

Correlation Between Diagnostic Tests for Laryngeal Cancer Staging and Anatomopathological Staging: A Systematic Review Protocol

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Protocol

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Abstract

Background: Laryngeal cancer is one of the most prevalent types of cancer worldwide, which is more frequent in men mainly due to external factors such as alcohol consumption and smoking. Staging is an extremely relevant factor for better prognosis.

Methods: A literature search of the Embase, MEDLINE, Cochrane Library and LILACS VHL databases will be performed for original articles and studies on the assessment of diagnostic tests and laryngeal cancer staging that used imaging methods compared to anatomopathological staging. No criteria related to language or publication date will be used. To conduct this study, two reviewers will perform a search for eligibility criteria and data extraction. The Quality Assessment of Diagnostic Accuracy Studies-2 will be used to assess the methodological quality of the studies, and the Grading of Recommendations Assessment, Development and Evaluations will be used as a general quality assessment tool.

Discussion: This study aimed to evaluate the diagnostic accuracy of imaging tests in estimating TNM staging of laryngeal cancer compared to anatomopathological staging. This systematic review does not require approval from an ethics committee.

PROSPERO registration number: CRD42020155118.

Background

Laryngeal cancer is one of the most prevalent types of cancer worldwide, representing approximately 30% of malignant neoplasms diagnosed in the upper respiratory tract and 90% of malignant squamous cell carcinomas [1]. It develops approximately five times more in men than in women (5.8 cases per 100,000 inhabitants) and has an estimated incidence of 130,000 cases annually, with smoking and alcohol consumption as one of the main associated factors [2-4]. Ethnicity, socioeconomic status, and biological and genetic factors are some other variables that must be evaluated [5]. An American study demonstrated that black individuals, especially young adults, had a higher incidence of the disease [6].

The larynx is subdivided into supraglottic, glottic, and subglottic regions. Laryngeal cancer affects the supraglottic structures but can spread to other structures [2]. One of the most used methods to assess the disease is the TNM Classification of Malignant Tumors, which is based on the primary extension of the tumor (T), number of affected lymph nodes (N), and presence of metastasis (M), mostly used in the process of diagnosis and therapeutic conduct worldwide. Pathological TNM is determined through histopathological evaluation after the surgical procedure [7, 8].

Adequate clinical management is essential to establish a better prognosis, which is directly related to tumor staging. The assessment of preoperative (or clinical) TNM staging requires a set of imaging tests (magnetic resonance imaging, computed tomography, ultrasonography, and endoscopy) that are significantly important in clinical management and therapeutic follow-up [9, 10]. However, there is no

consensus in requesting such tests, and diagnostic accuracy is still a trap in determining preoperative TNM staging compared to postoperative (pathological) staging, a more invasive method [11].

In this sense, estimating the most sensitive method to detect the tumor in clinical staging will result in several benefits for the patient and healthcare service, such as reduced medical costs (direct and indirect) and greater survival and quality of life for the patient, providing a more effective therapeutic approach.

Objectives

This systematic review aimed to evaluate the diagnostic accuracy of imaging tests (magnetic resonance imaging, computed tomography, ultrasonography, and endoscopy) in estimating clinical TNM staging compared with anatomopathological staging in patients with laryngeal cancer.

Methods And Analysis

Protocol and registration

This systematic review and meta-analysis protocol was elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols. This review was registered in the PROSPERO International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO>) under number CRD42020155118. Approval from an ethics committee was waived due to the characteristics of the study.

Literature search

The primary literature search in the following databases will be conducted: Embase, PubMed/Medline, Cochrane Library, and LILACS VHL, with all articles published until August 2020. Relevant search terms will be included in titles, abstracts, and keywords, with the insertion of words and descriptors, such as laryngeal cancer, staging, diagnosis, and anatomopathological staging. The search strategy is available in the Supplementary File n. 01.

A Brazilian head and neck surgeon will follow the study to interpret the data and identify unpublished and ongoing studies. The website bancodeteses.capes.gov.br will be used in searching the gray literature to identify thesis in the thematic area and Google Scholar and websites of events and conferences on the theme to search for abstracts and unpublished studies. This research strategy will be reviewed by an expert using the Peer Review of Electronic Search Strategies [12].

Eligibility criteria

This review will include studies that met the following criteria: (i) observational studies (cohort, case-control, and prevalence) and (ii) randomized clinical trials and diagnostic test studies that assess laryngeal cancer staging. The PICO (Population; Intervention; Comparison; Outcome) structure will be

used in this study for the research question and eligibility criteria, adapting “Intervention” to “Index test,” as recommended by the Center for Reviews and Dissemination [13]. Studies that do not assess laryngeal cancer diagnosis and staging will be excluded from this analysis. Language and date of publication restrictions will not be used.

- *Population*: Studies that include patients with laryngeal cancer, regardless of age, sex, and geographic region.

- *Index test*: Anatomopathological staging will be used in this study as an index test to estimate adequate staging in open surgery and compare with imaging tests (magnetic resonance imaging, computed tomography, ultrasonography, and endoscopy).

Data management

Mendeley reference management software will be used to manage the search results, as well the Rayyan website. This tool allows search all databases, duplicates removed during the data screening process, and selected the articles for extractions steps. All references to the same study will be extracted and referred to in the text of the main report.

Selection of studies and data extraction

This step will be conducted by two independent reviewers who will search for the titles and abstracts of all investigated studies according to the inclusion criteria. Subsequently, during the full reading stage, the reviewers will proceed with the same inclusion criteria and then extract data independently, using previously standardized extraction spreadsheets. Disagreements will be discussed and resolved by consensus, and if necessary, the intervention of a third reviewer may be included.

The following data will be extracted to prepare the descriptive table: title and year of publication, authors, study design, sociodemographic characteristics of the population, cancer type and location, and staging method. If the study is reported in duplicate, the most recent publication providing more information will be used.

Risk of bias (quality) assessment

After the searches are completed, the Quality Assessment of Diagnostic Accuracy Studies-2 will be used to assess the quality of the studies. Additionally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used for a general quality assessment of the evidence of the studies using principles and characteristics to assess the quality of prognostic studies.

Data analysis

A descriptive table will be used to present a summary of the findings of the included studies. If possible, a meta-analysis will be conducted after data evaluation. Sensitivity, specificity, positive predictive value, negative predictive value, and 95% confidence interval will be calculated to estimate accuracy (true

positive, true negative, false positive, and false negative). The heterogeneity of the studies will be estimated by the Cochrane's χ^2 test and I^2 . As a parameter, values < 25% will be considered low heterogeneity; between 26 and 74%, moderate heterogeneity; and > 75%, high heterogeneity. The Spearman correlation test will be used to assess the threshold effect with a significance value of $p < 0.05$.

A funnel plot will be used to assess possible publication biases, such as the effect of small studies. The proposed subgroup analysis will include sex, age group, and geographic area (e.g., North America, Latin America, Europe, Africa, and Asia), and disease severity. A table with the characteristics of the studies will be prepared to assess the quality of evidence of the studies using the GRADE proposal. The RevMan 5.3 software will be used in the analyses.

Discussion

Staging is a fundamental factor in the establishment of better prognosis and development of cancer surveillance actions and epidemiological studies [9]. Several factors led to its use on a global scale, and over time, other factors were added, such as age and histological grade by type of tumor [14].

Considering diagnostic methods, histopathology is considered the gold standard for determining the presence of a malignant laryngeal tumor. However, anatomical clinical correlation by endoscopic evaluation and imaging tests (computed tomography, magnetic resonance imaging, and ultrasonography) contribute to determining the stage [11, 15]. Thus, staging becomes more effective with the association of different high-sensitivity diagnostic methods.

This study has some limitations. The lack of standardization in the performance of some imaging tests can impair the analysis. A trained professional is required to perform these tests and write the report, which in some situations can have a subjective interpretation. To minimize this effect, the criteria of quality of evidence will be applied to these variables.

This study aimed to present the accuracy of imaging tests to determine laryngeal cancer stage, identifying possible diagnostic flaws in the data found in the literature. Thus, this review will not be the end of the investigation but will provide subsidies to assess laryngeal cancer staging in the presurgical phase in the most reliable manner possible, directing new diagnostic strategies to assist the surgeon and oncologist to provide a better prognosis for the patient.

Abbreviations

TNM Classification: tumor (T), number of affected lymph nodes (N), and presence of metastasis (M); PICO: Population, Intervention, Comparison, Outcome; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Declarations

Ethics approval and consent to participate

Due to the characteristics of this study, which uses data published in the literature, ethical approval will not be necessary. Upon completion, the data obtained in this study will be sent to an interdisciplinary public repository (The Open Science Framework, [https:// osf.io/](https://osf.io/)).

Consent for publication

Not applicable.

Availability of data and materials

All data will be made available.

Acknowledgements

Not applicable.

Availability of data and materials

The data sets used and dissipated the current study available from the corresponding author, upon reasonable request.

Competing interests

All authors report no conflicts of interest.

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Authors' contributions

VGCD prepared the study proposal and edited this protocol. YMFT elaborated the study design and investigation strategy and edited and reviewed the protocol. VBD, JCO and VCG contributed to the study review. All authors approved the final version of the protocol.

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