

## Original Article

# Morbidity of Different Treatment Modalities in Advanced Carcinoma Larynx

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### Abstract

**Objectives:** To evaluate morbidity of different modalities of treatment in advanced carcinoma larynx (stage III and IV).

**Methods:** It was a cross sectional study conducted among selected 70 patients of advanced carcinoma larynx treated by different modalities of treatment from April 2009 to April 2010 in different tertiary hospitals in Dhaka.

**Results:** The age of the patients ranged from 30 to 79 years (mean  $\pm$  SD = 54 $\pm$ 10.94), maximum age incidence 5<sup>th</sup> decade. Almost all were male, habituated in betel nut and leaves chewing and smoking. Mostly (60%) from poor socioeconomic group. 70% cases were supraglottic and 30% cases were glottic carcinoma. Nature of lesion was exophytic 71.43% and ulcerative 28.57%. 22.86% had neck node metastasis. Histopathologically 60% were moderately differentiated and grade II squamous cell carcinoma (SCC). In the total laryngectomy patient pharyngocutaneous fistula (30%), wound infection (10%), haematoma (10%), stomal recurrence (10%), stenosis is tracheostomy (10%), recurrent chest infection (10%) and pharyngeal stenosis (10%) were the morbidities. Mucositis or painful erythematous reaction in larynx and pharynx (95%), pericondritis (2.5%), dryness of mouth and throat (100%), loss of test (100%), subcutaneous fibrosis (32.5%), nausea vomiting, skin rashes and alopecia (100%) were the morbidities of chemoradiotherapy and radiotherapy. After analysis the major and minor morbidities of different, modalities of treatment there was no significant ( $p > 0.05$ ) difference among those modalities.

**Conclusion:** The difference between the morbidity of single modality and combined modalities had not significant. So the combined modalities approach may be advocated for the treatment of advanced carcinoma larynx where required.

**Key Words:** Carcinoma larynx, Treatment modalities, morbidity of treatment in laryngeal carcinoma.

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### Introduction

The larynx is the most common site for primary malignant tumour in head and neck region which accounts for 25-30% of Head and neck malignancy<sup>1,2</sup> It is one of the most common cancers in Bangladesh<sup>3</sup>. It is male predominant<sup>4</sup>. >97% are squamous cell carcinoma<sup>7</sup>. strongly associated with smoking, alcohol and some environmental factors. Laryngeal carcinomas are diverse in their behavior and prognosis. Topographically it is more supraglottic in nature than other sub sites in this subcontinent<sup>4,5,6,7</sup> as well in Bangladesh (67-73%)<sup>8,9,10,11,12</sup>. Laryngeal

carcinoma has high rate of cure in certain sub sites and early stage, may reach over 85% and overall exceeds 50%<sup>13</sup>. Most of the failures in the treatment of laryngeal cancer are due to the delay in diagnosis can contribute to the presentation with later stage diseases and difficulty in eradicating the loco regional disease<sup>14</sup>.

Laryngeal cancer like all other head and neck cancer are best treated by multidisciplinary approach. The major goal of the treatment of cancer of the larynx is to maximize the cure rate while preserving speech and swallowing function. Treatment is based on the site of involvement and TNM stage of the tumour and some of the patient's factors also remain due consideration. Irradiation and surgery are two main modalities of treatment of cancer larynx. It can be treated by radical radiotherapy, by surgery or by combination of these two modalities. Chemotherapy has previously played a minor adjuvant or palliative role in the treatment of advanced carcinoma, but now it is increasingly used as combined in treatment of early stage of the diseases<sup>15</sup>. Historically, locally advanced carcinoma of the larynx (i.e., T<sub>3</sub> and T<sub>4</sub> and/or N<sub>2</sub> and N<sub>3</sub> disease) has usually been treated with combined surgery and pre- or post-operative RT or RT alone for unresectable disease. The disadvantages of a primary surgical approach include loss of organ function. Locoregional tumor control rates with total laryngectomy and postoperative RT are high (80%–90%). The addition of postoperative RT to a primary surgical approach is crucial to reducing the rate of locoregional failures. For advanced operable carcinoma of the supraglottis, management options include surgery combined with RT, chemotherapy combined with RT, or RT alone. When RT is combined with surgery, it is usually given postoperatively because of the ability to tailor the dose more

optimally on the basis of histopathologic information (i.e., the number of positive nodes, the presence of extracapsular extension, and/or the status of the primary surgical margins) and because there are generally lower rates of complications.

The acute and late effects of RT are directly dependent on such factors as total dose<sup>16</sup>, dose/fraction, treatment volume, overall treatment time, and daily interfraction interval with hyperfractionated RT.<sup>17</sup> Other factors that also influence the late complication rate include the stage of disease, the sequence of RT and surgery (i.e. post operative RT), and chemotherapy<sup>18</sup>. Both acute and late normal tissue effects may be exacerbated in the presence of other medical conditions, such as hypertension, diabetes, immune suppression, and collagen vascular disease.

Acute reactions occurring during fractionated RT for carcinoma of the vocal cords are usually mild. Increases in hoarseness, sore throat, dysphagia, patchy mucositis, erythema, and erythema of the skin in the radiation field may develop, generally beginning during the second to fourth week of RT. Laryngeal edema of varying degrees may persist after RT for carcinoma of the glottis or supraglottis. In patients who have been irradiated for carcinoma of the glottis, the incidence of mild to moderate laryngeal edema persisting for more than 3 months after RT is about 15.4% to 25%.<sup>21</sup> Late laryngeal necrosis after RT is rare, with a reported incidence of about 0.5% to 1.8% for glottic cancer.

This cross sectional comparative study tries to correlate the morbidity of different modalities of treatment in the laryngeal carcinoma management.

## Methods

This cross sectional observation study conducted in the Department of ENT and

Head-Neck Surgery, in Dhaka Medical College Hospital, Bangabandhu Sheikh Mujib Medical University and Shaheed Suhrawardy Medical College Hospital Dhaka, the three major tertiary level hospital in Bangladesh during January 2009 to December 2010. The study populations were selected by purposive sampling from the patients of advance carcinoma larynx (Stage III and IV) admitted into Otolaryngology and Head-Neck Surgery Department of these hospitals and matched the inclusion criteria. Advanced carcinoma (Stage III & IV) according to UICC involving the larynx confirmed by histological report. They were grouped and under went different modalities of treatment and attended periodic follow up visit. Patients were treated by either total laryngectomy or total laryngectomy followed by radiotherapy, chemoradiotherapy or radiotherapy alone. These are classified as single modality of treatment (treatment

either surgery or chemotherapy or radiotherapy) or Combined modalities of treatment (treatment more than one modalities of treatment like surgery plus chemoradiotherapy/ radiotherapy and chemotherapy plus radiotherapy). The morbidity status of different modalities was classified as major morbidity and minor morbidity. The clinical or physical states which significantly hampered the patient's physiological state and quality of life are grouped as major morbidity. Unavoidable minor complications which are tolerable and regress are defined as minor complications (table- 1). During this study ethical implication was thoroughly looked upon. All the data pertinent to the patient kept confidential. The accumulated data analyzed by standard statistical method. Statistical analysis was done by Sigma stat3.5 and SPSS -15 methods.

## Results

**Table- I**

*Presentation of different complication of different modalities of treatment of carcinoma of larynx*

Type of Treatment	Minor morbidity	Major morbidity
<b>Surgery-Total Laryngectomy</b>	Wound infection, haematoma, seroma, minor bleeding , scar	Pharyngocutaneous fistula flapnecrosis, stomal recurrence, stenosis of the tracheostomy, recurrence in neck, recurrent chest infections, distal metastasis, pharyngeal stenosis
<b>Radiotherapy</b>	Nausea, vomiting, skin rashes, mucositis or painful erythematous reaction in larynx and pharynx, dryness of mouth and throat, loss of taste, subcutaneous fibrosis	Severe reaction necrosis of skin, respiratory distress following radiation and perichondritis
<b>Chemotherapy</b>	Nausea, vomiting, skin rashes, alopecia, painful erythematous reaction.	

**Table-II**  
*Direct laryngoscopic findings (n=70)*

Findings	No of patients	Percentage (%)
Region of involvement		
Supraglottic	49	70.00%
Trans glottic	13	18.57%
Glottic	8	11.43%
Subglottic	0	0
Nature of lesion		
Exophytic	50	71.43%
Ulcerative	20	28.57%
Vocal cord Fixation		
Free or slight impairment	0	0
Fixed Vocal cord	70	100%
Right	30	42.86%
Left	30	42.86%
Both	10	14.29%

**Table- III**  
*Histopathological grading of the carcinoma larynx (n= 70)*

Degree of differentiation	Grading	Number	Percentage (%)
Well differentiated	I	15	21.43%
Moderately differentiated	II	42	60.00%
Poorly differentiated	III	13	18.57%
Undifferentiated	IV	0	0

**Table- IV**  
*Frequency of regional lymphnode involvement with different subsite of carcinoma larynx (n=70)*

Sl. No.	Site of carcinoma	Total case	Lymphnode involvement	Percentage (%)
1	Supraglottic	62	24	38.71%
2	Glottic	8	0	0
3	Subglottic	0	0	0

**Table- V**  
*Complications after total laryngectomy (n=10)*

Complications	No of patients	Percentage (%)
Early Complications		
1. Pharyngocutaneous fistula	3	30%
2. Wound infection	4	40%
3. Haematoma	2	20%
4. Seroma	1	10%
5. Flap necrosis	1	10%
Late Complications		
1. Stomal recurrence	1	10%
2. Stenosis tracheostomy	1	10%
3. Recurrence chest infection	1	10%
4. Pharyngeal stenosis	1	10%

**Table-VI**  
*Complications of radiotherapy in carcinoma larynx after total laryngectomy (n=3)*

General side effect	No of patients	Percentage (%)
Dryness of mouth and throat	3	100%
Loss of taste	3	100%
Pigmentation of skin	3	100%
Subcutaneous fibrosis	3	100%

**Table-VII**  
*Complications chemoradiotherapy in carcinoma larynx (n=20)*

Radiation complications	No of patients	Percentage (%)
Radiation Mucositis or painful erythematous reaction in larynx and pharynx	19	95%
Cancel the procedure following chemoradiotherapy	1	5%
Perichondritis	1	5%
Dryness of mouth and throat	20	100%
Loss of taste	20	100%
Nausea	20	100%
Vomiting	20	100%
Skin rashes	20	100%
Alopecia	20	100%

**Table-VIII**  
*Complications of radiotherapy (alone) in carcinoma larynx (n=40)*

Radiation complications	No of patients	Percentage (%)
Radiation Mucositis or painful erythematous reaction in larynx and pharynx	37	92.50%
Severe reaction necrosis of skin	3	7.50%
Respiratory distress following radiotherapy	1	2.50%
Perichondritis	1	2.50%
Dryness of mouth and throat	40	100%
Loss of taste	40	100%
Subcutaneous fibrosis	13	32.50%

**Table-IX**  
*Different types of Morbidity in different modalities of treatment (surgery plus chemoradiotherapy, chemoradiotherapy and radiotherapy alone) (n=70)*

Modalities	Major morbidities	Minor morbidities	Total
Surgery plus Chemoradiotherapy	15	12	27
Chemoradiotherapy alone	2	139	141
Radiotherapy alone	5	93	98
Total	22	244	266

Chi-square= 89.595 with 2 degrees of freedom. (P = <0.001)

**Table-X**

*Comparison of morbidity between single modality of treatment (radiotherapy alone) and combined modalities of treatment (Surgery+ Chemoradiotherapy or Chemoradiotherapy) (n= 70)*

Modality	Major morbidities	Minor morbidities	Total
Single (Radiotherapy).	5	93	98
Combined (Surgery+ Chemoradiotherapy or Chemoradiotherapy)	17	151	168
Total	22	144	266

Chi-square= 1.445 with 1 degrees of freedom. (P = 0.229)

### Discussion

In this study randomly selected 70 cases of advanced laryngeal carcinoma male were out numbered than female. Male to female ratio was 13:1. This result differ from that of studied of other 7.5:1<sup>1</sup>, 8.5:1<sup>13</sup>, 10:1<sup>16</sup>, 9:1<sup>19</sup> and 4.5:1<sup>20</sup>. Although all other the studies revealed male predominant with carcinoma larynx. The age of the subject range from 30-79(mean 54± SD10.94.) year and the maximum (38.57%) incidence of carcinoma larynx between 50 to 59 years of age. The age incidence is almost identical with the result of others and the results are age group of 55 to 64 years 46.19%<sup>13</sup>, 50.29%<sup>16</sup> and 48.33%<sup>25</sup>.

By direct laryngoscopy, supraglottic carcinoma was found 70%, the overall glottic carcinoma 30% and no cases were found subglottic carcinoma.. In USA, glottic carcinoma account for 60% of all laryngeal cancer, 35% of supraglottic cancer and 5% of subglottic cancers<sup>21</sup> which was not coincide. But in Korea, supraglottic and glottic cancers account for 49.5% and 37% of laryngeal cancers<sup>27</sup>, which was also reflected to this study. The similar observation was conducted by others, in our country and abroad. Supraglottic growth 67.2%, glottic 31.3% and subglottic 1.57%<sup>13</sup> which was also similar to this study In laryngoscopic

examination it was found that 100% cases vocal cord were fixed, 42.86% cases right vocal cord fixed, 42.86% left vocal cord fixed and 14.28% both vocal cord fixed. The nature of lesion was exophytic 71.43% and ulcerative 28.57%. Nodal involvement was found 38.71% cases of supraglottic carcinoma. Observed by others, nodal involvement was 52.53% in supraglottic carcinoma<sup>13</sup>. Level of lymphnode involvement 75% cases at level III and 25% cases at level IV.

Regarding histopathological examination among cases all were found to the squamous cell carcinoma with varying degree of differentiation (table-VII). Similarity was seen in other study that almost entirely squamous cell carcinoma over 95%. On the basis of degree of differentiation, carcinoma was graded, it was found 15(21.43%) well differentiated, 42(60%) moderately differentiated and 13(18.56%) was poorly differentiated. Majority of the subject belongs to grade II. Another study shown majority (49.25%) having grade II and 35.83%, Grade III and only 1.5% Grade IV lesion<sup>13</sup>.

Regarding the TNM staging, stage I and stage II tumour were excluded from the study and staging of tumour revealed that stage III 71.43%, stage IV 28.57%(table-VIII). This observation was not consistent with the result of others, and that was stage I 3.48%, stage

II 14.93%, stage III 32.84% and stage IV 48.16%<sup>14</sup> because in that study most of the cases (81.60%) were at advanced stages (stage III/IV) at the time of presentation.

Treatment is based on the stage of the cancer as well as its location and the health of the individual three types of treatment were given-surgery followed by radiotherapy, chemoradiotherapy and radiotherapy alone (fig. 1).

Among the total 70 study cases, 10 cases were done total laryngectomy followed by radiotherapy or radiotherapy followed total laryngectomy, 20 cases were treated chemoradiotherapy and rest 40 cases were treated by radiotherapy alone.

In the 10 cases of total laryngectomy, 7(70%) cases received preoperative radiotherapy full dose as curative therapy and 3(30%) cases received radiotherapy after surgery and these were advanced stages (stage III and IV), mean age of patient was  $58.90 \pm 11.789$ . Tracheostomy was done preoperatively in 7 patients and in remaining 3 patients; it was done at the time of operation.

In this study, following total laryngectomy pharyngocutaneous fistula developed 30% patients. These patients were irradiated preoperatively with preoperative tracheostomy. It was developed 8<sup>th</sup> to 10<sup>th</sup> day of operation. This result almost coincide by another study 12.7%<sup>22</sup> and this was not coincide by another studies 67.65%<sup>1</sup> and 51%<sup>23</sup> The fistulas were healed with daily dressing for 3-4 weeks with good nutrition supplied.

Wound infection 40% of total laryngectomies coincides with another study 41.18%<sup>13</sup>, Haematoma 20%, seroma 10%, flap necrosis 10%, coincide with another study 8.82%<sup>16</sup>. Stomal recurrence 10% not coincide with another study 5.88% (Alauddin, M 1992). Pharyngeal stenosis 10% a lower rate of

5%<sup>24</sup>. Stenosis tracheostomy 10%, loss of voice and oronasal airway and permanent tracheostoma cause considerable morbidity and disability.

Among the 10 cases of 3(30%) patients received radiotherapy after surgery for locoregional treatment and all the patient developed several side effect of radiotherapy like dryness of mouth and throat, loss of taste sensation, pigmentation of skin and subcutaneous fibrosis during study period (table-XI). Another study reveals the same type of morbidity of acute radiation like difficulty in tasting food 76.3%, dryness of mouth 92%<sup>25</sup> and taste changes and dry mouth<sup>26</sup>.

Platinum based chemotherapy particularly the combination of cisplatin and 5 fluorouracil (5FU) were applied prior to radiotherapy. This appears the ability of neoadjuvant chemotherapy to predict radiosensitivity<sup>27</sup>. In this study, 20 patients were treated with chemoradiotherapy, 95% patients developed radiation mucositis in the larynx and pharynx, 5% patients cancel the procedure following chemoradiotherapy, 5% patients developed pericondritis(table-XII). All the patients were developed dryness of mouth and throat and loss of taste, nausea, vomiting, skin rashes and alopecia. The same type of morbidity also reveals in another study (Solomon, MN 2009).

In this study out of 70 patients, 40 were treated by radiotherapy alone in Dhaka Medical College Hospital, Dhaka the machine was Telecobalt-60 total dose was received 6600cGY and 33 fractions, once daily, 05 days per week, 200cGY per fraction. The dose to the tumor bed, extra nodal extension or close surgical margins. After the delivery of radiotherapy 92.5% patients develop mucositis in larynx and pharynx, 7.5% developed severe reaction necrosis of skin, 2.5% developed respiratory distress following radiotherapy, 2.5% developed pericondritis,

100% patients developed dryness of mouth and throat, and loss of taste, 32.5%, patients developed subcutaneous fibrosis. These type of morbidity due to radiation also reveals in another study pain and soreness of mouth 86.8%, pain and itching of the skin 86.8%, difficulty in chewing 55.3%<sup>31</sup>

Over all this study shows that major morbidities for surgery plus chemoradiotherapy / radiotherapy major 15 and chemoradiotherapy major was 2 and minor morbidities for surgery plus chemoradiotherapy / radiotherapy were 12 and chemoradiotherapy 139. The morbidity due to radiotherapy alone were major 5 and minor 93. At the end of the table (table-XVI) it was shown different major and minor morbidities after combined and single modality of treatment. Finally comparison between the single modality and combined modalities were done and the test of significant (the Chi-Square test) was done to see the association between different modalities. But after the Chi-Square test it was found that the difference between the different modalities was not statistically significant ( $p > 0.05$ ).

### Conclusion

By comparing the morbidity of different modalities of treatment as a single or in combination in the treatment of advanced carcinoma larynx, it had found that each modality had its own morbid state which were differs from others. The morbid state was varies significantly among each of the individuals depending on their different confounding status. In case of total laryngectomy with or without radiotherapy the post operative complications and morbidity were more than organ preservation treatment e.g. radiotherapy with or without chemotherapy. The difference between the morbidity of single modality and combined modalities had not significant. So the

combined modalities approach may be advocated for the treatment of advanced carcinoma larynx where required.

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