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Organ preservation with chemoradiation in advanced laryngeal cancer: The problem of generalizing results from randomized controlled trials☆

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ABSTRACT

Background: The primary goal of treatment in advanced laryngeal cancer is to achieve optimal oncologic outcomes while preserving function and quality of life. Combination of chemotherapy and radiation has been popularized as an alternative to surgery for patients facing total laryngectomy. However, survival analyses from large, population-based databases have not duplicated results reported from randomized trials.
Methods: A comprehensive literature review was undertaken to try to better understand the reasons why results differ among randomized trials and population cohort studies.
Results: A variety of reasons are discussed, including differences in patient staging, selection bias, complexity bias, inconsistent terminology, patient compliance and treatment expertise.
Conclusions: Personalized treatment considering all factors is critical for optimal outcomes. In general, evidence supports total laryngectomy for patients with T4 cancers. Definitive chemoradiotherapy strategies are acceptable alternatives for T3 cancers, provided that all resources for the administration of the treatment, follow-up and surgical salvage are available.

1. Introduction

The primary goal of treatment in advanced head and neck cancer is to achieve optimal oncological outcomes while preserving function and quality of life as much as possible. This is particularly important in the treatment of laryngeal cancer. The larynx has important functions—including breathing, voice making and swallowing, and therefore both the disease and its treatment may significantly affect quality of life.

Data from the Surveillance, Epidemiology, and End Results Program (SEER) database in USA have shown that the incidence of larynx cancer has been decreasing in the last few decades, and 5-year survival decreased 1.3% in a 30-year period, although this change was not statistically significant (63.2% in 1975 to 61.9% in 2007) [1]. However, the International Agency for Research on Cancer (IARC) database has shown a progressive increase in 5-year survival in the same time period for European countries [2].

There is an important amount of contradictory data about prognosis of patients with advanced laryngeal cancer and the effectiveness of different treatments that can impair decision making in clinical practice, mainly related with the selection of non-surgical organ preservation protocols. As most results of effectiveness are obtained from randomized controlled trials (RCTs) and most reports of worse outcomes come from observational studies, it is possible that protocol results are not correctly extrapolated to daily practice. The aim of this review is to comprehensively evaluate the information and the potential factors that explain these conflicting data.

2. Non-surgical organ preservation protocols

In the 1990s, organ preservation treatment protocols combining chemotherapy and radiotherapy were introduced as an alternative to total laryngectomy with the objective to preserve a functional larynx without compromising oncological outcome.

The effectiveness of concomitant chemoradiotherapy (CRT) as an effective organ preservation strategy was initially established by The Department of Veterans Affairs (VA) Laryngeal Cancer Study Group in 1991 [3]. Their conclusions were subsequently confirmed by the GETTEC [4] and RTOG 91-11 [5] trials and two individual data meta-analyses [6,7]. Although initially not addressed by the VA protocol [3], it was recognized later that instead of organ preservation, functional preservation is a more relevant outcome. This functional preservation is defined as an in situ larynx without need for permanent tracheostomy and permanent gastrostomy at 2 years after finishing the treatment [8,9]. Despite the various randomized trials that have all confirmed that the CRT approach achieves survival rates similar to treatment with total laryngectomy, none have shown improvement in survival rates with an organ preservation approach. Furthermore, some investigators have been concerned about the long-term toxic effects of CRT treatment on laryngeal function and the decreases in overall survival rates with non-surgical treatment reported more recently from large tumor registries and long-term follow-up of original trials [10]. This raises a critical question of whether the results of a complex multidisciplinary treatment approach developed in controlled clinical trials by skilled investigators can be effectively generalized to standard practice.

3. Non-surgical organ preservation protocols and survival trends

Since 2005, observational studies started to suggest that contrary to results reported by RCTs, survival of larynx cancer patients was decreasing. Carvalho et al. [11] in an analysis of the SEER database from 1974 to 1997 were the first to suggest a decrease in survival for patients with larynx cancer. The authors found an increase in the percentage of patients with advanced tumors (37.4 to 50.6%) treated with combined non-surgical therapies that were associated with a statistically significant

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