A Cross Sectional Study on Loco-Regional Recurrences and Overall Survival Rate among Patients with Stage II (T2N0M0) Glottis Carcinoma Treated with Chemoradiation and Surgery

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ABSTRACT

BACKGROUND

Single modality treatment for stage I and stage II squamous cell carcinomas of glottis region gave excellent results. Since a long time these are treated either with definitive radiation therapy or surgical excision with endoscopes. There was not much difference with regard to voice preservation, local recurrence and disease-free survival period. Our aim was to study the clinical presentation and management protocol of glottis carcinoma in a tertiary hospital and observe the final outcome of stage II (T2N0M0) glottis carcinoma and specific factor for survival in patients treated with surgery, radiotherapy and concurrent chemoradiation.

METHODS

43 patients of glottis carcinoma stage II (T2N0M0) attending a tertiary teaching hospital between May 2015 and April 2017 were included in the study. Demography and smoking status of subjects were recorded. Staging of the disease was according to American Joint Committee on Cancer (AJCC) Staging System 7th edition. Paraglottic space infiltration was taken as a criteria to upgrade the staging. The overall survival rate, recurrence free survival, disease specific survival rate and laryngeal function preservation rate were calculated.

RESULTS

Out of 43 patients, males were 90.69 % and 09.30 % were females. Male to female ratio was 10.57 : 1. Mean age was 58.62 ± 2.35 years. 67.44 % were current smokers, 27.90 % were former smokers and 02.32 % were non-smokers. The overall survival scores and disease specific survival was 100 % with 11.62 % locoregional recurrences. The voice preservation was 86.04 %. Radiotherapy was used in 72.09 %, chemoradiation in 18.60 % patients and 11.62 % patients underwent surgery. 11.62 % patients presented with locoregional recurrence during 24 months of follow up. 02.32 % patients had to undergo tracheostomy.

CONCLUSIONS

The overall survival scores and disease specific survival were 100 % with 11.62 % loco-regional recurrence. Voice preservation was 86.04 %. Proactive prevention rather than escalation of treatment protocol gives better prognosis.

KEYWORDS

Glottis, Larynx, Supra Glottis, Sub Glottis, Squamous Cell Carcinoma, Chemo Radiation and Trans Oral Laryngeal Surgeries

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BACKGROUND

Among all the cancers in the body, carcinoma larynx is the second most common head and neck cancer.[1] All over the world annually more than 1,59,000 new cases are registered and nearly 90,000 cancer deaths occur,[1] which accounts for 2 % of all cancers. In South Asia laryngeal cancers are more common among men and male to female ratio was 9: 1.[1]

Conservative surgery or radiotherapy (RT) offers equal cure rates in its early stage but RT is more popular worldwide.[1] For intermediate and advanced staged tumours (stage III and early IV a), total laryngectomy followed by RT was in practice until 1991. Later "Veterans Administration Larynx" Study and organ preservation trials established combination of chemotherapy with radiation. After the reports in New England Journal of Medicine in 1991 by the Veterans' Affairs Administration[2] reports and Radiation Therapy Oncology Group (RTOG 1991),[2] the treatment protocols have changed to organ-preserving non-surgical type from conventional partial and total laryngectomies.[2] Among the currently used surgical methods are trans per oral voice preserving conservative surgeries either preceded or followed by radiotherapy.[3] These procedures have replaced conventional open partial laryngectomy.

However, surgery plays a definite role in the management of laryngeal cancer.[4] Single modality treatment of early squamous cell carcinomas of the larynx have given good prognosis historically.[5] At present, stage I (T1N0M0) and stage II (T2N0M0) glottis cancers are being treated with definitive radiotherapy or trans oral micro laryngeal surgeries using cold instrument or laser. The final outcomes of either modality have no significant differences in loco regional control rates.[6,7]

Whenever there are incidences of loco regional failure; both these modalities allow using salvage option of surgical procedures.[8] Presently the focus of management is on preservation of the anatomy and function of larynx, quality of swallowing and speech. According to Indian Council of Medical Research (ICMR) guidelines the glottis carcinoma T1 is defined as the tumour involving one (T1a) or both (T1b) vocal cords, (may involve anterior and posterior commissures) with normal mobility of vocal cords.

T2 is defined as tumour that may extend to supra glottis and / or may extend to sub glottis and / or with restricted mobility.[1] The 5 year disease specific survival (DSS) for stage I glottis cancer patients was reported as 94 – 99 % with laryngeal preservation of 95 %.[9,10] For stage II glottis cancers with similar treatment modalities, the 5 year disease specific survival dropped to 79 - 95 % with voice preservation rates of 76 – 82 %[10] giving a scope to question the rationale behind treating the stage I and II glottis cancer with the same management algorithm.[11,12]

In this study the clinical presentation and management protocol of glottis carcinoma of larynx in a tertiary hospital was analysed with an objective to observe the final outcome of stage II (T2N0M0) glottis carcinoma of larynx and specific factors for survival in patients treated with surgery, radiotherapy and concurrent chemo radiation.

METHODS

The present study was a cross sectional observational study of 43 patients with the provisional diagnosis of stage II (T20N0M0) glottis cancer, who were treated with single modality treatment protocols as per a tertiary hospital protocol. After obtaining an institutional ethics committee approval, study was conducted over a period of two years from May 2015 to April 2017 at Viswabharathi Medial College and Hospital, Kurnool, Andhra Pradesh.

Sample Size and Procedure

Based on the previous year records the sample size was calculated as 43 by using sample size formula: $N = 4pq / d^2$, $N = 4 \times 85. 1 \times 14.9 / (9.7)^2 = 44$; Hence, 43 applications were included in the study. All consecutive patients who met the eligibility criteria were included till the required sample size was attained.

43 patients with stage II glottis cancer (T2N0M0) were given radiotherapy using three-dimensional conformal radiation therapy (3DCRT) techniques with two parallel opposed fields using "wedge" and high-energy photons (Co60 or 6 MVX). A total of 70 Gy RT was applied in 35 fractions with 2 Gy / fraction, 5 fractions / week. LL the patients were treated with cisplatin ranging from 30 to 40 mg / m2 weekly for 6 weeks. The total period of follow up was for 24 months.

Inclusion Criteria

1. Patients aged between 18 and to 70 years.
2. Patients of both genders.
3. Patients with glottis cancer stage II (T2N0M0).
4. Patients willing to undergo the treatment as per the institutional protocol.

Exclusion Criteria

1. Patients below the age of 18 and above 70 years.
2. Patients who previously underwent surgery of larynx.
3. Patients who had already undergone radiotherapy to the larynx or to thyroid gland.
4. Patients with co-morbid conditions of the heart, lung, breast and renal diseases.
5. Patients with diabetes mellitus and other hormonal imbalances.

Clinical history of all patients was elicited, ENT examination, video laryngoscopy, haematology and biochemical lab investigations were undertaken. Radiological imaging with computed tomography (CT) scan of neck and wherever necessary magnetic resonance imaging (MRI) of neck was performed.

Smoking Status

Current smoker was one who smoked within 1 year before onset of symptoms, former smoker was one who smoked till 12 months prior to the onset of symptoms and non-smoker

is one who never smoked in lifetime. Disease was staged according to American Joint Committee on Cancer (AJCC) Staging System 7th edition.[13] Paraglottic space infiltration was taken as a criterion to upgrade the staging. Bulky primary tumours with doubtful vocal cord mobility were treated with concurrent chemo-radiation as per hospital protocol. Well circumscribed vocal cord lesions which were not bulky (per oral endoscopic removal of the primary tumour) was undertaken. All the remaining patients were treated with radiotherapy alone.

Radiotherapy

3DCRT technique with bilateral fields using high energy photons (4/6MVX) is used for treatment. A total of 70 Gy RT was applied in 35 fractions with 2 Gy / fraction, 5 fractions / week for T2 disease extending from the superior thyroid notch to the bottom of the cricoid cartilage and from 5 – 10 mm anterior to thyroid cartilage to the posterior of arytenoid cartilage.

Chemoradiation

Cisplatin was given in addition to radiation with a dose ranging from 30 to 40 mg / m2 weekly for 6 weeks. The total period of follow up was for 24 months. The period of survival was calculated from the date of diagnosis to the last date of consultation. Preservation of function of larynx during follow up was defined as intact larynx, without tracheostomy or gastrostomy to bypass the larynx. Period of recurrence free survival (RFS) was calculated from the date of diagnosis to the first symptom of occurrence of recurrence. Overall survival (OS) was calculated from the day of diagnosis to the death or last day of follow up. Disease specific survival was calculated by eliminating the patients dying from other causes than carcinoma larynx and calculating the survival rate. Patients who expired before the follow up date were eliminated from the list of subjects for the calculation of RFS, OS and DSS.

Statistical Analysis

Data was entered in Microsoft Excel and analysed using appropriate statistical software. The methods used were percentages and mean values; chi-square test calculator was used to find the statistical significance between final outcomes of treatment modalities. P value was taken as significant at < 0.05.

RESULTS

Among the 43 patients with stage II glottis cancer (T2N0M0) included in this study, there were 39 males (90.69 %) and 04 (09.30 %) females with a male to female ratio of 10.57 : 1. Youngest patient was aged 44 years and the eldest patient was 73 years with a mean age of 58. 62 ± 2.35 years. The status of smoking among the patients was tabled in Table 1. The site of malignant growths in the glottis space was classified and tabled in Table 1. None of the patients presented with either restriction of vocal cord mobility or fixation of the vocal cords. 31 patients were treated with radiotherapy alone (72.09 %), 08 / 43 (18.60 %) patients were treated with chemo radiation and 04 / 43 (11.62 %) patients underwent surgery alone. 05 / 43 (11.62 %) patients presented with loco-regional recurrence during 24 months of follow up. 01 (02.32 %) patient had to undergo tracheostomy and laryngeal function (Table 1).

	Observation	Number	Percentage
Mean age in years		58.62 ± 2.35	
Gender ratio	M 39 F 04	10.57: 1	M: 90.69 F: 09.30
Smoking status	Current	29	67.44
	Former	12	27.9
	Never	01	2.32
Tumour site	Left vocal cord with anterior commissure	22	51.16
	Right vocal cord with anterior commissure	14	32.55
	Isolated left vocal cord lesion	05	11.62
	Right vocal cord with posterior commissure	02	04.65
Treatment	Radiotherapy alone	31	72.09
	Chemo radiation	8	18.60
	Surgery	4	09.30
Loco-regional recurrence	Yes	5	11.62
	No	38	88.37
Laryngeal function preserved	Yes	37	86.04
	No	06	13.95
Tracheostomy		01	02.32
Follow up period		24 months	100

Table 1. Demographic and Incidence of Site of Lesions and Their Survival Rates (n = 43)

Observation	Radiotherapy 31	Chemoradiation 08	Surgery 04
Free of recurrences- 38 (88.37 %)- RFS	28 (90.32 %)	06 (75 %)	04 (100 %)
Retained laryngeal function- 37 (86.04 %)	28 (90.32 %)	05 (62.5%)	04 (100 %)
Loco-regional recurrence- 05 (11.62 %)	03 (09.67 %)	02 (25 %)	0
Stridor with airway obstruction- 01 (02.32 %)	0	01 (12.5 %)	0
Lost laryngeal function- 06 (13.95 %)	03 (09.67 %)	02+ 01 (37.5 %)	0
Survival -43- DSS and OS- 100 %	31	08	04
P value (significant at < 0.05)	0.723	0.614	0.510

Table 2. Final Outcome after 24 Months Follow Up among the 3 Modalities of Treatment and in Relation to Mortality, Locoegional Recurrence and Laryngeal Function (n = 43)

The overall survival was observed in 100 % of the patients in the study as there were no deaths and all the subjects survived were under follow up for 24 months. The loco regional recurrence was observed in 05 (11.62 %) patients in whom partial vertical partial laryngectomy was done later resulting in loss of laryngeal function. The remaining patients 38 / 43 (88.37 %) were free of recurrence till the end of 24 months follow up. The recurrence free survival period in these 05 patients was ranging from 16 months to 23 months with a mean period of 21. 20 ± 0.75 months. One patient developed sudden

stridor and tracheostomy had to be done to create airway resulting in overall 6 / 43 (13.95 %) patients losing function of larynx in this study. The 2 year DSS was 24 months in 100 % patients in this study and RFS was 19.16 ± 0.1.05 months in 88.37 % patients (Table 2). Chi-square test calculator was used to find the statistical significance between final outcome and modalities of treatment used. There was no statistical significance as P value was > 0.05 (Table 2). It was concluded that as this study was of small group and the follow up period was under 5 years, significant difference in the long term benefits between the treatment protocols could be proved.

DISCUSSION

Among the head and neck malignancies, carcinoma of larynx is common.[13] Calculation of survival rates makes one understand, the success of the treatment. Such calculations help us to understand the percentage of people with similar cancers surviving, after treatment for a period of 5 years. But they do not indicate how long all the persons would survive.[14] In comparison with patients with advanced stage disease of laryngeal cancer, stage II glottis cancer with squamous cell carcinoma have overall better 5-year survival rates despite the treatment similarity.[15]

In this study, the overall survival was observed in 100 % of the patients as there were no deaths, all the subjects survived were under follow up for 24 months only. The 2 year DSS was 24 months in 100 % patients in this study and RFS was 19.16 ± 0.1. 05 months in 88.37 % patients. Similar 2 and 5-year survival rates (DSS) were reported by Mendenhall et al[9] and Howell-Burke D, Peters L J et al.[10]

Currently Clinical Practice Guidelines in Oncology (NCCN Guidelines) for head and neck cancer recommend the same treatment for stage I and II glottis cancer with escalation of therapy with chemoradiation in patients with deep infiltration of growth based on radiological imaging.[17] However, there was limitation in accurately assessing the stage II lesions of glottis cancers especially in terms of determining involvement of thyroid cartilage and / or paraglottic space involvement on cross-sectional imaging to up grade to stage III, which was a factor resulting in recurrences and development of respiratory obstruction[18] in early-to-mid stage laryngeal tumours.[13] All of them cause mortality in T2N0MO of laryngeal squamous cell carcinoma.

Among the 43 patients with stage II laryngeal SCC considered to be "early-stage disease", the overall survival was 100 % and the recurrence free survival was 88.37 % after 24 months of follow up; the treatment being same for "advanced stage disease" of larynx.[11] Review of literature showed that in a 2 – 5 year study by Mendenhall WM et al.[5] treating stage II laryngeal SCC observed OS of 91 % and RFS of 83 %. In this study laryngeal function was observed in 86.04 % of the patients consistent with the study of Haapaniemi A et al.[6]

The current Clinical Practice Guidelines in Oncology for Head and Neck Cancer recommends same treatment protocols for early stage I and stage II cancer larynx.[12] In such situations searching for prognostic indicators would improve the outcomes further. Downstaging of stage III laryngeal cancers as stage II leading to under treatment was an explanation for lower RFS rates and OS rates all over the world.[13] It may be due to difficulty in determining thyroid cartilage and / or paraglottic space involvement on cross-sectional imaging in early-to-mid stage laryngeal tumours.[13] But in this study a thorough analysis of the radiographic pictures was done to avoid such discrepancies.

Comparing surgery and RT results of treatment for stage II cancer larynx were found to be equivocal in terms of survival and functional voice outcomes, from single institute studies, where stage I and II cancers were combined. But they were primarily retrospective in nature.[14-17] In the present study preference was given to RT followed by concurrent chemo radiation and surgery in that order. The overall results were good especially in surgery group (04 patients) even though it was small.

CONCLUSIONS

The overall survival scores and disease specific survival were 100 % in this small study group with 11.62 % loco-regional recurrence. This may be due to careful selection, staging, and avoiding under-staging of the disease. Voice preservation was 86.04 %. As the follow up period was below 5 years, the late treatment effects and complications could not be recorded. Proactive prevention rather than escalation of treatment protocol gives better prognosis.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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