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# Comparison of Different Treatment Modalities in Advanced Laryngeal Hypopharyngeal Squamous Cell Carcinoma

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## ABSTRACT

**Objective:** To compare outcome of patients with advanced laryngeal hypopharyngeal squamous cell carcinoma treated surgically or with chemotherapy and/or radiotherapy.

**Study Design:** Observational study.

**Place and Duration of Study:** The Aga Khan University Hospital, Karachi, from January 2000 to December 2005

**Methodology:** Medical records of already treated stage-III and IV squamous cell carcinoma of larynx/hypopharynx patients were reviewed. Group-A comprised of patients treated with surgery ± adjuvant therapy whereas non-surgically managed patients were labeled as group-B. One hundred and nineteen out of 275 met the inclusion criteria. Kaplan Meier technique was used to estimate mean recurrence time with standard errors. Cox proportional hazard regression was used to estimate the hazard ratio with 95 percent confidence interval for gender, age and tumour location.

**Results:** Sixty two percent of group-A and 49% patients of group-B were stage-III. In group-A, 40% patients received postoperative adjuvant therapy while in group-B, 45% received concomitant chemoradiation. Mean follow-up duration was 18.3 months. Mean recurrence time was 1369±193 days. In group-A, mean recurrence time was 2097±277 days. It was 399±68 days for group-B patients ( $p < 0.001$ ). The hazard ratio of recurrence in hypopharyngeal tumours was 1.5 times (95% CI 0.68, 3.30) as compared to tumours of larynx. The hazard ratio of recurrence was 1.98 times (95% CI 0.99, 3.95) when both larynx and hypopharynx were involved as compared to when tumour was localized to larynx only. No residual disease was noted at the completion of treatment in surgical group-A while 62% patients of the group-B had residual disease at the completion of treatment. Larynx was retained in only 25% patients in group-B.

**Conclusion:** Statistically significant difference was noted in disease free outcome when stage-III and IV larynx hypopharynx cancer was managed surgically as compared to non-surgical management. Chances of retaining larynx are only 25% when managed non-surgically.

**Key words:** Advanced squamous cell carcinoma larynx/hypopharynx. Concomitant chemoradiation. Organ preservation. Hazard ratio.

## INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer in men, with a worldwide incidence of approximately 780,000 new cases per year.<sup>1</sup> It is widely spreading disease in Southeast Asia due to increased use of tobacco. Among all the sites of Head and Neck, oral cavity takes the lead followed by larynx and hypopharynx.<sup>2</sup>

Hypopharyngeal cancers are usually squamous cell carcinomas (SCCs) that has the worst prognosis among the head and neck cancers. Overall, 5-year survival rate remains poor despite recent advancements in diagnostic imaging, radiation, chemotherapy and improved surgical techniques. Hypopharyngeal cancers tend to present in advanced stage, and nodal metastasis is mostly present

at initial presentation. The most important features determining prognosis are the size and extent of local spread of the primary carcinoma and the extent of involvement of regional lymph nodes. Distant metastasis at presentation is commonly seen in hypopharyngeal cancers than in other head and neck cancers. Poor survival is partly due to emergence of second primary cancers but also secondary to development of distant metastasis.<sup>3</sup>

Until the early 1990s, the standard treatment for locally advanced disease was total laryngectomy followed by radiation.<sup>4</sup> Induction chemotherapy (cisplatin plus fluorouracil) followed by radiotherapy, and surgery plus adjuvant radiotherapy for advanced laryngeal hypopharyngeal cancer shows comparable results.<sup>5</sup>

Decision of modality of treatment for advanced (stage-III and IV) laryngeal/hypopharyngeal cancer needs consideration to matters other than tumour type and staging, like general health of the patient, socio-economic status of the patient, patients understanding the importance of regular follow-up and possibility of salvage treatment either in the middle of chemoradiation protocol or at its completion. Chemoradiation is frequently

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associated with serious toxicity, which is aggravated in malnourished patients.<sup>6</sup> Swallowing dysfunction is a devastating complication of chemoradiation therapy (CRT) for head and neck squamous cell carcinoma. Pre-treatment swallowing exercises improve post-treatment swallowing-related quality of life.<sup>7</sup>

Low socioeconomic status and uncommon practice of medical insurance largely affects medical access of the patient,<sup>8</sup> Like other diseases, head and neck cancer is commonly seen in patients belonging to low socio-economic group and that also affects treatment outcomes.<sup>8</sup> The only disadvantage of surgical treatment for advanced laryngeal hypopharyngeal cancer is a permanent tracheostomy in the neck and loss of voice, which can very well be taken care by conservative laryngeal procedures, where applicable.

The objective of this study was to compare disease free outcome of patients with advanced laryngeal hypopharyngeal squamous cell carcinoma treated either surgically or with chemotherapy and/or radiotherapy.

### METHODOLOGY

This was an observational study carried out at The Aga Khan University Hospital between January 2000 until December 2005. Patients were selected on a convenient sampling method from Head and Neck cancer registry. Medical records of already treated advanced stage (III and IV) squamous cell carcinoma larynx/hypopharynx patients were reviewed. Only those cases of advanced larynx hypopharynx squamous cell cancer were selected where treatment was offered with curative intention and no prior treatment was acquired for this disease. Out of 275 cases treated during this period, 119 cases were selected being stage-III and IV. Non-squamous pathology and early laryngeal/hypopharyngeal cancer were excluded from the study. Patient's treatment selection was biased depending where patient presented, whether it be surgical clinic, radiation oncologist or medical oncologist.

Patients who underwent surgery alone or with adjuvant therapy were placed in Group-A whereas patients who received radiotherapy and/or chemotherapy were categorized in Group-B by the investigators.

Data on demographic information, recurrence rate and rate of larynx preservation was collected on a proforma. Data was analyzed using SPSS 14. Frequencies by groups (surgical and non-surgical) for gender, stages of the disease, tumour location, neck metastasis, adjuvant therapy and patterns of recurrence have been observed. Kaplan Meier technique was used to estimate mean recurrence time with standard errors. Graph of recurrence rate was made for overall recurrence time, tumour location and by groups. Cox proportional hazard regression was also used to estimate the hazard ratio with 95% confidence interval for gender, age and tumour location.

### RESULTS

One hundred nineteen patients were selected for this review. Seventy four patients (62%) were in the surgical group (group-A) and rest in the group-B. In both the groups, mean ages of the patients were 59 years. There were 69 males in group-A and 32 males in group-B. In group-A, 46 patients (62%) were stage-III whereas in group-B, 22 patients (49%) were stage-III. Forty nine patients in the group-A had lesion limited to larynx only, 3 patients had lesion limited to hypopharynx and 22 patients had lesion involving both larynx and hypopharynx. Ten patients in the group-B had lesion limited to larynx only, 20 patients had lesion limited to hypopharynx and 15 patients had lesion involving both larynx and hypopharynx. Ipsilateral neck node involvement was seen in 16 patients (22%) of the group-A out of which 13 patients underwent neck dissection along with surgery for primary disease. Twenty one patients (47%) of group-B had neck metastasis, out of which 13 patients (29%) had ipsilateral and 8 patients (18%) had contralateral metastasis. In group-A, 30 patients (40%) also received postoperative adjuvant therapy, 27 patients (36%) received radiotherapy and 3 patients (4%) received postoperative chemotherapy. In group-B, 45% received concomitant chemoradiation and the rest received single modality treatment either radiation or chemotherapy.

Overall censoring was 47%. Mean follow-up duration was 18.3 months. Mean recurrence time was 1369 ± 193 days. In group-A, mean recurrence time was 2097 ± 277 days. On the other hand in group-B, mean recurrence time was 399 ± 68 days. Significant difference in recurrence time was observed in both the groups (p < 0.001, Figure 1). There is no difference in recurrence time for different tumour locations (Figure 2). The hazard ratio of recurrence in hypopharyngeal tumours was 1.5 times (95% CI 0.68, 3.30) as compared to tumours of larynx. Hazard ratio of recurrence was 1.98 times (95% CI 0.99-3.95) when both larynx and hypopharynx were involved as tumour is localized to

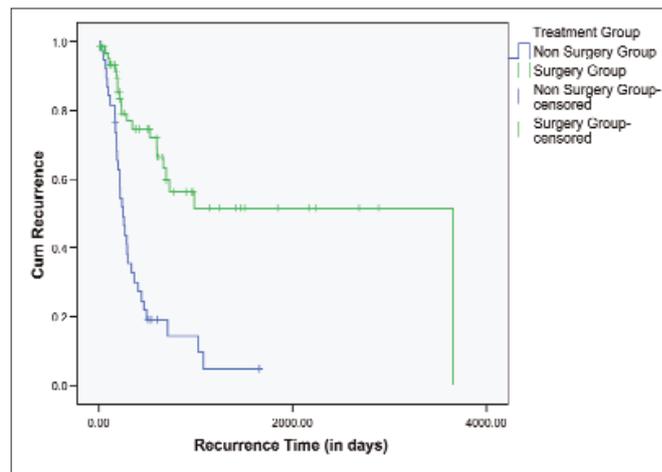


Figure 1: Surgical vs. non-surgical recurrence pattern.

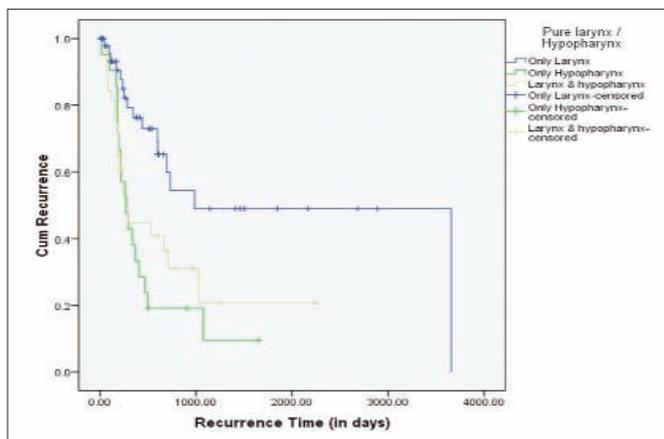


Figure 2: Recurrence pattern with tumour location.

larynx only in Table I. No significant difference in the recurrence was observed by gender, although females had higher chance of recurrence as compared to males (hazard ratio=1.15; 95% CI 0.49-2.67). Similarly, in consideration of age, chances of recurrences were higher in patients younger than 40 years of age but this difference was also not statistically significant (hazard ratio 2.72; 95% CI 0.99 7.48, Table II).

Table I: Hazard ratio of recurrence with tumour location.

Tumour location	Mean recurrence time (SE)	Hazard ratio (95% CI)
Only larynx	2030.4 (329.8)	1
Only hypopharynx	468.1 (105.5)	1.50 (0.68, 3.30)
Both larynx and hypopharynx	753.4 (179.0)	1.98 (0.99, 3.95)

Table II: Hazard ratio of recurrence with age.

Age group	Mean recurrence time (SE)	Hazard ratio (95% CI)
< 40	280.2 (86.4)	2.72 (0.99, 7.48)
41-50	886.6 (183.0)	0.69 (0.24, 2.01)
51-60	1069.4 (268.1)	1.06 (0.49, 2.30)
61-70	1816.8 (344.7)	0.74 (0.34, 1.62)
71 and above	911.7 (242.3)	1

In group-A, no patient had residual disease at the completion of treatment and 21 patients (28%) later developed locoregional recurrence. On the other hand 28 patients (62%) of the group-B had residual disease at the completion of treatment. Out of those 28 patients, 10 patients died during treatment and rest of them were lost to follow-up because of no improvement in their disease process. Locoregional recurrence was observed in 5 patients (11%) and larynx was retained in 12 patients (25 %) in group-B.

### DISCUSSION

Laryngeal cancer for males has been reported in Karachi as highest in Asia.<sup>2</sup> Increase use of tobacco either in the form of cigarette smoking or chewing smokeless tobacco is regarded as the reason for this high incidence. Bhurgari has reported 36% males and 44% females chew pan or pan with tobacco in Southern Karachi,<sup>2</sup> while in this study, 85% of the patients were male.

Cervical node metastasis is frequently encountered in larynx and hypopharyngeal tumours. Buckley and others have noticed 36% of ipsilateral and 27% of contralateral nodal metastases in surgical specimen for no neck and rate was 90% and 37%, respectively in N+ necks.<sup>9</sup> In this series, overall neck node involvement was noticed in 32% cases, 23% had ipsilateral neck node involvement and 9% had contralateral neck metastasis.

Bova and others evaluated patients with total laryngopharyngectomy in the treatment of hypopharyngeal cancer squamous cell carcinoma.<sup>10</sup> Thirty one (17.8%) and 43 (24%) patients developed locoregional and distant metastasis respectively. Two and 5 years disease specific survival rates were 72 and 52%, respectively. Univariate analysis shows advanced nodal stage, perineural invasion, lymphovascular invasion, and positive margins as predictors of poor survival and lymphovascular invasion was an independent prognostic factor on multivariate analysis.<sup>10</sup>

Byers and others have reported improved survival in patients who received postoperative radiotherapy in the management of laryngeal cancer.<sup>11</sup> In group-A of this series, 40% received postoperative adjuvant therapy. Single modality treatment for advanced laryngeal and hypopharyngeal cancer is not widely accepted but is still practiced. Haugen and others used radiotherapy for advanced (T3 and T4) laryngeal cancer with or without chemotherapy. He reported an overall poor outcome of the disease but more importantly his results have revealed no change in outcome whether chemotherapy was combined or not with radiotherapy.<sup>12</sup> Similarly, in group-B of this study, 45% received concomitant chemoradiation and the rest received single modality treatment with no change in outcome.

Lohynska *et al.* has reported median follow-up time of 36 months.<sup>13</sup> In this series, the mean follow-up duration was only 18.3 months. Poor follow-up is attributed to lack of financial recourses, poor understanding of the importance of follow-up on patient's part and patients belonging to remote areas outside the city.

Stoekli *et al.* have reported mean recurrence time for laryngeal cancer after radiotherapy as 14.5 months (435 days) and 10.6 months (318 days) for hypopharyngeal cancers.<sup>14</sup> In this series, mean recurrence time of all the patients was 46 months, while mean recurrence time in group-A was 70 months and mean recurrence time for group-B was 13 months. Gleich and others reported 48 recurrences in their series of 940 stage T3 or T4 squamous cell cancer patients.<sup>15</sup> Twenty four patients developed primary site recurrence, 20 patients developed regional recurrence, and 4 patients developed locoregional recurrence. Mean time for recurrence was 14.0 months and the mean survival time was 26.2 months. Survival is poor once recurrence is noted after treatment for advanced primary site head and neck cancer.<sup>15</sup>

Lohynska *et al.* reported worse prognosis in females as compared to males and in their series, age had no

bearing on outcome.<sup>13</sup> Similarly, in this series, chances of recurrences were higher in females as compared to males but chances of recurrences were higher in patients younger than 40 years of age as compared to patients with age more than 40 years.

Timely identification of recurrence is essential to plan salvage treatment. In cases of advanced laryngeal hypopharyngeal cancers managed non-surgically, repeated CT scans/diffusional MRI are done to identify recurrences. It is difficult to differentiate between recurrence and radionecrosis on computed tomography scan and conventional magnetic resonance imaging.<sup>16</sup> Diffusion weighted MRI or FDG PET are showing promising results in identifying early recurrence. Sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET scanning are reported as 100%, 81%, 46%, and 100%, respectively.<sup>17</sup>

Urba *et al.* has reported 30% residual disease in non-surgical management of advanced laryngohypopharyngeal cancer, twenty percent of which was identified in the early part of treatment and underwent early salvage surgery, 3% had late salvage surgery after completion of chemoradiotherapy.<sup>18</sup> In this series, 62% of group-B had residual disease out of which 22% died during the treatment and rest 40% were lost to follow-up because of no response to treatment. Those 11% of the patients who had locoregional recurrence, 7% were given palliative chemotherapy because of late identification of recurrence and only 4% could be offered salvage surgery. Salvage surgery for recurrence after non-surgical management of advanced larynx-hypopharynx cancer ranges between 7-10%,<sup>18,19</sup> similarly, in this series salvage surgery was only possible in 4% of patients. If repeated examinations under anaesthesia and biopsies or FDG PET scan would be available, these non-responders to treatment could be timely identified and salvage treatment could be possible.

Limitations of this study were small sample size and bias in selection of treatment, which in turn was influenced by patient's presentation.

## CONCLUSION

There was significant difference in disease free outcome when advanced larynx-hypopharynx cancer was managed surgically as compared to non-surgical management but at the expense of loss of voice and a permanent stoma in the neck. Chances of retaining larynx are only 25% when managed non-surgically.

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