Management of an early stage carcinoma of the true vocal cord.

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Abstract

Objective : *Early stage carcinoma of the true vocal cord, can be effectively treated with surgery or radiation therapy. This article aims to find out the best management option for patients of early stage cancer of the true vocal cord.*

Data source and review method : *The data collection was done using MEDLINE and PubMed database along with hand search of books using key words vocal cord cancer, early stage, management and true cord.*

Results : *No single treatment modality was found to be superior over other (surgery versus radiation therapy).*

Conclusion : *Choice of treatment should depend on the patient specific factors, tumor related factors and an expertise of treating physician or surgeon.*

Key words : Vocal cord cancer, early stage, management, true cord

Introduction

Cancer larynx is the eighteenth most common cancers in males with a sex ratio of 5:1 [1]. In India, the incidence of cancer larynx is 6.2 per 100000 [2].It is rare below 40 years of age and peak after 70 years. The causative factors stated are smoking, alcohol, gastro-esophageal reflux disease, voice abuse and Human Papilloma Virus (HPV) [3,4,5].

As the chief complaint of patients of true vocal cord cancer is change of voice, mostly hoarseness which is easily perceived by patient and his relatives; it is commonly detected in its early stage. The treatment of choice for early stage vocal cord cancer (ESVCC)(Table 1)[9] depends on the best oncological outcome with maximum function preservation. It can be effectively treated with surgery (microlaryngosurgery-MLS, open partial laryngectomy-OPL) and radiation therapy (RT) [6,7]. When both the treatment gives similar survival end points, other outcomes such as quality of life, organ function and cost becomes relevant. Open partial laryngectomy is costlier [6]. Cost for laser surgery and radiotherapy are usually the same with exception of few countries. RT is costlier in Europe [16]. In India because of limited surgical resources RT is widely used to treat ESVCC.

The literature was reviewed and data was collected using MEDLINE and PubMed database along with hand search of books using key words vocal cord cancer, early stage, management, and true cord. Many studies and meta-analysis have evaluated functional outcomes of treatment with surgery and RT. The conclusion of superiority of single treatment modality cannot be drawn because of lack of comparison between different study groups (Table 1[8-11]). Also, there is no randomized control trial to guide the treatment hence the management is controversial. Patient, disease and expertise of treating physician/surgeon specific choice of treatment modality is important [12]. Factors deciding the same are discussed in this article.

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Examination and investigation

Outpatient evaluation is done using an indirect laryngoscopy examination. Hopkins telescope provides a magnified view. More detailed examination is done using direct laryngoscopy(DLS). It is a gold standard investigation which helps in an accurate assessment of a lesion. Digital laryngeal stroboscopy is a specialized viewing of vocal fold vibration which involves controlled high-speed flashes of light timed to the frequency of patient's voice. It gives slow motion and high resolution images thereby picking up subtle and complex vocal cord movements. It helps to assess presence or absence of a mucosal wave, which implies an absence or presence of involvement of underlying vocalis muscle. Also it is used to compare appearance and movements of vocal cord before and after treatment. A cord which appears mobile before DLS may show sluggish motion or even fixation after biopsy [13]. This suggests the need of DLS and biopsy through experienced hands.

Brian et al had shown that OCT images compared favorably with conventional histopathology and has unique ability to detect laryngeal tissue microstructure along with detail microanatomy [15].

Pathology and differential diagnosis

Most common site of involvement for carcinoma of the true vocal cord is upper surface, along the free margin and anterior 2/3rd of vocal cord. It is limited to one vocal cord in 2/3rd of the cases. Pure anterior commissure (AC) involvement is seen in 1-2% [13]**.**

Malignant lesion of the true vocal cord need to be differentiated from the benign lesions like papilloma, vocal cord polyp or nodule**,** ulcerative lesions like contact ulcer (the granuloma of one side fits into the creator created by ulceration on the other side), syphilitic ulcer (affects anterior 3rd of the cord and is a deep ulcer with wash leather slough), tubercular ulcer (involves mainly the posterior 1/3rd portion and ulceration produces a 'mouse-nibbled' appearance and pseudoedema causes turban like appearance) and the per-malignant lesions like leukoplakia**.**

Prognostic Factors

Females do better than males[6]. Tobacco use is associated with high mortality with a strong dose response relationship [3]. Tobacco/smoking directly injures the mucosa. Carcinogens in the tobacco damage important genes that control growth of the cells. It is also a predisposing factor for field cancerization. Low pretreatment hemoglobin level and poor histological differentiation affects negatively [6]. T stage and primary tumor volume are inversely related to the probability of local control after treatment. Same is true for AC involvement [16]. Ashwatha et al had shown that five year local control rate for small tumor versus large/ bulky tumor was 91% versus 48%. Over expression of p53 was a negative prognostic factor (94% vs 48%). When both, bulky/ large tumor and p53 overexpression were present five year local control rate decreased to 23% as compared to 92% in absence of both [17]. Importance of DNA ploidy was studied by Noriko et al. He showed that aneuploid tumors have large lesion size and more local failure [18]. Ki 67 has direct correlation with an aggressiveness and radioresistance of disease [19] while cyclin A is directly correlated with tumor recurrence [20]. Bcl-2, bcl-xl and Bax expression predicts radiation failure [21]. Laryngeal tumors with Cox 2 overexpression are also correlated with radioresistance [22]. Such patients should be treated with alternative treatment modality.

Treatment

Aim of the treatment should be function preservation with best oncological outcome. Equal oncological outcome in terms of local control and ultimate organ preservation is seen in ESVCC when treated with surgery or RT. Bulky T2N0M0 lesions (defined as the presence of visible rather than subclinical disease and with impaired vocal cord movements) should be considered for concurrent chemo-radiation therapy (CTRT). Few treatment modalities like photodynamic therapy are investigational.

Factors deciding the choice of a treatment are described in table 2.

Surgery

In the past, voice sparing surgery was most widely practiced treatment modality for ESVCC. It can be performed either through a transoral route or by open partial laryngectomy. The first partial laryngectomy for cancer was performed by Sir Billroth (1875). Entire cord with as much as 3rd of the opposite cord and adjacent

thyroid cartilage along with intervening paraglottic tissue was removed. The main advantage is better visualization of a lesion. There are different subtypes of partial laryngectomy depending upon the site of a lesion**.** It is mainly indicated in lesions with impaired vocal cord mobility and AC or arytenoids involvement. The relative contraindications are involvement of more than 3rd of opposite vocal cord, bilateral arytenoids, posterior commissure and bulky transglottic lesion. For partial laryngectomy that conserves voice the laryngeal remnants must have an intact cricoid and at least one mobile vibrating arytenoid. The local control rate with partial laryngectomy is 82-93% [24]**.**

Supracricoid laryngectomy is indicated in moderate size lesions involving supraglottis and horse shoe lesions. In this type of surgery preservation of arytenoid is important to have posterior glottic bulk to avoid aspiration and preserve voice. Hence it is generally avoided in elderly and patients with compromised lung function. Local control rates with supracricoid laryngectomy are 86% [24]. Laryngofissure with cordectomy is the simplest and oldest open surgical procedure to treat early stage carcinoma larynx described by Sir Gordon Buck (1853). It is indicated in mid-cord lesions without anterior commissure involvement with mobile vocal cords. Local control rate with laryngofissure cordectomy is 84 – 98% [25].

Reconstruction of glottis after partial laryngectomy is important. Mucosal defect heals by granulation and fibrosis. The remnant of normal vocal cord is reattached to adjacent thyroid cartilage or soft tissue. Arytenoids can be reconstructed using tissue from a cartilage, fat, muscle, tendon or epiglottis and glottis reconstruction with regional muscle laryngoplasty. Zeitels et al had suggested a laryngeal reconstruction technique called "laryngoplastic phonosurgery" which may restore glottic closure, and hence a proper voice, after these more extensive surgical procedures [26].

There are three minimally invasive surgical treatment options for ESVCC: cold instrumentation, powered instrumentation and transoral laser excision. Laser surgery is now widely used instead of open partial laryngectomy because of better functional results without compromise of local control rates. European Laryngological Society had classified laser cordectomy into eight types (Table 3) [27]. Tumor is removed along with normal tissue margin. This defect heals by granulation within few weeks to form a pseudocord. Most important in laser surgery is to get a good exposure of the lesion to microlaryngoscope. If for any reason satisfactory exposure is not possible best to go ahead with an alternative treatment option. Laser surgery is ideal for mid cord and superficial lesions where good functional outcome can be achieved because of limited tissue resection. It is relatively contraindicated in lesions involving AC, vocal process of arytenoids, sub/supra glottic extension of disease. Local control with laser surgery is 77 – 91% [28]. Angiolytic KTP laser treatment with ultra narrow margins allows maximum preservation of paraglottic soft tissue and has shown good functional outcomes. But the local control rate has not been studied while keeping radiotherapy preserved as an oncological treatment option [29]. Prolonged hospitalization, tracheostomy and nasogastric tube placement can be avoided in laser surgery.

As a solution for inadequate exposure during MLS, Rebeiz et al introduced a combined endoscopic and open technique called window partial laryngectomy [30, 31].

Role of excision biopsy alone in the management of selective T1 glottic cancer was studied by Blakeslee et al way back in 1984. He concluded that it is adequate for micro and mini squamous cell carcinoma of glottis with clear cut margins. An enblock removal of lesion is done to get complete histopathology report and patients with positive margins are advised further treatment with surgery or RT [32]. Transoral endoscopic coblation surgery is now evolving as a treatment modality in selected ESVCC with minimal postoperative complications (only mild pain) [33].

Radiotherapy

At the beginning of twentieth century, cancer larynx was one of the first tumors treated and cured with RT. It evolved over a time from a classical chicken wing position to Intensity modulated radiotherapy (IMRT). RT planning is done clinically, with conventional simulator or computed tomography based planning system. It has been shown that CT based simulation and planning

provides better locoregional control and less acute side effects of radiation [34].

StageT1and selected T2 lesions are treated with small portals limited to primary because of very less chance of nodal metastasis. The radiation field extends from the level of the hyoid bone superiorly to the bottom of the cricoids cartilage inferiorly and anterior border in air to posterior border either on the anterior or middle surface of the vertebral bodies. Few physicians consider involvement of primary and draining lymph node stations in bulky T2 lesions. Different gantry angles and appropriate wedge pairs are used depending on the site of the lesion and neck thickness of the patients. Dose distribution can be checked using CT based treatment planning. Number of fractionation schedules have been tried to treat the vocal cord lesions. Dinshaw et al had shown that the shorter fractionation schedule (5504cGy in 16 fractions) had comparable local control, without increased complications in comparison to the protracted schedule and is best suited for a busy department. Fraction size and overall treatment time also has an important role in disease control. Fraction size of more than 2 Gy per day is significantly better than the fraction size of 2 Gy or less per day. stage wise local control rate at the end of 10 year was 82% and 57% for TI and T2 lesions respectively [35].

The potential doubling time for glottis T1 tumor clonogens is 5.5 days [36]. For total dose of 66 Gy given in 2 Gy per fractions, each 1 day of extension of overall treatment time produces 1.3% loss in the local control. Common but less frequent side effects after laryngeal irradiation are xerostomia, dysphagia (7%), chronic laryngeal edema (18%) and hypothyroidism (18%) [37]. Chondronecrosis of arytenoid cartilage or arytenoid edema is rare delayed side effect which can be avoided with arytenoid sparing RT. At 20 years probability of second malignant tumor is 23% and the risk increases in long term survivors and smokers [3]. Hence RT as a treatment option should be taken with caution in a young adult patient and smokers who are at increased risk of second malignancy and/or field cancerization.

Conformal RT like 3-Dimentional Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) are now used in the treatment of ESVCC. IMRT produces more ideal dose distribution than 2D/ 3DCRT. Major disquiet of conformal RT are risk of over or under dosing at the skin surface, air-tissue interface in small vocal-cord cancers, treatment time of 10–20 min and most important is movement of larynx during treatment. Contradictory to this Osman et al had shown that intrafraction movements of vocal cord are small and not prohibitive of executing conformal radiation like IMRT [38]. The use of Cone Beam Computed Tomography for daily image guidance in combination with standard mask fixation reduced systematic and random set-up errors of the vocal cords. But the movement of a target in between imaging and treatment delivery cannot be rull out. Normal tissue sparing with IMRT is superior to conventional RT [39]. IMRT and single vocal cord irradiation is proposed to give high quality of voice and hypofractionation with relatively high dose per fraction (8.5Gy). It appeared feasible to irradiate one vocal cord with 1-2 mm accuracy [40]. But the practical results are awaited. A dosimetric study was performed comparing Intensity modulated arc therapy (IMAT) with IMRT and 3DCRT. IMAT had less treatment time with acceptable homogenous target coverage and low carotid dose [41].

Concern about injury to adjacent critical structures and salivary-gland is minimal or nearly zero in irradiation of ESVCC. Good local control can be achieved with conventional radiation therapy. There is minimal risk of severe complications with conventional radiation for ESVCC. So, is it possible to reduce what is already a less than 2% risk of major morbidity using these newer techniques? Vassilis et al had treated EGC with hypofractionated schedule using 3DCRTand showed the results were comparable to conventional radiation in terms of local control, acute and late RT reaction [42].

Chemotherapy (CT)

Concurrent CTRT has been tried for bulky T2N0M0 disease and it has been shown to have a positive impact on the local control. Tetsuo et al. had shown significantly superior 5 year survival rate and voice preservation (89% vs. 61%) in CTRT group when compared with RT alone group in patients of T2N0 vocal cord cancer [43]. Olliver et al. had used CT alone to treat T1-T3 vocal cord

cancer and shown 5 year survival rate with exclusive CT was better than induction CT followed by larynx preservation treatment modality. Also, nodal relapse rate and distant metastasis rate were zero in exclusive CT arm as compared to induction CT arm. But local recurrence was significantly more with exclusive CT (p=0.002) which was salvaged with partial laryngectomy or RT giving ultimate local control and larynx preservation in 100% cases [44].

Other

Photodynamic therapy can be used effectively for superficial early stage lesions of head and neck cancer especially in case of field cancerization, with minimal side effects, absence of systemic toxicity, preservation of oral function and voice quality [45]. But its use in exclusive ESVCC needs to be evaluated.

Carcinoma in situ (CIN)

Stripping of diseased vocal cord tissue which is required for initial diagnosis acts as both investigational and treatment modality for CIN. It can be repeated if required. But repeated stripping will cause mucosal thickening with resultant hoarseness of voice. Watchful waiting after initial stripping is a good treatment option in selected cases of CIN. Carbon dioxide laser excision gives optimal local control and function preservation. But the tumor tissue is not available for histopathology report to comment on microinvasiveness. Advantage of RT is that it takes care of invasive component. RT is given with small portal hence it is well tolerated with minimal side effects. Laryngectomy is reserved only for salvage. Quynh et al had shown 10 year local control rate and larynx preservation with stripping, MLS and RT as 56%, 71% , 79% and 92%,70%,85% respectively. AC involvement was associated with poor initial local control rate and larynx preservation particularly in surgically treated patients [46].

Management of recurrence

Persistent or progressive vocal cord edema and worsening voice quality are suggestive of disease recurrence. Recurrence in early stage can be managed with MLS, OPL or RT. Careful selection of patients with ESVCC that recur or progress after treatment allows patients to undergo voice sparing therapy with excellent survival outcome. A question was raised on an efficacy of surgery for glottis recurrence after RT as initial therapy. Post RT changes in skin, subcutaneous tissue and blood vessels may hamper surgical dissection and postoperative healing. Lydiatt et al [48] reported on 78 patients treated by vertical partial laryngectomy following RT failure. There was no increase in wound complications, time to decannulation and length of hospital stay or ability to swallow. Quer et al [49] reported on 24 patients in whom RT had failed and who were treated subsequently with transoral laser surgery, resulting in 75% rate of voice preservation and a 76% five-year survival rate. Thus recurrence after initial RT can be well managed with MLS or OPL without additional risk. Re-irradiation is a treatment option for small recurrence after primary RT especially in patients who refuse or are not fit for surgery. Patients who refuse or are not fit for surgery or RT can be considered for palliative chemotherapy.

Follow up

After completion of treatment and response assessment at first follow up, patients are advised three monthly follow up for at least two years; six monthly to yearly thereafter. There is no indication that asymptomatic locoregional recurrence detection results in better treatment option, decreased cancer mortality or improved survival. There should be no difference in the follow up program of low or high risk group patients. There is no advantage of increasing number of follow up visits as the lead time is very short (2-4 weeks) [50].

Conclusion

ESVCC is generally detected in its early stage. It can be successfully treated with surgery or radiotherapy. Proper case selection is needed for good oncologic and functional outcomes. Superficial mid-cord lesions with mobile vocal cord are easiest to treat with surgery or radiotherapy and are ideal for laser surgery. Other lesions can be effectively treated with surgery or RT with few exceptions like very young age, verrucous carcinoma and previous radiotherapy to head and neck region. Bulky stage T2 lesions are effectively managed with CTRT.

Tables:

Table 1: Review and meta-analysis comparing functional outcomes after surgery and RT as treatment for ESVCC

Sr No	Authors	Study specification	Results	Conclusion
1	Christien et al [8]	T1-T2N0 tumors, laser Sx n=51, RT n=126, comparison with 100 controls	Voice impairment was 44% in RT group vs 29% in Sx group	Sx better than RT
2	Cohen et al [9]	Metaanalysis of six studies, T1a& T1b, Laser Sx n=208, RT N=91	Comparable levels of voice handicap index	Sx equal to RT
3	Higgins et al[10]	ESVCC. N=7600	Sx favouring trends towards overall survival	Trend towards improved voice quality with RT but no objective difference
4	Spielma et al[11]	ESVCC, Sx n=448, RT n=442	Need for consensus on which easures of voice quality and life satisfaction to be used in research trails to allow comparison	Equal voice quality

Table 2: Factors deciding choice of treatment

Patient factors	age, performance status, co-morbidity, lung diseases, previous treatment, patient choice, occupation, second primary, reliability of follow up
Tumor factors	stage, site, cord mobility, volume
Treatment factors	expertise, physician philosophy, cost and feasibility, functional outcome/ quality of voice

Table 6: Subtypes of laser cordectomy

Type of laser cordectomy	Structures removed
I	Subepithelial cordectomy (resection of epithelium),
II	Subligamentous cordectomy (resection of epithelium, Reinke's space and vocal ligament)
III	Transmuscular cordectomy (proceeding through vocal muscle)
IV	Total cordectomy
V	Extended cordectomy – Va.Encompassing contralateral vocal fold and anterior commissure, Vb.Encompassing contralateral vocal fold, anterior commissure and arytenoids, Vc.Encompassing contralateral vocal fold, anterior commissure, arytenoids and ventricular folds, Vd.Encompassing contralateral vocal fold, anterior commissure, arytenoids, ventricular fold and subglottis

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