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Is Primary Radiotherapy an Acceptable Treatment Modality for Verrucous Carcinoma of the Larynx?

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BACKGROUND

Verrucous carcinoma is a well-differentiated variant of squamous cell carcinoma. The oral cavity is the most common site of occurrence, followed by the larynx. Treatment of laryngeal verrucous carcinoma (LVC) is controversial. LVC is often approached with a different mindset compared to that for conventional laryngeal squamous cell carcinoma. Radiotherapy, commonly used in all stages of conventional laryngeal squamous cell carcinoma, is often avoided in LVC because early reports described a potential for anaplastic transformation with this treatment modality. Early studies also suggested inferior locoregional control compared to surgery. As such, surgery has traditionally been the preferred treatment modality for LVC. However, more contemporary reports have questioned this preference and challenged the early concerns of anaplastic transformation and inferior prognosis with radiotherapy.

LITERATURE REVIEW

A number of retrospective studies have been published on the treatment of LVC since it was initially described in 1948. Hagen et al. in 1993 reviewed the existing literature and included their own data on surgery versus radiation for LVC. Their article included studies from 1977 to 1987, and patients in their own series had a follow-up period until 1990. In their combined series, 37 patients were treated with radiotherapy. In this group, they suggested a high initial treatment failure rate (51%) and a significant proportion undergoing anaplastic transformation (11%) with primary radiation. They found superior results in patients treated with surgery (144 patients), with a 7.6% initial failure rate (defined as recurrence during the follow-up period or no response of tumor).

A number of other early studies identified similar results. Previous studies were recently summarized in a systematic review by Echanique et al. in 2017. In this review, 37 studies were included with 369 cases of laryngeal verrucous carcinoma. Treatment modality was recorded in 347 patients (n = 251 surgery alone, n = 19 surgery with radiation, n = 67 radiotherapy alone, n = 4 radiotherapy and chemotherapy, and n = 6 other treatment modalities). Only articles that contained individual patient data were included. In this meta-analysis, they compared outcomes in 286 patients with at least 6 months of follow-up. Of 204 patients treated with surgery alone, 86.8% were disease-free at 6 months. Of 59 patients treated with radiotherapy alone, 67.8% were disease-free at 6 months. However, of 18 patients treated with combined surgery and radiotherapy, a comparable 66.7% were disease-free at 6 months. No statistical comparison was described, although there does seem to be a noticeably higher control rates with surgery compared to radiotherapy in this meta-analysis. Additionally, no mention was made of any assessment of study quality or bias in this systematic review. Only eight of the 37 studies summarized by Echanique et al. were published after the year 2000. Half of these were single patient case reports, and only one study contained patients treated with radiotherapy (7 patients).

Since publication of many of the early LVC studies, there has been significant progress in our ability to improve local control in laryngeal cancer with primary radiotherapy. In addition to improved radiation technology, we now know there are significant radiobiological factors to consider when treating low-grade slow-growing tumors such as verrucous carcinoma. Studies from the past several decades have demonstrated that altered fractionation radiation schemes can have a significant effect on local control. Decreasing overall treatment time and increasing the dose per fraction has shown to improve local control rates in early glottic carcinoma. Although this has not been studied specifically for LVC, well-designed prospective studies have shown...
that this improvement in local control is more pronounced in well-differentiated glottic laryngeal cancers, which comprise the large majority of LVC patients, are now treated very differently in the contemporary era of radiotherapy.

Huang et al. published a retrospective review in 2009 of all LVC treated with primary radiotherapy at a single institution. In the 62 included patients, 5-year disease specific survival was 97%; overall survival was 87%; and locoregional control was 66%. There were no cases of anaplastic transformation. The study by Huang et al. was not included in the systematic review performed by Echanique et al.

A recent retrospective population-based study was published in 2015 utilizing the Surveillance, Epidemiology, and End-Results database. In this study, Dubal et al. compared outcomes in LVC versus other laryngeal malignancies from 1973 to 2011. Of 516 LVC patients, tumor-node-metastasis (TNM) staging was only available for 176 patients. Of these patients, most were T1 (52.3%) or T2 lesions (30.1%). Nodal metastasis was expectedly rare with 94.3% of patients staged as N0. Five-year disease-specific survival was significantly higher with surgery compared to radiation: 92.3% with surgery alone, 85.6% with combined radiation and surgery, and 75.8% with radiation alone ($P = 0.0021$). Comorbidity or performance status was not specifically assessed in this study.

The existing literature on radiation for LVC suffers from significant bias. Previous reports are all retrospective case or cohort series. Heterogeneous study methodology abounds. There is a noticeable lack of prospective studies. Current literature, despite concerns with study methodology, still suggests better survival and locoregional control with surgery compared to radiotherapy. However, the degree of this advantage may be overestimated due to the potential for selection bias because patients treated with radiation in previous retrospective studies may be more predisposed to worse comorbid health status and poor surgical candidacy. Randomized controlled trials are required to fully elucidate this. In addition, current radiotherapy techniques and fractionation schemes are likely not comparable to those used in early studies that suggested inferior locoregional control rates and risk of anaplastic transformation.

**BEST PRACTICE**

The existing literature still suggests that the highest locoregional control and survival rates are achieved with surgery. However, a direct comparison between surgery and radiotherapy is challenging due to lack of well-designed, randomized studies. Despite initial concerns of early studies, radiotherapy is an acceptable contemporary treatment modality for LVC with reasonable locoregional control and survival outcomes. Currently radiotherapy methods carry a negligible risk of anaplastic transformation and expectedly good functional results, as seen in treatment for non-verrucous histologies. However, surgery remains the gold standard for LVC when organ preservation is possible. In patients who are poor surgical candidates or in settings in which acceptable functional results cannot be achieved with surgery, radiotherapy can be considered as an alternative treatment option.

**LEVEL OF EVIDENCE**

This best practice recommendation is based on level 3 evidence (a systematic review of retrospective studies and case reports, population-based cohort studies) and level 4 evidence (case series). Also referenced is a review article summarizing level 1 studies (well-designed randomized controlled trials).

**BIBLIOGRAPHY**