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Definition of locally recurrent head and neck squamous cell carcinoma: a systematic review and proposal for the Odense - Birmingham definition

Abstract

Purpose: The objectives of this study were (1) to systematically review current definitions of head and neck squamous cell carcinoma (HNSCC) recurrence and (2) to propose a definition of locally recurrent HNSCC.

Methods A systematic literature review was performed according to the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ statement in Medline, Embase, and Cochrane databases guided by the study question “What is the definition of local recurrence for patients with HNSCC?”. All retrieved studies were reviewed and qualitatively analyzed.

Results: The systematic literature search resulted in 3,467 publications after removal of duplicates. Forty studies were examined as full text, and a total of five were found suitable for inclusion. All five included studies dealt with definitions of second primary HNSCC and were based on the Warren and Gates Criteria; (1) each of the tumors are malignant, (2) each must be distinct, and (3) the probability of one being a metastasis of the other must be excluded. Each of the included studies added specific anatomical and/or temporal separation measures to the criteria of second primary HNSCC. We propose the definition of locally recurrent HNSCC to be: (1) Same anatomical subsite or adjacent subsite within 3 cm of the primary lesion, (2) time-interval no more than 3 years (from completed treatment of the primary lesion), and (3) same p16-status for oropharyngeal carcinomas.

Conclusions: No uniform definition of locally recurrent HNSCC currently exists. We propose the Odense – Birmingham definition based on the anatomical subsite combined with a specific measurable distance, and a temporal separation of three years.

Introduction

Despite aggressive primary treatment, relapse frequently occurs in patients with head and neck squamous cell carcinoma (HNSCC) [1,2]. These patients also have an increased risk of second primary carcinomas, often adjacent to the primary lesion within the oral cavity, pharynx, or larynx [3,4]. Distinction between locally recurrent HNSCC (LRS) and second primary HNSCC (SPS) is imperative for proper diagnosis and treatment. Furthermore, patients suffering from LRS are generally considered to have a poorer prognosis than their counterparts with SPS [5,6]. Surgery with curative intent in LRS is usually extensive and requires advanced reconstructive procedures. As a result, a substantial proportion of these patients are treated palliatively [7,8]. Conversely, SPS tends to be associated with significantly better patient survival and can often be treated with a simpler and curatively intended approach [9]. **Finally, from a scientific and epidemiological perspective, clear distinction between LRS and SPS is mandatory to avoid selection bias when attempting to compare study outcomes involving local recurrence (e.g., treatment effects, incidence rates, risk factors, and detection methods of recurrent HNSCC).**

To our knowledge, no uniform definition of LRS exists, resulting in confusions as to when a malignant lesion is designated as LRS versus SPS in patients who have previously been diagnosed with HNSCC. Therefore, the objectives of this study were (1) to systematically review current definitions of HNSCC recurrence and (2) to propose a definition of locally recurrent HNSCC.

Methods

A systematic literature review was performed according to the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) statement [10].

Systematic literature search

A systematic literature search guided by the study question “What is the definition of local recurrence for patients with HNSCC?” was constructed as a block search combining all available free text and Medical Subject Heading terms for head and neck neoplasm, recurrence, and guideline. The complete search strategy is available from the supplemental appendix. The search strategy was developed with assistance from a science librarian, and on June 27, 2019 the electronic databases Medline, Embase, and Cochrane were searched by the first and second authors (MR and TR). No restrictions on study design or publication date were used.

Study Selection

Studies identified by the literature search were entered into Endnote version X8 (Thompson Reuters, Carlsbad, CA). Duplicates were automatically removed. Eligibility of the studies was assessed in two steps. First, titles and abstracts were screened independently by two authors (MR and TR) using predefined criteria for inclusion and exclusion. **In essence, studies on other cancers were excluded in the screening process.** Subsequently, the same two authors independently evaluated the full-text version of the publications that passed through the first screening. Discrepancies were resolved by discussion, and in case of disagreement, the article proceeded to the

next step. Reference lists were reviewed for relevant studies not identified through the electronic search. Conference abstracts, studies written in other languages than English, German, Norwegian, Swedish, or Danish, and studies without relevant data (e.g., studies on other cancers and studies on N-site or M-site recurrence) were excluded. Therefore, the present systematic review only included studies defining local recurrence in patients with HNSCC.

Data item and collection process

MR and TR also performed data extraction. **Data were collected regarding specifications of temporal and anatomical separation between the primary HNSCC and subsequent development of a new local carcinoma.** In addition, data on the application of any given definition were extracted (e.g. definitions used in clinical examinations, for molecular classification, or for cancer registries).

Quality assessment

Relevant quality assessment tools were sought. However, none were found to fit our specific research question as available assessment tools consider general study qualities, such as study design, statistical methods, etc. Therefore, the Centre for Evidence-Based Medicine at Odense University was consulted, and on the basis of this, we constructed a suitable quality assessment tool. Each study was evaluated considering three questions: Is the definition specific for HNSCC? Does the definition mention both anatomical and temporal separation? Has the definition been tested in later studies? The evaluation was performed by authors MR and TR and limited to the specific research question in the present review.

Results

Study Selection and Characteristics

The systematic literature search resulted in 4,046 publications. After removal of duplicates, 3,467 studies remained for screening. The study selection process is illustrated in Figure 1. Forty studies were examined as full text, and among these, two studies were found suitable for inclusion. In addition, three studies were included through the process of cross-checking reference lists, resulting in a total of five included studies.

Results of Individual Studies

All five included studies dealt with definitions of SPS and were based on the Warren and Gates Criteria from 1932 [11]; (1) each of the tumors are malignant, (2) each must be distinct, and (3) the probability of one being a metastasis of the other must be excluded. Four of the five studies added a specific distance or anatomical separation to the Warren and Gates criteria [9,12-14]. Hong et al. [12] and Jovanovic et al. [13] both defined this distance to be >2 cm, whereas Braakhuis et al. [9] determined SPS to be separated to another anatomical site. SEER [14] limited SPS to appear in a separate anatomical subsite. Three studies also employed a temporal separation criterion, defined as a minimum of 3 to 5 years for a SPS to occur after diagnosis of the primary tumor [12,14,15].

An overview of the included studies is provided in Table 1.

Quality assessment

The quality of the individual studies was evaluated according to a self-constructed, non-validated assessment tool. Overall assessments of the five included studies according to this tool deemed all of them acceptable. The quality assessment is summarized in Table 2.

Discussion

This is the first systematic review to evaluate current definitions of LRS. Our primary result was that no recognized definition exists.

Numerous studies have investigated treatment effects, incidence rates, risk factors, and detection methods of recurrent HNSCC [8,16,17]. However, misclassification of SPS as LRS may represent a major selection bias. Indeed, reported incidence rates of recurrent HNSCC have varied considerably from 12% [18] to 54% [1]. Results aiming to change existing treatment approaches (towards potential new ones) may therefore be skewed if favorable subjective criteria are used to define LRS. From a clinical standpoint, it is of utmost importance to distinguish LRS from SPS to ensure proper prognostication and treatment approach. For example, at present there is no consensus on how a new HNSCC lesion is classified when arising 2 cm from a previous primary site that was treated four years earlier. Since the prognosis is considerably better in SPS, extensive resection can be undertaken much more readily than in LRS where palliative treatment may be considered more often.

Both LRS and SPS may be caused by the same environmental factors that caused development of the first primary tumor. Although smoking and alcohol consumption are the traditional, principal carcinogens [19,20], human papillomavirus (HPV) infection has also been identified as a cause of HNSCC, when arising from the oropharynx [21,22]. However, patients with HPV-positive oropharyngeal cancer have distinct demographic characteristics (e.g., younger age at onset of disease and better socio-economic status), better locoregional control, and higher survival than HPV-negative patients [23,24].

The detection of multiple adjacent carcinomas was first described by Slaughter et al. 1953 as “field

cancerization” [25] . Two theories have been proposed to explain this concept. The first considers development of a malignant cell as a rare event, which originates from a monoclonal cell population, disseminates throughout the mucosa, and eventually causes multiple malignant lesions [26]. The second theory anticipates that carcinogen exposure affects the independent transformation of diverse epithelial cells to different degrees at different times and may result in development of multiple tumors [27,28]. The first hypothesis supports that a new malignant lesion may be considered as LRS, whereas the second hypothesis suggests that multiple tumors may well be SPSs. How can these theoretical deliberations be converted into a clinically meaningful definition? Based on our systematic literature search, it appears that both temporal and anatomical separation should be taken into account.

All included studies are based on the Warren and Gates criteria, which were formulated to distinguish a primary carcinoma from a separate carcinoma (i.e., termed second primary *or* synchronous carcinoma) that arises adjacent to one another in the primary setting. Several studies have used the Warren and Gates criteria in the assessment of LRS versus SPS, including amendments on specific anatomical and temporal separation. All appear to specify LRS as a new indistinct carcinoma and SPS as a distinct new carcinoma in patients with previously treated HNSCC.

However, as mentioned, no consensus on the exact anatomical or temporal separation exists. Some authors suggest <2 cm or <3 cm as anatomical separation [12,13], whereas others propose LRS as a new carcinoma within the same site or subsite [9,14]. Could anatomical subsite localization alone be used for distinction of LRS versus SPS? If a patient with previous tonsil cancer presented with a carcinoma at the palatopharyngeal fold, one could argue that it may be considered as LRS, since the two lesions could be localized within a few millimeters, although appearing in two anatomically different sites.

Three of the included studies specify a temporal separation in their definition of LRS. Hong et al. [12] and Zukauskaitė et al. [15] both determine LRS as a new adjacent carcinoma arising within 3 years of treatment. However, the criterion is only used as part of their methodological study approach, without any further rationalizations. SEER [14], which is a manual for cancer staging and coding, does not include any reasons for their temporal definition of LRS within 5 years. Thus, no rationale is currently described regarding a temporal time-span criterion in defining LRS.

We suggest that the definition of LRS should be based on the anatomical subsite combined with a specific measurable distance, and an explicit temporal distinction. **Thus, we propose the definition of LRS to be: (1) Same anatomical subsite *or* adjacent subsite within 3 cm of the primary lesion, (2) time-interval no more than 3 years (from completed treatment of the primary lesion), and (3) same p16-status for oropharyngeal carcinomas.**

According to our systematic literature review this definition includes the most used criteria for LRS, it is based on clinical standard examinations, and in our opinion, it seems reproducible and easy to remember. As earlier stated no accepted definition of LRS exists.

Limitations

The included studies were evaluated according to a self-constructed, non-validated assessment tool, since no appropriate validated tool was found for this review.

Further, the applied search terms were based on LRS, and identification of studies on SPS was secondary. The applied search strategy may have missed studies including only SPS. **Accordingly, it is possible that the literature review would have been strengthened if the search had included SPS. Limitations regarding our definition proposal of LRS also deserve mention. Our proposed definition**

has the advantage of being simple, reasonable, and developed based on the different definitions stated in the literature. However, since all the studies included in our systematic literature review are without solid scientific base, our suggested definition also lacks firm evidence. In other words, our definition of LRS is pragmatic. Application of our definitional rigid criteria regarding anatomical separation is not straight forward in the clinical setting, since there is no visible border from the previous tumor site. Thus, determining LRS from SPS will always depend on a subjective clinical decision-making.

Future research

Despite development of numerous molecular and immunohistochemical methods during recent years, none have shown to be applicable in the clinical management of patients with HNSCC, other than p16 for oropharyngeal cancers. To our knowledge, no appropriate molecular or immunohistochemical methods currently exist to discriminate LRS from SPS. However, this may well change in the future.

It is also imperative that we validate our proposed definition, preferably in a prospective fashion. From a purely clinical perspective, tumors fulfilling our definition would need to demonstrate the prognostic features that characterize true LRS, to set realistic patient expectations and avoid futile treatment efforts. From a more basic perspective, the microscopic features would need to display predefined similarities. Such a study could potentially be conducted by rigorously collecting information on all patients with either suspected LRS or SPS, including spatiality, temporality, immunohistochemical features, and long-term outcomes. This would allow us to compare patients with one, two, or all three proposed features, and derive their individual and combined sensitivity and specificity for outcomes and possibly, preferred management. Furthermore, clinical and constitutional features should be collected to deduce whether they may aid in proper classification.

Accordingly, even if the proposed definition appears to be suboptimal, we would be able to statistically derive a model for optimizing discrimination.

Conclusions

No uniform definition of locally recurrent HNSCC currently exists. We propose The Odense – Birmingham definition based on the anatomical subsite combined with a specific measurable distance, and a temporal separation of three years.

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Figure 1: Study selection, flow chart.

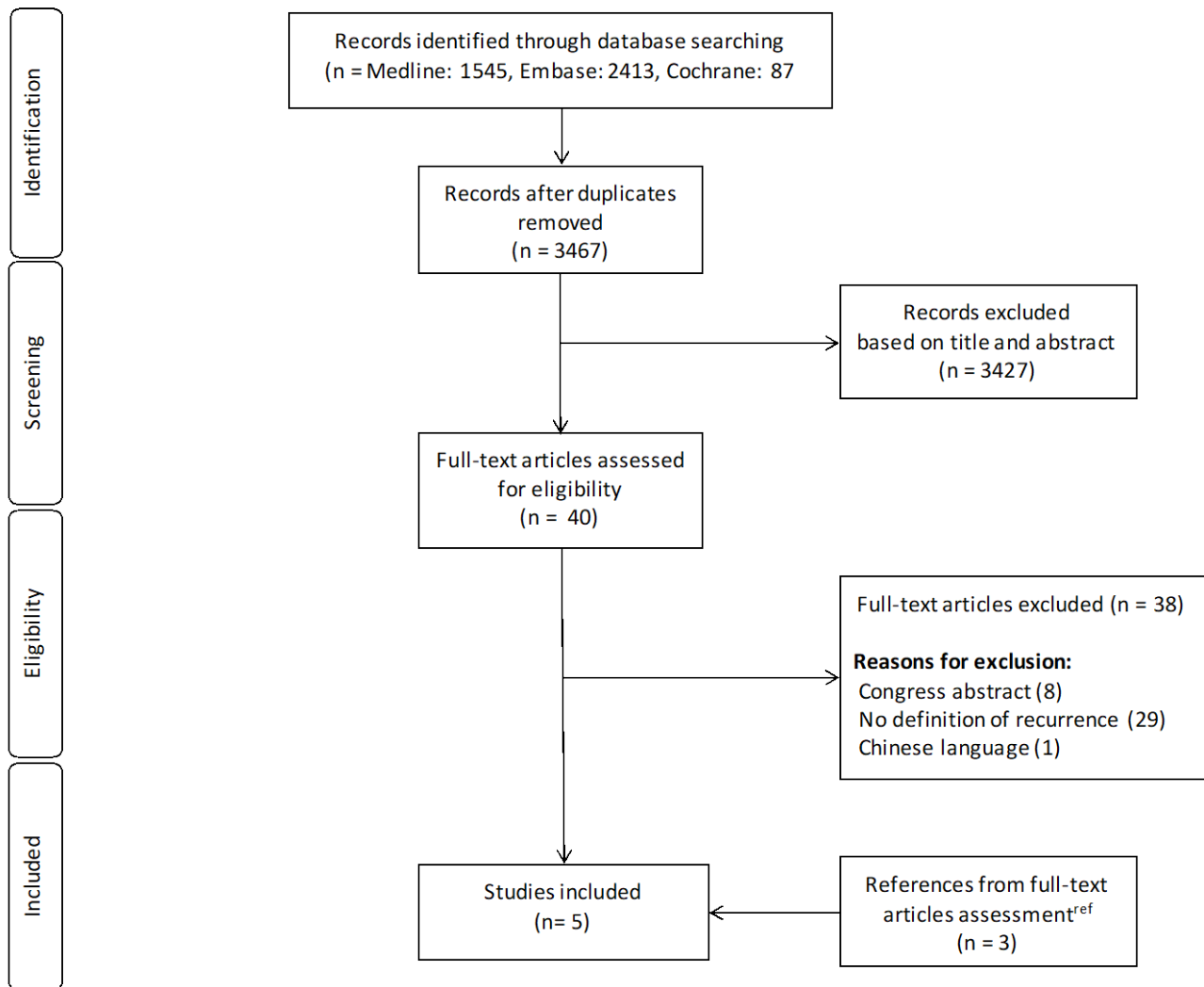


Table 1 Existing descriptions of locally recurrent HNSCC sought through systematic literature search.

Study (Author, year)	Study population (cancer, n)	Temporal separation	Anatomical separation	Context of definition
Braakhuis et al. 2002	HNSCC, no specific study population,	None	Same (or adjacent) anatomic site	Review and proposal for molecular classifications of SPS
Zukauskaite et al. 2018	HNSCC, 1576 patients	< 3 years	None	Retrospective cohort study analyzing failure rates after curatively intended IMRT
SEER, 2018	HNC in general, no specific study population,	< 5 years	Same anatomical subsite	Program Coding and Staging Manual
Hong et al. 1990	HNSCC, 103 patients	< 3 years	< 2 cm	RCT study on the effect of isotretinoin
Jovanovic et al. 1994	Oral SCC, 727 patients	None	< 2 cm	Retrospective cohort study calculating the risk of MPT following oral SCC

Abbreviations: HNSCC: Head and Neck Squamous Cell Carcinoma; IMRT: intensity modulated radiotherapy; HNC: Head and Neck cancer; MPT: multiple primary tumors; SCC: Squamous Cell Carcinoma

Table 2 Existing definitions of locally recurrent HNSCC sought through systematic literature search.

Study (Author, year)	Is the definition specific for HNSCC?	Does the definition mention both anatomical and temporal separation?	Has the definition been tested in later studies?*	Overall assessment
Braakhuis et al. 2002	Yes	Yes	No	Acceptable
Zukauskaite et al. 2018	Yes	No	No	Acceptable
SEER 2018	No	Yes	No	Acceptable
Hong et al. 1990	Yes	Yes	No	Acceptable
Jovanovic et al 1994	Yes	No	No	Acceptable

Abbreviations: HNSCC: Head and Neck Squamous Cell Carcinoma

* To the knowledge of the authors