



Risk factors for radiation failure in early-stage glottic carcinoma: A systematic review and meta-analysis



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ABSTRACT

Background: Radiotherapy is one of the main treatment modalities for early-stage glottic carcinoma. Unfortunately, local failure may occur in a group of cases with T1-T2 glottic carcinoma. This meta-analysis sought to determine risk factors for radiation failure in patients with early-stage glottic carcinoma.

Methods: A systematic and comprehensive search was performed for related studies published between 1995 and 2014. The primary end-point was 5-year local control. Data extraction and analysis were performed using the software STATA/SE 13.1 for Windows.

Results: Twenty-seven studies were eligible. A higher risk of radiation failure was demonstrated in male patients [relative risk (RR): 0.927, $p < 0.001$] and those with low hemoglobin level (RR: 0.891, $p < 0.001$) with a high agreement between studies (I-squared = 0.0%). Moreover, T2 tumors (RR: 0.795, $p < 0.001$), tumors with anterior commissure involvement (RR: 0.904, $p < 0.001$), tobacco use during/after therapy (RR: 0.824, $p < 0.001$), and “bulky” tumors (RR: 1.270, $p < 0.001$) or tumors bigger in size (RR: 1.332, $p < 0.001$). Poorly differentiated tumors had a questionable risk of local failure, although a moderate to high interstudy heterogeneity was determined. A statistically significant contribution was not detected for age, presence of comorbidity, alcohol use or subglottic extension.

Conclusion: This is the first meta-analysis which assessed the potential risk factors for radiation failure in patients with early-stage glottic carcinoma. Gender and pretreatment hemoglobin level are major influential factors associated with radiation failure in patients with early-stage glottic carcinoma. However, prospective, randomized clinical trials may permit better stratification of their relative contributions, and those who may benefit more from upfront surgery.

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Introduction

Larynx cancer is the second most common head and neck cancer worldwide [1]. In 2012, the estimated worldwide incidence of new cases with larynx cancer was approximately 160,000 and cancer-related death was more than 80,000 [2]. The overall 5-year survival rate of larynx cancer is approximately 60%; however, this rate increase up to 75% when there is localized disease (confined to primary site) [3]. A recent population based report from U.S. demonstrated that approximately 50% of patients with larynx

cancer are diagnosed at early stage, which has a considerably better prognosis and survival outcome [4].

Larynx cancers are generally separated as glottic and supraglottic, based on their location, as well as due to differences in tumor biology, clinical behavior, and prognosis [5–7]. Supraglottic cancers, even at early stages, have a more aggressive nature, high risk of nodal metastasis and poorer prognosis [5,8]. In contrast, early-stage glottic carcinoma has a low risk of lymph node involvement due to absence of lymphatic drainage in true vocal folds and significantly better prognosis [5,9]. Therefore, *American Journal of Clinical Oncology* recommended the selection of a single treatment modality with larynx preservation for the management of early-stage glottic carcinoma [10]. Hence, current treatment modalities for

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early-stage glottic carcinoma are: (i) conservation laryngeal surgery with transoral laser surgery or an open surgical technique, and (ii) radiotherapy (RT). Unfortunately, the best treatment of early-stage glottic carcinoma is still controversial due to the lack of prospective, randomized studies. Systematic review and meta-analysis, that are mostly depending on retrospective studies, demonstrated insignificant/slight differences between all treatment modalities according to locoregional control, survival, larynx preservation, speech and voice quality, and economic burden [11–14]. However, data from the U.S. National Cancer Institute showed that RT is the most widely applied treatment modality for early-stage larynx cancers [4].

Radiotherapy has a high rate of cure in early-stage glottic carcinoma with 5-year overall and disease specific survival rates of 79% and 96%, respectively [15,16]. Unfortunately, a group of cases (% 10–41) may have radiation failure, which is generally worrisome and devastating due to treatment time delay, psychological disturbances, economic burden, complications and morbidities related to the salvage laryngeal surgeries [17–19]. Although organ-preservation surgeries can be performed successfully for selected patients with radiation failure; total laryngectomy is more frequently required as a salvage surgery [20–22]. Moreover, complications and morbidities are considerably high in patients who undergo a salvage laryngectomy after RT with/without chemotherapy [23,24]. Furthermore, locoregional recurrence is relatively high, and survival is worse in patients undergoing salvage laryngectomy. Therefore, the patient selection is of utmost important in order to optimize the RT outcome. Moreover, the determination of risk factors for radiation failure would be valuable and might help those patients who might benefit from upfront larynx surgery. Hence, the purpose of this meta-analysis is to determine the risk factors that have a key role in predicting the radiation failure in patients with early-stage glottic carcinoma for more individualized cancer treatment.

Methods

Study design and search strategy

A structured literature search of the PubMed (National Library of Medicine of U.S.), Google scholar and Web of Science database was undertaken using keywords of “radiotherapy”, “early”, “stage”, “glottic”, “larynx”, “cancer”, “carcinoma” and a total of 398 citations have been found between 1995 and 2014. The literature survey demonstrated several risk factors for radiation failure in early-stage glottic carcinoma, and grouped as follows: (i) patient status, (ii) tumor location and involvement of laryngeal structures, (iii) clinical and radiological examination, (iv) molecular/biological characteristic of tumor and its microenvironment, (v) genetical variations and aberrations (Table 1).

Data extraction and eligibility criteria

Articles published in English literature were included. Clinical studies in which RT applied to previously untreated cases with early-stage glottic carcinoma and reporting the risk factors for RT failure were assessed. Two investigators (GE and YB) independently examined and reviewed the titles and abstracts related to the topic; thereafter read the full-text and selected the potential articles for analysis. The exclusion criteria and flowchart were presented in Fig. 1.

Statistical analysis

The meta-analysis was performed by combining the outcomes of clinical studies in which the potential risk factors for radiation failure were evaluated. The main end-point was 5-year local

control. The risk ratios (RRs) and 95% confidence intervals (95% CIs) were calculated, and the weight of each study was also indicated in percentages. Heterogeneity was evaluated by the inconsistency statistics (I-squared). The values less than 25% were considered to refer low heterogeneity whereas values higher than 50% were high heterogeneity [25]. All statistical tests of this meta-analysis were conducted using the software STATA/SE 13.1 for Windows (64-Bit x86-64) (StataCorp LP, TX).

Results

Characteristics of included studies

The literature search strategy described above retrieved 398 related articles (Fig. 1). Initial review excluded of 136 articles, leaving 262 articles for further evaluation. Secondly, abstract review excluded of 115 articles, and 147 articles had the potential to be included into the meta-analysis. All the remained articles were meticulously read, and 112 articles were excluded due to non-original articles (reviews, letters, etc.), their content (questionnaire, etc.), absence of data, and different study groups (combination of patients with supraglottic and glottic larynx cancer). Seven articles, focused on molecular risk factors such as CD-44, carbonic anhydrase-IX, etc. were excluded, because of inadequate reproducibility of clinical studies for meta-analysis, although they met other inclusion criteria. Eventually, 27 articles were included into the meta-analysis (Fig. 1, Table 2) [17–19,26–49].

The effect of patient status on radiation failure

Fifteen of the 27 reports evaluated the effect of gender by comparing the 5-year local control between female and male patients with early-stage glottic carcinoma who were treated by RT. The statistical analysis demonstrated a significant difference in the favor of female patients with high interstudy homogeneity [RR: 0.927 (0.892–0.963), $p < 0.001$; I-squared: 0.0%] (Fig. 2A). Moreover, seven clinical studies examined the role of pretreatment hemoglobin level on radiation failure, and a better outcome in patients with normal/high hemoglobin level was determined [RR: 0.891 (0.838–0.946), $p < 0.001$; I-squared: 0.0%] (Fig. 2B). The statistical analysis of four clinical trials, in which the effect of tobacco use during/after treatment on radiation failure was examined, revealing a significant difference in favor of cessation of tobacco use [RR: 0.824 (0.760–0.893), $p < 0.001$], although the interstudy heterogeneity was remarkably high (I-squared = 78.8%) (Fig. 2C). We determined no effect of age (>65 years vs. ≤65 years) [RR: 1.004 (0.914–1.103), $p = 0.931$], comorbidity (presence vs. absence) [RR: 0.988 (0.910–1.073), $p = 0.780$], or alcohol use (yes vs. no) [RR: 1.001 (0.901–1.112), $p = 0.979$] on radiation failure.

The effect of tumor location and involvement of laryngeal structures on radiation failure

Sixteen studies examined the influence of anterior commissure involvement (ACI) on local control of patients with early-stage glottic carcinoma who underwent RT. A statistically significant difference in the favor of patients without ACI was detected [RR: 0.904 (0.879–0.930), $p < 0.001$] with a moderately high interstudy heterogeneity (I-squared: 51.7%) (Fig. 2D). On the other hand, no statistically significant difference was determined when the presence and absence of subglottic extension was reported [RR: 0.880 (0.758–1.023), $p = 0.095$].

The effect of clinical and radiological examination on radiation failure

The role of stage (T1 vs. T2) on radiation failure was evaluated by seventeen clinical studies. Although a statistically significant

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