconstruction needed as

1. Primary closure, local flaps, skin grafts etc and loco regional pedicled flap reconstructions, mainly pectoralis major myocutaneous flap, LD flap etc. (these were done by the primary surgeon or the plastic surgeon)
2. Microvascular free flaps- free radial flap, anterolateral thigh flaps, free fibular flaps etc. These were done by the plastic surgeon only. All free flaps irrespective of recipient or donor vessel or donor site were included.

The histopathology evaluation was standard. The pathology factors considered for evaluation were T stage (grouped as early- T1/T2 and advanced- T3/T4), margins of resection (positive or close and negative), n stage(positive and total nodes), presence or absence of perinodal extension or lymphovascular emboli.

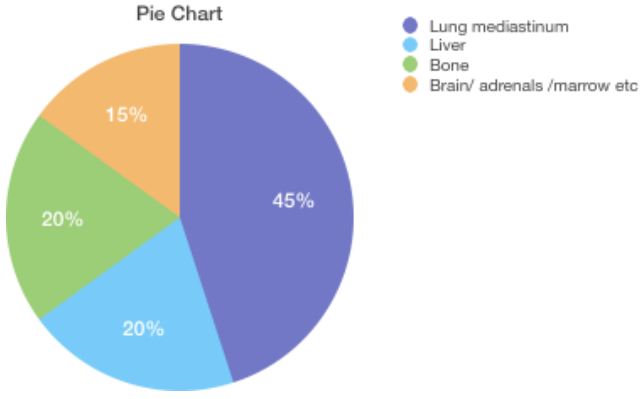
Follow up.

Standard recommended follow up record -3 monthly for first two years, 6 monthly for next 2 yrs and yearly later was available for most patients. Thorough loco regional clinical evaluation, abdominal usg and chest x-rays were done as a routine in addition to symptom based investigations for all patients. CT/PET were done in clinically relevant scenario. The data was collected once recurrence had been documented. Further follow up and treatment remained as per standard protocols.

Results

From a data of 418 patients treated for upfront localized hnscc, 48 patients having distal metastatic disease recurrence were considered for this study. All patients were initially diagnosed to have hnscc between may 2011 and may 2016. They underwent standard surgery followed by appropriate adjuvant treatment for the malignancy and were on regular follow up.

Total Patients	**418**	
Age group	**27-68 years**	**Mean 47.5 yrs**
Distal metastasis	**48**	**11.4%**
initially diagnosed Site of disease (approx percentage)	**Lungs/mediastinum**	**45%**
	Liver	**20%**
	Bone	**20%**
	Others (adrenal/brain/ marrow etc)	**15%**
Associated with locoregional disease recurrence	**yes**	23%
	no	77%
average time of recurrence	**3 months - 6 years**	37.5 months



The characteristics of all these patients were stratified mainly along 8 criteria; Viz. history of tobacco intake, T stage of the primary lesion, nodal status, margins of resection, presence or absence of lymphovascular emboli or perinodal extension, history of neoadjuvant chemotherapy, adjuvant treatment received and type of reconstruction done at time of surgery.

		n	%
tobacco intake	**yes**	**39**	**81**
	no	**9**	**19**
T stage	**T1/T2**	**13**	**27**
	T3/T4	**35**	**73**
Nodal disease	**N0**	**4**	**8**
	N+	**44**	**92**
LVE/PNI	**Present**	**26**	**55**
	absent	**22**	**45**
Neoadjuvant chemo	**received**	**6**	**13**
	not received	**42**	**87**
margins	**positive /close**	**28**	**58**
	negative	**20**	**42**
reconstruction during primary surgery	**local/locoregionalpedicled flaps**	**18**	**37**
	microvascular free flaps	**30**	**63**
adjuvant treatment advised	**yes**	**44**	**92**
	no	**4**	**8**

81% of the patients were tobacco abusers while 19% had no history of tobacco intake. 27% of patients were T stage I/II while the majority i.e. 74% had an advanced T stage (III/IV) of the primary disease. More than 17% of patients had close or positive surgical margins compared to 83% of patients having a surgically clear margin. Only 8% of the patients were node negative compared to 44 patients i.e 92% node positive patients. Amongst these more than half had two or more positive neck nodes. Lymphovascular emboli or perinodalextension, was seen in 26 patients compared to 22 patients who showed none (55% vs 45%). 92% of the patients were advised adjuvant treatment (CT/RT), while only 4 were not. Of the 44 who were advised adjuvant treatment 13 patients did not take or complete the said treatment for various reasons. Surgical modality of reconstruction of the defect created by primary surgery was also evaluated. Amongst all the DM patients, 37% Patients had a Local or locoregional reconstruction done in contrast to 63% patients having a microvascular free flap reconstruction during the primary resection.

Discussion

According to Sacco, despite the site-specific multimodality therapy, up to 60% and 30% of patients will develop local and distant recurrence respectively[3]. In a study, Vázquez-Mahía *et al.* have reported that the recurrence rate was 44.9% in patients with hnscc[7].

Overall incidence of distal metastasis has been reported to be between 4-26%. A total of 9.2% developed DM in a study[9]. Lix et al reported an incidence of distal metastasis in 11.3% patients. [10]. Ferlito noted that Pulmonary metastases are the most frequent in hnSCC, accounting for 66% of distant metastases. Other sites include bone (22%), liver (10%), skin, mediastinum and bone marrow[11].

In our study, 48 patients out of 418 developed distant metastases i.e.11.4%, similar to the available literature. Only about a quarter (23%) were associated with locoregional recurrent disease while 77% were pure distant metastasis. Location of metastatic disease was more or less similar to reported studies with lung and pleural mets accounting for half the cases. Liver and bone mets were next common sites with lesser involvement of adrenals, bone marrow and brain.

Occurrence of DM was more common in patients who had a history of tobacco abuse compared to

patients who were tobacco naïve. Also the patients who had a locally advanced disease and received preoperative chemotherapy showed more propensity to have distal metastatic recurrence. Locally extensive diseases as shown by T stage III/IV, more nodal involvement, lymphovascular emboli or perinodal extension also showed more chances to have distal recurrence. Patients who had a clear negative margin had less distal recurrence when compared to those having close or positive margins but the difference was minimal. Patients who deferred adjuvant treatment, in spite of being advised, had more incidence of distal recurrence. Also it was seen that patients who had microvascular free flap reconstruction were relatively higher in number amongst recurrent disease patients as compared to patients who had a primary closure or a local flap done.

Chang jh et al report that along with age and clinical stage, recurrence-free interval is significant independent prognostic factor for overall survival of recurrent HNSCC patients[5] In a study by Vázquez-Mahía I et al, analysis showed that comorbidities, degree of tumor differentiation, and tumor stage were important prognostic factors for recurrence[7]. Bo Wang et al report that T stage, degree of differentiation, pN stage, flap application, resection margin, and lymphovascular invasion were factors of recurrence in univariate analysis ($P < 0.05$) while multivariate analysis showed that T stage, degree of differentiation, and pN stage were only independent factors for recurrence ($P < 0.001$) [8].

Looking specifically at incidence of distant metastasis, Garavello W et al reported that age <45 years, hypopharyngeal localization, an advanced T stage and/or N stage, high histologic grade, and locoregional control were found to be significantly associated with the risk of DM [9]. According to Li X et al, clinical N stage, primary tumor site, level of tumor invasion, pathologic N stage and number of levels with pathologic lymph node were found to be significantly associated with the risk of DM[10]. The presence of pathologically positive nodes is the most critical factor to influence the eventual development of DMs[13]. Most of the factors analysed in this study were commensurate with the findings described by various authors. Tobacco intake, extensive local disease, nodal involvement, positive or compromised margins and need for neoadjuvant and adjuvant treatments were clearly more evident in patients having distant metastatic disease.

Notably, analysis showed that type of surgical reconstruction done was a important factor in patients who had distant metastases. 63% of all patients who had distal mets were having microvascular free flaps done as against to only 37% who had a local or locoregional modality for reconstruction. We analysed this data further to evaluate the statistical significance of this finding. From the data of all the 418 patients forming the substrate group, 125 had received a microvascular free flap reconstruction as against 293 who had a primary closure or a loco regional reconstruction done. This number was 30 and 18 respectively amongst the subgroup of 48 patients having distant metastases. Applying the chi square test it was seen that reconstruction using a free flap was significantly associated with occurrence of distal mets ($p<0.02$).

Microvascular free flaps are a commonly used modality for reconstruction in complex head and neck resection to reduce the eventual surgical morbidity and improve the functionality post op. Safety of these flaps has been evaluated by multiple authors and is accepted by word of mouth. De Vicente *et al* followed up 98 patients with Hnscc. They found that the mortality was 47.0% in patients with flap repair and was 67.3% in patients without flap repair ($P < 0.05$) justifying that the application of free flap repair can improve the 5-year survival rate of patients.[12]

Mucke et al followed up 773 patients with Hnscc treated with curative intent. 274 patients were immediately reconstructed using free microsu-rgical flaps. They concluded that reconstruction of defects, especially in patients presenting with higher tumor stages, is not associated with shorter

overall survival rates[20]. In an experience of 130 cases of free flap reconstruction, Alamdori et al observed an increase in survival with use of free flaps[19]. In a cohort of 242 patients with locally advanced oral hnscc, 93 with free flaps and 149 with local flaps, authors Hsieh et al comment that although cancer stages were more advanced in patients requiring free flap reconstruction, patient survival, and cancer recurrence in the patients with free flap reconstruction were maintained as patients without free flap[18]. Follow up of a cohort of 98 patients, 49 with free flap and 49 with local reconstruction, free-flap reconstruction after oral cancer resection showed a trend toward better 5-year survival[17]. Follow up of 42 patients enrolled from March 1999 to December 2004, for duration of 1 to 94 months was done. The actuarial 5-year survival rate was 41.9% (SD=9.6%) and the authors concluded that this study would not provide definitive statistical evidence, but it could certainly suggest a trend supporting that microvascular free tissue transfer does not change the survival of these patients [16]. Further a study concluded that the site or location of the free flap donor or application area or the vessel used for the flap did not affect survival overall in a study of 184 patients (15). In a review Wong et al have also justified use of microvascular free flaps [21]

All findings of our study other than the use of microvascular free flaps are in concordance with all the available literature. In contrast to other studies, Free flaps in this review show increased chance of distant metastasis which is definitely debatable. This can be attributed to several factors:

1. Oral malignancies present in this region in a relatively advanced stage with most being T4 and node positive diseases. In our study, out of the patients who had distant mets, very few had an early disease. 4-12%
2. Use of free flaps for reconstruction are a logical first choice in the western world and at tertiary centers in India even for early diseases. In the geographical area concerned here, free flaps are done more as a necessity when local flaps like PMMC with/without deltopectoral flap or Nasolabial flap or similar are technically not possible as for example with extensive skin involvement by primary, neck nodes involving or close to skin, extensive soft tissue involvement, middle third mandibular resection etc. Eventually, patients receiving free flaps were indirectly biased to have relatively advanced disease.
3. Most of the studies in past have evaluated the overall survival and disease free survival as the endpoint and not the occurrence of distant metastasis as one. We evaluated the patients who had distant metastasis. Locoregional recurrence was also not taken into consideration. Though presence of distant metastasis does project dismal survival, mere occurrence has to be further followed to reach the desired end point which may alter the results to bring them at par with the available literature.

Having discussed so, still the statistically significant finding of this study stays that patients with microvascular free flaps did have a higher chance of getting distant metastasis in the long run and eventually had a chance of poorer outcome compared to the patients with local or locoregional flaps used in reconstruction. This needs to be evaluated and possibly refuted by further studies of longer follow ups and preferably randomised trials before the all acceptable oncological safety of microvascular reconstruction is established beyond doubt for all comers in oral cancers.

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