ACTA ONCOLOGICA
2023, VOL. 62, NO. 9, 1102–1105
https://doi.org/10.1080/0284186X.2023.2245550

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LETTER TO THE EDITOR

Diagnosis of locally recurrent head and neck squamous cell carcinoma in the Nordic HNC centers and feasibility of the Odense-Birmingham definition

Max Rohde[a,b], Jesper Grau Eriksen[c], Manan Pareek[d], Åse Bratland[e], Antti Mäkitie[f,g,h], Lalle Hammarstedt-Nordenvall[h], Irene Wessel[i], John Sigurd Lybeck[j], Hanna Mäenpää[k], Maria Gebre-Medhin[l] and Christian Godballe[a,b]

[a]Research Unit for ORL – Head & Neck Surgery and Audiology, Odense University Hospital, Odense, Denmark; [b]Faculty of Health Sciences, Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [c]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark; [d]Center for Translational Cardiology and Pragmatic Randomized Trials, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [e]Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Nydalen, Oslo, Norway; [f]Department of Otorhinolaryngology – Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [g]Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland; [h]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; [i]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [j]Department of Ear, Nose and Throat, Head and Neck Surgery, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway; [k]Department of Oncology, Tampere University Hospital, Tampere, Finland; [l]Department of Hematology, Oncology, and Radiation Physics, Skåne University Hospital, Lund University, Lund, Sweden

ARTICLE HISTORY Received 7 November 2022; Accepted 20 July 2023

Background

Local recurrence of head and neck squamous cell carcinoma (LRC) is often encountered in patients treated with curative intend [1,2]. However, the reported frequencies and onsets of LRC have shown wide variation [3–5]. At the same time, patients diagnosed with head and neck squamous cell carcinoma have a high risk of second primary carcinomas (SPC) [6,7], although the reported rates of SPC also vary [8,9].

A recent systematic review showed that no generally accepted definition of LRC currently exists [10], which is likely a predominant explanation for inconsistencies in diagnosing LRC and SPC. Based on these findings, the Odense-Birmingham definition was suggested, defining LRC as (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 [10].

Clear distinction between LRC and SPC is essential for appropriate patient management. LRC typically requires advanced surgical procedures, and as a consequence, many patients are treated with palliative radiotherapy, chemotherapy or best supportive care [11,12]. On the other hand, SPC more often has a good prognosis and may be treated with a simpler and curatively intended approach [13]. Finally, from a scientific perspective, misclassification of SPC as LRC may result in major selection bias [8,10].

This study hypothesized that the lack of a generally accepted LRC definition causes high variation in diagnosis of both LRC as SPC (and vice versa) among the Nordic head and neck cancer (HNC) centers. The objectives were (1) to investigate the clinical practice for classification of LRC versus SPC in the Nordic HNC centers, and (2) to evaluate the feasibility of the Odense-Birmingham definition for uniform diagnosis of LRC in the Nordic HNC centers.

Methods

Material and participants

The principal authors (MRO and CG) designed 36 clinical cases involving patients with history of head and neck squamous cell carcinoma and subsequent occurrence of a new verified carcinoma near their prior T-site (Appendix 1 & 2).

The 36 cases consisted of 12 similar cases for each of the three primary cancer sites; oral cavity, pharynx and larynx. The cases involved varying scenarios of onset, distance, and p16 status of the new carcinoma from the prior T-site accompanied by an illustrative drawing. In each of the clinical cases, HNC surgeons and oncologists from the Nordic HNC centers were asked to classify the new carcinoma as either LRC or SPC.

The Scandinavian Society for Head and Neck Oncology (SSHNO) is a multidisciplinary society including the five Nordic countries (Finland, Iceland, Norway, Sweden, and Denmark). A major aim for the society has been to harmonize the guidelines for HNC management.

All board members from SSHNO were invited to participate. Each board member was asked to be responsible for handing out the cases and to collect responses from six HNC

CONTACT Max Rohde Max.Rohde@rsyd.dk

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2245550.

specialists (three oncologists and three surgeons, including themselves) from their own HNC center.

The cases were to be answered twice. First, the participants were instructed to respond to the cases according to the current clinical practice at their center (Round 1). Subsequently, they were instructed to read the Odense-Birmingham definition article [10] prior to answering the cases again (Round 2). The participants were not requested to solve the cases according to the principles of the Odense-Birmingham definition, but simply to answer the cases again, based on their overall clinical assessment, after having carefully read the paper. The participants could still respond according to their own personal experience and opinion. Through this process, we aimed to test whether the Odense-Birmingham definition had any impact on the participants' decision-making.

Participants were asked not to discuss the cases with any colleagues, but to answer them individually. No time delay was required between the two rounds, and the cases were not scrambled for Round 2. MRO and CG were available for any questions or problems in answering the cases. MRO gathered the responses from each of the SSHNO board members and composited the results.

Outcomes

The primary endpoint was the overall change of diagnosis from LRC to SPC for each case answer from all participants between Round 1 and Round 2. In this way a 'non-event' counted as LRC and an 'event' as SPC. Answers of the equivalent cases for oral cavity, pharynx and larynx were combined, meaning that the 36 case responses were merged into 12 responses (i.e., case 1 results were merged with those from cases 13 and 25, case 2 results with cases 14 and 26, etc.). Diagnosis of the new primary carcinoma (LRC or SPC) from the participants for each of the 12 merged cases was displayed according to specialty (oncology and surgery) and overall, for both Round 1 and Round 2.

Statistical analysis

Categorical variables were presented as counts and corresponding percentages. Fisher's exact test was applied to examine the overall difference between Round 1 and Round 2. The significance level was 5% (two-sided). All analyses were performed with Stata/IC 15.1 (StataCorp LP, College Station, Texas, USA).

Results

Study participation

Eight board members, representing nine HNC centers in Denmark, Finland, Norway, and Sweden agreed to participate. Only the two board members representing the HNC center of Reykjavik, Iceland did not participate.

Not all board members were able to assemble six participants from their HNC center. For example, board member and coauthor AM was able to acquire case responses from one oncologist in Helsinki, and additional responses from oncologists at the HNC center in Turku instead. Conversely, coauthor JSL could not achieve participation from any colleagues in Trondheim, Norway. A total of 42 HNC specialists from the Nordic HNC centers participated; 22 oncologists and 20 surgeons. An overview of the participants is shown in Table 1.

Table 1. Overview of participants.

	Participants ($n = 42$)	
HNC Center	Oncologists ($n = 22$)	HNC Surgeons ($n = 20$)
Aarhus, Denmark	3	2
Rigshospitalet, Denmark	3	3
Lund, Sweden	3	3
Karolinska, Sweden	3	3
Oslo, Norway	3	3
Trondheim, Norway	0	1
Helsinki, Finland	0	3
Turku, Finland	4	0
Tampere, Finland	3	2

Outcome results

Diagnosis of the new primary carcinoma (LRC versus SPC) for each case, in both Round 1 and Round 2, are presented in Table 2. Overall differences in case responses between Round 1 and Round 2 were found to be significant for cases 2, 4, 5, 7-8, and 12.

Discussion

This is the first study to investigate differences in the clinical practice for diagnosing LRC at HNC centers from the Nordic countries. Our results appear to demonstrate variation among the Nordic HNC centers, including differences between oncologists and surgeons. In short, the treating HNC clinicians disagree upon what exactly constitutes LRC versus SPC, in terms of criteria for anatomical distance, duration, and p16 status.

Our results emphasize the lack of a clear LRC definition as a fundamental cause of variation in LRC and SPC diagnostics. In this way, the recent article suggesting the Odense-Birmingham definition for LRC [10] seems highly relevant. Reading the paper proposing this definition significantly changed the participants' responses in half of the cases between the study rounds. The participants were not instructed to directly apply the Odense-Birmingham definition in Round 2, but simply to answer the cases again, based on their overall clinical assessment. Some participants may have answered strictly according to the Odense-Birmingham definition, whereas others may have continued with their normal clinical practice to some extent. Interpretation of the results from Round 2 is therefore challenging. The used methodology was not a direct test of using the Odense-Birmingham definition. Rather, the used approach show how specialized HNC clinicians classify a new primary carcinoma in their daily practice when familiar with the Odense-Birmingham definition. No difficulties regarding

Table 2. Diagnosis of new primary carcinoma (local recurrence versus second primary tumor) for each case displayed by specialty and overall, for both Round 1 and Round 2 of case responses.

Case	Specialty		Overall	Overall difference Round 1 vs. Round 2 (*p*-value, Fishers-exact test)
	Surg. ($n = 60$*)	Onc. ($n = 66$*)		
1. Round 1	0	3 (4,6%)	3 (2,6%)	0.62
Round 2	1 (1,7%)	0	1 (0,8%)	
2. Round 1	16 (26,7%)	21 (31,8%)	37 (29,4%)	<0.001
Round 2	53 (88,3%)	53 (80,3%)	106 (84,1%)	
3. Round 1	58 (96,7%)	58 (87,9%)	116 (92,1%)	0.62
Round 2	60 (100%)	59 (89,4%)	119 (94,4%)	
4. Round 1	5 (8,3%)	12 (18,2%)	17 (13,5%)	<0.001
Round 2	1 (1,7%)	1 (1,5%)	2 (1,6%)	
5. Round 1	17 (28,3%)	28 (42,4%)	45 (35,7%)	<0.001
Round 2	53 (88,3%)	55 (83,3%)	108 (85,7%)	
6. Round 1	58 (96,7%)	60 (90,9%)	118 (93,6%)	>0.99
Round 2	60 (100%)	58 (87,9%)	118 (93,6%)	
7. Round 1	38 (63,3%)	35 (53,0%)	73 (57,9%)	<0.001
Round 2	55 (91,7%)	52 (78,8%)	107 (84,9%)	
8. Round 1	44 (73,3%)	46 (69,7%)	90 (71,4%)	<0.001
Round 2	58 (96,7%)	56 (84,9%)	114 (90,5%)	
9. Round 1	60 (100%)	60 (90,9%)	120 (95%)	>0.99
Round 2	60 (100%	59 (89,4%)	119 (94,4%)	
10. Round 1	40 (66,7%)	46 (69,7%)	86 (68,3%)	0.43
Round 2	40 (66,7%)	39 (59,1%)	79 (62,7%)	
11. Round 1	39 (65,0%)	48 (72,7%)	87 (69,0%)	0.50
Round 2	42 (70,0%)	39 (59,1%)	81 (64,3%)	
12. Round 1	36 (60,0%)	31 (47,0%)	67 (53,2%)	<0.001
Round 2	17 (28,3%)	15 (22,7%)	32 (25,4%)	

*Three responses per oncologist and surgeon, respectively.
The counts and percentages reported pertain to a diagnosis of a second primary tumor.

interpretation or application of the definition were reported. This emphasize that use of the Odense-Birmingham definition is straightforward.

Prior studies have suggested the anatomical separation criterion for LRC to be below either 2 cm or 3 cm [9,14]. The Danish HNC Study Group (DAHANCA), on the other hand, defines all new malignant tumors as LRC. In our opinion, the specific criteria for defining LRC are not paramount (i.e., whether the criteria use 2 cm or 5 cm of anatomical distance and 3 years or 5 years between occurrences, respectively). What remains truly important is to reach consensus, as it will facilitate proper comparison of different study results.

However, to establish generally accepted rigid criteria is difficult. Some clinicians may not acknowledge anatomical tumor localization reported by other clinicians, in particular for difficult accessible tumors. Moreover, anatomical separation from a previous tumor site is challenging since there is no visible border in the clinical setting. Distinguishing LRC from SPC will, to some extent, always depend on subjective clinical decision making. Still, the current discrepancy concerning such a central clinical matter for this patient population is challenging. The reported incidence rates of recurrent head and neck squamous cell carcinoma vary significantly from as low as 12% to as high as 54% [2,15,16]. Studies aiming to change existing treatment approaches toward potential new ones may therefore be skewed if subjective criteria are used to define LRC. Patients with the same condition may be treated differently if the classification of these lesions is not harmonized. The question may be – is the treatment incorrect or inappropriate in case the diagnosis is incorrect or inappropriate?

Development of a consensus definition for LRC would potentially enhance the clinical treatment of patients with LRC or SPC, but also research initiatives that address these conditions. A suggested platform would be an international working group that in collaboration with SSHNO agrees upon a general LRC definition, e.g., the Odense-Birmingham definition or a modification hereof. If this process is successful, the next stage could be to present and acquire acceptance from other international scientific communities and implement a globally accepted definition. Importantly, a consensus definition should also lead to improved patient outcomes, which need to be studied as part of a potential introduction of a new generally accepted definition.

Conclusions

The diagnostic principles of LRC differ significantly among the Nordic HNC centers. The Odense-Birmingham definition of LRC is feasible, but consensus building is still warranted to improve the clinical care, and to ensure standardized endpoints in the research of HNC patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Jesper Grau Eriksen http://orcid.org/0000-0002-1145-6033
Antti Mäkitie http://orcid.org/0000-0002-0451-2404

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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