Evidence and guidelines in otorhinolaryngology: the merits of evidence-based case reports

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Evidence and guidelines in otorhinolaryngology: the merits of evidence-based case reports

Bewijsvoering en richtlijnen in de Keel-Neus-Oorheelkunde:
de waarde van evidence–based case reports
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 3 februari 2012 des middags te 4.15 uur

door

Markus Cornelis Josephus Aarts

geboren op 29 november 1978 te Waalwijk

Promotor:	Prof. dr. W. Grolman
Co-promotoren:	Dr. G.J.M.G. van der Heijden
	Dr. M.M. Rovers

Aan mijn ouders en Ilja

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Chapter 1

General introduction and thesis outline

Introduction

Evidence-based medicine refers to the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of patients. The first step in evidence-informed decision making involves converting information needs at point of care into focused clinical questions[1]. In this context, information refers to new medical knowledge, rather than additional patient data or non-medical information. In daily practice physicians frequently require such new medical information. For example, physicians pay more attention to the usefulness of suggested clinical tests with the positive and negative predictive values for detecting a disease in mind. After the correct diagnosis has been made, together with the patient we choose the best possible of the existing treatment options. For this we compare their absolute risks for cure and benefit, side effects and harm. And before choosing and initiating a treatment we like to inform the patient about his prognosis and possible prognostic factors that can influence the course and outcome of the disease[1].

Nowadays it is highly preferable to use the most recent scientific evidence for meeting information needs and answering pertinent questions before making decisions in patient care. Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough[2]. However, given the limited time available during our consultation, finding relevant evidence that is of sufficient quality and also applies to our individual patient is hardly possible. That is, despite the introduction of the Cochrane Collaboration and TRIP database[3 4]. To facilitate our quest for answers, several evidence based otorhinolaryngology guidelines have been developed[5-10]. They are based on sound approaches using explicit and transparent criteria for the development of evidence based guidelines[11-13]. These include instructions for guideline work group composition, searching and appraising evidence, rating conclusions, grading recommendations and updating guidelines. The aim of these guidelines is to provide a comprehensive overview of diagnostic and therapeutic management concerning a certain disease or syndrome. Since they are

developed with the intention to make patient care safer, more effective and improve its quality, they have become a very important tool in current healthcare[14].

On the other hand, potential limitations in implementing these guidelines in daily practice have also been reported, i.e.:

- The recommendations in the guideline do not apply to individual patients.
- Not all pertinent questions for clinical decision making are answered in the guidelines.
- When the evidence is weak it is often unclear to separate evidence from judgement.
- It is often unclear whether all the evidence available is indeed cited in the guideline.
- It is not unusual that the reported outcomes are indistinct and therefore it is difficult to inform our patients about their absolute risks.

Overall aim of this thesis

The general objective of this thesis is to address whether the current otorhinolaryngology guidelines sufficiently serve the effectiveness, safety and quality of patient care in terms of uptake of new medical knowledge. In addition, evidence-based case reports (EBCR's) are presented as a novel potential important instrument to further improve the effectiveness, safety and quality of patient care in otorhinolaryngology.

Thesis outline

In **Chapter 2** we will present the results of a survey among otorhinolaryngologists in which we studied the dissemination of the current evidence-based otorhinolaryngologists guidelines. In **Chapter 3** we will compare several available national evidence-based guidelines for the diagnosis and treatment of patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS) regarding their content, conclusions on the available evidence and their recommendations. In **Chapter 4** we will introduce an EBCR as answer to a *diagnostic* question: "what is the *diagnostic* value of diffusion-weighted magnetic resonance imaging in detecting a residual cholesteatoma?" With the EBCR we answer a clinical question on *therapy* in **Chapter 5**: "What is the value of a mandibular repositioning appliance for the treatment of non-apnoeic snoring?" In **Chapter 6** we will report an EBCR answering the *prognostic* question: "Salvage laryngectomy after primary radiotherapy: what are prognostic factors for the development of pharyngocutaneous fistulae?" The predictive value of the Mallampati score in diagnosing OSAHS in patients suspected for OSAHS is evaluated in the EBCR of **Chapter 7** as an answer to differences between guidelines. In **Chapter 8** the main findings of the studies described in this thesis together with the added value of EBCR's are discussed and put into a wider perspective.

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Chapter 2

Awareness, opinion about and adherence to evidence-based guidelines in otorhinolaryngology

Mark CJ Aarts[1]

Geert JMG van der Heijden[1,2]

Charlotte Siegers[1]

Wilko Grolman[1,3]

Maroeska M Rovers[1,2]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

3) Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

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Abstract

Background

Guidelines may assist physicians and patients in decisions about effective and safe care. To date little is known about the awareness of, opinion about and adherence to evidence-based guidelines in otorhinolaryngology.

Methods

We performed a survey among 440 otorhinolaryngologists of the Dutch Society of Otorhinolaryngology and Head & Neck Surgery. The questionnaire consisted of questions about the characteristics of the respondents, their knowledge and opinion of available evidence-based guidelines and their adherence to them. Furthermore two clinical scenarios were included to test their knowledge regarding the guideline "Diagnosis and treatment of obstructive sleep apnoea-hypopnoea syndrome"

Results

The daily practice of most otorhinolaryngologists (70%) was influenced by evidence-based guidelines; 62% stated that evidence-based guidelines supported their clinical practice, 32% stated that guidelines directed their clinical practice. The mean confidence in the evidence of recommendations stated in the guidelines was 77%. The mean percentage non-adherence to guideline recommendations was 45%. The guideline adherence was higher in younger otorhinolaryngologists. Gender, type of hospital and PhD grade did not affect the preferences of the responders. In general, patients are treated in accordance with the guideline. However if disease characteristics become less distinct, on the one hand guidelines include a wider range of treatment options, and on the other hand variation in chosen treatment by otorhinolaryngologists increases.

Conclusion

Dutch otorhinolaryngologists are well aware of the available evidence-based guidelines and many use these to support their clinical practice. The treatment by Dutch otorhinolaryngologists is in accordance with the Dutch guideline. If guidelines, however, do not provide strict recommendations and allow flexibility in treatment, larger variations in chosen treatment are found. This may reflect that otorhinolaryngologists still may encounter difficulties when applying the current guidelines to an individual patient.

Introduction

During the last decade the number of published guidelines has rapidly increased. Awareness of and adherence to evidence based clinical guidelines is considered vital for improving effectiveness, quality and safety of patient care. Clinical guidelines are considered valid if they are developed in a rigorous way, independently of vested interests of their developers and if they support decision making in practice and affect actual care. National health care improvement institutes (e.g. the National Institute for Health and Clinical Excellence in the UK, the Agency for Healthcare Research & Quality in the United States and the Institute for Healthcare Improvement in the Netherlands) follow validated systematic approaches for guideline development such as AGREE and GRADE[1,2]. Guideline statements may assist physicians and patients in decisions about appropriate clinical and health care for specific circumstances. Guidelines have limited impact on clinical practice unless they are successfully integrated in the clinical settings[3]. Several otorhinolaryngology guidelines have been developed worldwide, e.g. adult sinusitis, surgical management of otitis media with effusion, allergic and non-allergic rhinitis, respiratory tract infections, head and neck cancer, disease of adenoid and tonsils (DAT) and obstructive sleep apnoea-hypopnoea syndrome (OSAHS)[4-9]. One survey about guideline awareness among pediatricians has been published before[16]. However, to date little is known about the dissemination of evidence-based guidelines by otorhinolaryngologists.

We performed a survey among otorhinolaryngologists to study their current awareness, knowledge, and opinion of evidence based otorhinolaryngology guidelines. In addition, we used two clinical scenarios to assess their adherence to a guideline.

Methods

We performed a survey among Dutch otorhinolaryngologists between September and December 2010. We contacted 440 Dutch otorhinolaryngologists of the Dutch Society of Otorhinolaryngology and Head & Neck Surgery by mail and asked them to complete a structured postal questionnaire. To maximize the response rate a reminder was posted 5 weeks later. All questionnaires were processed anonymously.

The first part of the questionnaire consisted of 6 questions concerning the characteristics of the respondents i.e. gender, age, PhD grade, type of hospital, area of interest and time registered as otorhinolaryngologist. Furthermore we evaluated if they were aware of evidence-based guidelines, which guidelines they knew, how often they used them and what their general opinion about evidence-based guidelines was. We also asked them which of the current guidelines they knew by heart. The current existing guidelines used in the Netherlands are: chronic rhinosinusitis, DAT, OSAHS, facial nerve paralysis, laryngeal carcinoma, oral cavity/ oropharyngeal carcinoma and hypopharyngeal carcinoma[4 10-16]. The respondents also rated their agreement with the following three statements on a visual analogue scale ranging from 0 to 100%; “To what extent do you have confidence in the correctness of evidence-based guidelines?”, “To what extent do you deviate from evidence-based guidelines in your daily practice?”, “To what extent do the guidelines influence your daily practice?” In the second part two clinical scenarios were described in order to test the knowledge of the otorhinolaryngologists regarding the available evidence-based guideline “Diagnosis and treatment of OSAHS” **(Table 1)**[4]. Data from completed and returned questionnaires were analyzed using SPSS (version 17). To test for differences in percentages we used a chi-square test and for continuous data we used a t-test or a Wilcoxon test.

Table 1: two clinical scenarios concerning patients with OSAHS

Scenario A:
A 46 year old male with a Body Mass Index (BMI) of 29 was referred for complaints of nightly snoring and apnoeas. Polysomnography showed an Apnoea-Hypopnoea Index (AHI) of 35 (severe OSAHS). Sleep endoscopy showed a collaps of the lateral pharyngeal wall and a velopharyngeal flutter.
Scenario B:
A 35 year old male with a BMI of 26 was referred for complaints of nightly snoring and apnoeas. Polysomnography revealed an AHI of 17 (moderate OSAHS). Sleep endoscopy showed a collaps of the lateral pharyngeal wall and a velopharyngeal flutter.

Results

Of the 440 otorhinolaryngologists, 187 (43%) returned a complete questionnaire, 7 (2%) indicated that they did not want to participate and 246 (55%) did not respond at all. The baseline characteristics of the respondents did not differ from the characteristics of all Dutch otorhinolaryngologists. Data for this comparison were kindly provided by the Dutch Society of Otorhinolaryngology and Head & Neck Surgery **(Table 2)**.

The guidelines were used daily by 114 (61%) respondents, 2-3 times a week by 38 (20%) respondents, and once or less than once a week by 35 (19%) respondents. Most otorhinolaryngologists (62%) stated that evidence-based guidelines supported their clinical practice, 32% stated that the guidelines even guided their clinical practice, 1% stated that the guidelines impeded their clinical practice. The remaining 5% of the otorhinolaryngologists had an other opinion. The percentage of otorhinolaryngologists whose practice was guided by guidelines was higher in academic as compared to general otorhinolaryngologists: 59% versus 29% (difference 30%, (95%CI: 11 ; 49), respectively.

Table 2: Characteristics of the respondents compared to the characteristics of all Dutch otorhinolaryngologists which data were kindly provided by the Dutch Society of Otorhinolaryngology and Head & Neck Surgery

		Respondents: n = 187 (%)	Data DS-OHNS n = 440 (%)
Gender:	**Male:**	150 80%	347 79%
	Female:	37 20%	93 21%
Age (years):	**30-39 y:**	31 17%	106 24%
	40-49 y:	68 36%	149 34%
	50-60 y:	68 36%	132 30%
	> 60 y:	20 11%	53 12%
Hospital type:	**General:**	154 82%	340 77%
	Academic:	30 16%	91 21%
	Both:	3 2%	9 2%
Registry time(years):	**< 10 y:**	58 31%	176 40%
	11-20 y:	73 39%	132 30%
	21-30 y:	46 25%	110 25%
	> 30 y:	10 5%	22 5%
PhD grade:		89 48%	198 45%

The respondents had the best knowledge of the guidelines on DAT, chronic rhinosinusitis, and OSAHS and the least knowledge of the guidelines on oral cavity/oropharyngeal and hypopharyngeal carcinoma, with percentages for 'exact knowledge of 68%, 61%, 60%, 18% and 17%, respectively. Accurate knowledge of the guideline on laryngeal carcinoma was reported by 57% and 14% of the academic and general otorhinolaryngologists (difference 43%, 95% CI: 25 ; 62), respectively. Similar differences were found regarding the guideline on hypopharyngeal carcinoma (44%, (95%CI: 25 ; 63)) and oral cavity/oropharyngeal carcinoma (47% (95%CI: 29 ; 65)). Regarding the guideline on DAT, OSAHS, chronic rhinosinusitis, and facial palsy these differences were reversed i.e. 75%, 71%, 69%, and 60% of the general otorhinolaryngologists reported to have accurate knowledge of these guidelines versus 37%, 13%, 27% and 40% of the academic otorhinolaryngologists (differences: 42%, (95%CI: 25 ; 60); 58%, (95%CI: 44 ; 72); 38%, (95%CI: 19 ; 57) and 20%, (95%CI : 1 ; 39).

The mean probability of the respondents regarding their confidence in the evidence of recommendations stated in the guidelines was 77% (median 80; IQR: 75 ; 85). The mean percentage non-adherence to guideline recommendations was 45% (median 50; IQR: 25 ; 75). The mean percentage of the influence of evidence-based guidelines on daily practice was 70% (median 75; IQR: 61 ; 85). There was more guideline adherence in younger otorhinolaryngologists (age group 30-39) compared to older ages. Gender, type of hospital and PhD grade did not affect the preferences of the responders.

Twenty-eight (15%) of the respondents who returned a questionnaire indicated that OSAHS was not their area of interest. In addition, 35 (19%) did not answer the questions about scenario A, and 42 (22%) did not answer the questions about scenario B.
Concerning scenario A (patient with severe OSAHS), the current Dutch OSAHS guideline recommends CPAP as first-line treatment, and weight reduction in obese patients with OSAHS as an additional treatment goal.

Of the 152 respondents, 92% preferred CPAP, 2% preferred UPPP and 6% preferred another policy than those listed (e.g. LAUP, MRA, weight reduction or other surgery). A quarter of the otorhinolaryngologists chose weight reduction as only treatment or as a part of it. Gender, type of hospital and PhD grade did not affect the preference of the responders. The treatment preference is in line with the current guideline which recommends CPAP as first-line treatment in patients with 'severe OSAS'. No large differences in preferred treatment were found between the OSAHS and non-OSAHS specialists. **Figure 1** shows the estimated reduction of AHI for each of the 5 preferred treatment options. The probability of an AHI reduction varied from 31% for LAUP to 85% for CPAP.

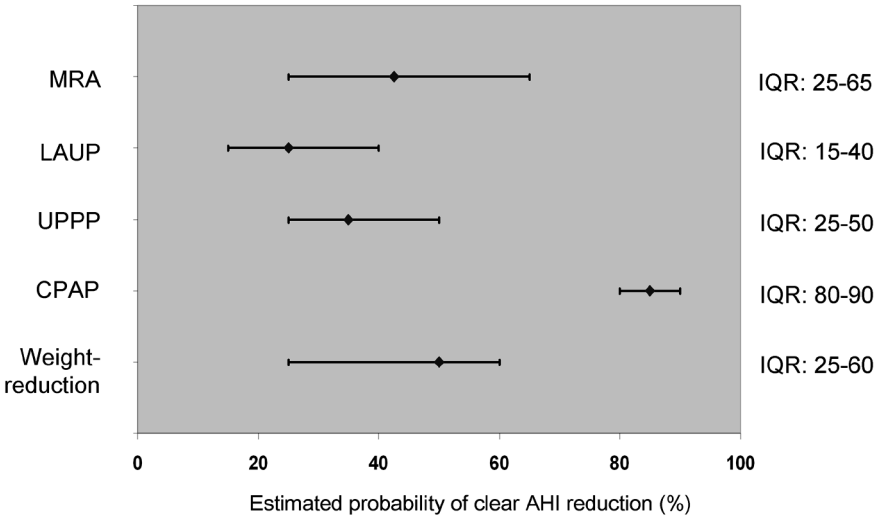

Figure 1: Median estimates and interquartile ranges (IQR) regarding the probability of a significant AHI reduction for the 5 preferred treatment options in the patient with severe OSAHS (scenario A).

Concerning scenario B (moderate OSAHS), the current guideline recommends MRA as well as CPAP or surgery (UPPP or LAUP) as primary treatment. Of the 145 respondents 42% preferred MRA, 20% UPPP, 13% CPAP, 7% weight- reduction and 2% preferred LAUP. The remaining 16% preferred a combination of treatments **(Table 3)**. 19% of the otorhinolaryngologists chose weight reduction as only treatment or as part of it. No large differences in preferred treatment were found between OSAHS and non OSAHS specialists. Respondents aged 30-39 years more often preferred a surgical policy as compared to those aged 50 years or older. Gender, type of hospital and PhD grade did not affect the preferences of the responders.

Table 3: distribution of the preferred treatment by Dutch otorhinolaryngologists concerning scenario B (patient with moderate OSAHS).

Treatment	Number of respondents	Percentage
MRA	**61**	**42%**
UPPP	**29**	**20%**
CPAP	**19**	**13%**
Conservative/weight reduction	**10**	**7%**
LAUP	**3**	**2%**
Other/combination of treatments	**23**	**16%**
Total n=187	**145***	**100%**

*** 42 respondents did not answer this question**

The mean probability of an AHI reduction varied from 34% for weight reduction to 79% for CPAP (**Figure 2)**. We also stratified the estimates for treatment effect of CPAP, MRA and UPPP according to respondents who preferred this treatment and those who did not. For scenario A (severe OSAHS), a reduction of AHI after CPAP, MRA and UPPP was estimated by 85%, 50% and 45% of the respondents who preferred each of these treatments compared to 85%, 35% and 35% of the respondents who preferred another treatment. For scenario B (moderate OSAHS), a reduction of AHI with CPAP, MRA and UPPP treatment was estimated by 85%, 75% and 75% of the respondents who preferred this treatment as compared to 85%, 40% and 50% of the respondents who preferred another treatment **(Table 4)**. The estimated probability of an improvement in quality of life of OSAHS patients treated with CPAP was 76% (95% CI: 74 ; 78).

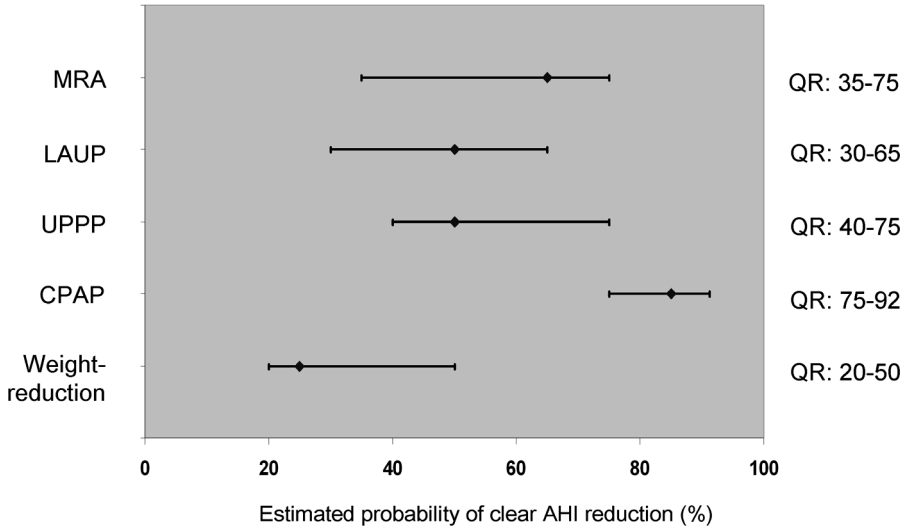

Figure 2: Median estimates and interquartile ranges (IQR) regarding the probability of a significant AHI reduction for the 5 preferred treatments options in patients with moderate OSAHS (Scenario B).

Table 4: Median estimates and IQR regarding the probability of a significant AHI-reduction after CPAP, MRA and UPP stratified for respondents who preferred and those who did not prefer these treatments.

Scenario A		**Respondents preferring**	
	Total	**This treatment**	**Other treatment**
CPAP	**85%** (80-90) N=158	**85%** (80-90) N=121	**85%** (75-90) N=37
MRA	**43%** (25-65) N=154	**50%** (39-65) N=50	**35%** (25-54) N=104
UPPP	**35%** (25-50) N=157	**45%** (25-80) N=4	**35%** (25-50) N=153
Scenario B		**Respondents preferring**	
	Total	**This treatment**	**Other treatment**
CPAP	**85%** (75-91) N=153	**85%** (80-90) N=28	**85%** (71-95) N=125
MRA	**65%** (35-75) N=153	**75%** (65-85) N=70	**40%** (25-65) N=83
UPPP	**50%** (40-75) N=156	**75%** (65-80) N=51	**50%** (30-60) N=105

Discussion

Our results show that the Dutch otorhinolaryngologists are familiar with the currently available evidence-based guidelines. Their confidence in the guidelines is high, and most otorhinolaryngologists reported that they use evidence-based guidelines in their daily clinical practice. Still, non-adherence to these guidelines is reported in 45%. In case of a severe OSAHS patient (scenario A) the treatment by Dutch otorhinolaryngologists shows a homogenous pattern, which is in accordance with the strict recommendations of the guideline. If disease characteristics become less distinct (scenario B), a much larger variation in treatments was found which reflects the wide range of treatment options described in the guideline.

Our results corroborate previous studies that also showed that young/less experienced professionals use guidelines more often than older or more experienced professionals[17]. Medical training programs may explain the increased guideline adherence over the last decade[18]. In contrast to previous studies we found no differences between academic and general otorhinolaryngologists regarding their use of guidelines in daily practice[18]. Incorporating graded recommendations from evidence based guidelines as learning goals in the current medical training programs may diminish practice variations within a medical specialty.

The relatively high proportion of non-adherence to guidelines is in line with earlier reported adherence rates[19-21]. If the guideline is non-specific, controversial and not compatible with current values and does recommend change of existing routines, poor adherence is more likely. If there is a firm scientific base, the guideline is explicit and precise, has been mentioned in media and is in accordance with existing routines poor adherence is less likely[22].

Some limitations of this study should be mentioned.

First, our response rate is moderate, which may influence the validity of our results. Since, the general characteristics of our respondents are in agreement with data of the Dutch Society of Otorhinolaryngology and Head & Neck Surgery, we consider our sample of respondents to be representative enough for all registered otorhinolaryngologists in the Netherlands (see also **Table 2**).

Second, we used clinical vignettes to assess physician practice variation. Clinical scenarios have proven to be effective tools for the evaluation of medical decision behaviour[23-25]. Moreover, research has shown that, when used to study differential diagnosis, selection of tests, and treatment decisions, validity of data on quality of care derived from vignette-based surveys is higher than those from medical record reviews[23-25]. Nevertheless many respondents reported that they would like to know more about the patient in both scenarios for their judgement and decisions: e.g. information about dentition was missing and there was no record of the chin lift. We, however, consider it unlikely that more detailed information on diagnostic criteria for the case scenario would have markedly changed our results.

Third, we conducted our study among Dutch otorhinolaryngologists. This may restrict the generalizability of our results to other medical specialties and countries. We do not believe, however, that the characteristics that may influence knowledge of guidelines and adherence to them are typically related to the Dutch setting. Hence, our results on the knowledge and use of guidelines may be relevant for other medical specialties and countries

Concerning the clinical scenarios a high level of guideline adherence was shown in this survey. This is quite remarkable since impaired dissemination of practice guidelines and clinical research into daily practice has been reported repeatedly[17 19-21 26-28]. Since the OSAHS patients in the scenarios were well treated according to the guideline, the implementation of the current OSAHS guideline in clinical practice can be considered successful. The OSAHS guideline work group reported several actions to promote

awareness and implementation of the guideline: It was actively distributed among all relevant associations and hospitals, an abstract of the guideline was published in the Dutch journal of medicine and several related clinical journals, the content of the guideline was published on the Dutch Institute for Health Care Improvement (Centraal Begeleidings Orgaan,CBO) website, and the guideline was discussed on several scientific conventions and audits of the related societies. These actions can be considered sufficient in achieving awareness of the guideline.

However, the increasing heterogeneity that we found for treatment recommendations that were less explicit deserves further attention when a revision is considered. For this, we recommend to turn away from guidelines produced and written in medical textbook style. This may make implementation ineffective, particularly when it requires new behavior and organizational change. Instead, we advise to produce a limited number of graded practice recommendations and present these in a very concise manner. In an additional source document each recommendation should be accompanied by an explanatory text which should covers the explicitly filtered best evidence. By using graded recommendations, guidelines may become more explicit about where the best evidence leads to strong recommendations and where the best evidence leaves more room for personal judgments and preferences with weaker recommendations . In the source document the best evidence should also be placed in the context of norms and values of target users.

In conclusion, Dutch otorhinolaryngologists are well aware and use the available evidence-based guidelines to support their clinical practice. The treatment by Dutch otorhinolaryngologists is in accordance with the Dutch guideline. If the guideline, however, does not provide strict recommendations and allows flexibility in treatment, larger treatment variation was found. This may reflect that otorhinolaryngologists still may encounter difficulties when applying the current guidelines in individual patient care.

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Chapter 3

Remarkable differences between three evidence-based guidelines on management of obstructive sleep apnoea-hypopnoea syndrome

Mark CJ Aarts[1]

Geert JMG van der Heijden[1,2]

Maroeska M Rovers[1,2]

Wilko Grolman[1,3]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

3) Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

Abstract

Background

The aim of this study was to compare available guidelines for the diagnosis and treatment of patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS) regarding their content, conclusions on the available evidence and recommendations.

Methods

We retrieved guidelines from Embase, Pubmed, Web of Science and from websites of several health care improvement centres and with a 'Google Scholar' search. We appraised the quality of selected guidelines according to AGREE. For similar clinical questions we compared the conclusions, the attached levels of evidence and the references used. If differences were found, we checked search strategies, appraisal criteria and publication date, as possible sources for these differences.

Results

We selected the guidelines on diagnosis and treatment of OSAHS of the Scottish SIGN, the Dutch CBO and the American ICSI for this comparison. For similar clinical questions these 3 guidelines showed conflicting conclusions (11%-18%), differences in attached levels of evidence (32%-62%), and remarkable discrepancies in cited studies. A plausible reason for these differences is the citation preference for papers from members of the guideline work group and from own country. Despite different publication dates, more recent guidelines fail to cite earlier published guidelines.

Conclusion

Despite the generally accepted approach regarding the development of evidence-based guidelines, remarkable differences exist between guidelines from different countries on the same clinical subject.

Introduction

Clinical practice guidelines provide building blocks for improving health care. They are useful means of translating evidence from scientific research to clinical practice. Due to their significant impact on clinical practice, utilization of clinical guidelines is gaining popularity[1]. Clinical guidelines are defined as systematically developed documents including statements to assist physicians and patients about appropriate health care for specific clinical circumstances. They are valid if they are developed in a rigorous way, independent from vested interests of their authors, and if they support decision making in patient care.

In the last decade several national health care improvement institutes have been founded to improve the development of evidence-based guidelines, e.g. The National Institute for Health and Clinical Excellence (NICE), The Institute for Clinical Systems Improvement (ICSI), The Dutch Institute for Health Care Improvement (CBO), The New Zealand Guidelines Group (NZGG), The Scottish Intercollegiate Guidelines Network (SIGN) and The United States Preventive Services Task Force (USPSTF). As a result several national evidence-based guidelines concerning similar topics have been developed.

To produce valid and effective guidelines several criteria and approaches for explicit and transparent development of evidence-based guidelines have been published[2-4]. As a consequence most guidelines nowadays are developed by multidisciplinary panels. These include instructions for guideline work group composition, searching and appraising evidence, rating conclusions, grading recommendations and updating guidelines. When guidelines follow a similar systematic approach in answering the same clinical questions, very large discrepancies in their answers, their coverage of the body of evidence, and their recommendations are not expected.

In the past few years these national health care improvement institutes developed several guidelines in the ENT-field, notably on the management of sinusitis, otitis media with effusion, allergic and non-allergic rhinitis, head and neck cancer and obstructive sleep apnoea-hypopnoea syndrome (OSAHS)[5-9]. The aim of this study is to compare guidelines concerning a similar topic for similarities and differences of their conclusions, the level of evidence attached, the references used, the recommendations made and the grade attached. As an example we used the guidelines for the management of patients with OSAHS that have been developed in different countries.

Methods

Retrieval of OSAHS guidelines - We searched and selected English, French, German, Dutch, Italian or Spanish language guidelines on the management of patients with OSAHS using all possible synonyms for guidelines and obstructive sleep apnoea syndrome **(Table 1)**. We performed a title and abstract field search in Embase, Pubmed and Web of Science. To retrieve guidelines not published in medical journals, we also searched for relevant guidelines on websites of several health care improvement centres and used the 'Google Scholar' search engine **(Table 1)**. We excluded:

- publications other than guidelines,
- guidelines developed before 2000 not updated the subsequent (last) 10 years,
- guidelines describing only one or a few diagnostic or therapeutic aspects of the management of patients with OSAHS,
- single centre guidelines,
- guidelines which were developed by one individual,
- guidelines in other languages than English, German, Dutch, Spanish or Italian.

Table 1: Search strategy (18-08-2010)

Database	Search	Hits
Pubmed	guideline[publication type] OR "Health Planning Guidelines"[Mesh] OR guidelines[MesH] AND (OSAHS[tiab] OR (obstructive[tiab AND sleep[tiab] AND (apnoea[tiab] OR apnea[tiab] OR apnoeas[tiab] OR apneas[tiab]) AND (syndromes[tiab] OR syndrome[tiab])) OR (sleep[tiab] AND disordered[tiab] AND breathing[tiab]) OR snoring[tiab] OR sleep apnea, obstructive[mesh] OR snoring[mesh])	**110**
Embase	See Pubmed	**141**
Web of Science	See Pubmed	**119**
Google	'guideline' AND 'obstructive sleep apnoea syndrome'	**1**
Internet search	National Coordinating Centre for Health Technology Assessment (NCCHTA). NICE; UK HTA database (Southampton) Institute for Clinical Systems Improvement (ICSI). Canadian Agency for Drugs and Technologies in Health (CADTH) Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) Denmark Guidelines international Network GIN website National Institute for Health Research (NHS) United Kingdom Database of Abstracts of Reviews of Effects (DARE) United Kingdom Agency for healthcare,research and quality (AHRQ), USA International Network of Agencies for Health Technology Assessment (INAHTA) database Dutch Institute for health care improvement (CBO), Netherlands The National Health and Medical Research Council (NHMRC), Australia The New Zealand Guidelines Group (NZGG), New Zealand The Scottish Intercollegiate Guidelines Network (SIGN), Scotland The U.S. Preventive Services Task Force (USPSTF), USA American Academy of sleep medicine (AASM), USA Guidelines Advisory Committee at the Centre for Effective Practice (GAC) Sowerby Centre for Health Informatics at Newcastle (SCHIN)	**8**

Quality appraisal - The quality of selected guidelines was appraised by 2 authors, independently, with reference to following validity criteria**:**

1. clear composition of a guideline development panel and the included stakeholders,
2. evidence filtering: retrieval and selection, assessment and rating of the primary evidence and systematic literature search,
3. clinical recommendations: formulating and rating of evidence and grading of recommendations and referencing for and the supporting primary evidence used to support the recommendations.

The selected guidelines were also assessed using the AGREE instrument[3]. The AGREE instrument is a 23 item checklist that, on the one hand, provides a structured framework for guidelines development, on the other hand can be used for assessing the quality of guideline before adopting the recommendations. It is promoted for the assessment of the guidelines and we used it as such. The legend of **Table 2** includes a description of the AGREE instrument.

Data extraction – We extracted conclusions regarding diagnosis and treatment of OSAHS answered in the guidelines. We looked for conclusions concerning a similar clinical question and for these we compared the level of evidence attached, the references used, the recommendations made and the grade attached. If differences were found, we checked publication date, search strategies and appraisal criteria as possible sources for these differences. Finally, we calculated the percentage of domestic and foreign citations and the percentage of self-citations for members of the guideline development group.

Results

Retrieval of OSAHS guidelines - We identified 110 records in Pubmed, 141 in Embase, and 119 in Web of Science **(Table 1).** Our internet search led to the retrieval of another 9 guidelines originating from several guideline development organisations. After removing the duplicates 272 unique records remained. After screening of titles and abstracts 19 publications qualified for further assessment of their full text **(Figure 1).** Thereafter 7 guidelines remained for full text screening **(Table 2)**[9-15].

Table 2: Methodological aspects of existing major guidelines for OSAHS.

Guideline	Reporting Criteria					AGREE Criteria					
	Development group described	Literature Search performed	Systematic Literature Search	Grading of evidence	Grading of recom-mendations	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence
CBO 2009	●	●	●	●	○	**92**	**100**	**86**	**94**	**100**	**100**
SIGN 2003	●	●	●	●	●	**92**	**100**	**93**	**94**	**100**	**100**
ICSI 2008	●	●	**?**	●	●	**92**	**88**	**82**	**94**	**83**	**100**
CTS 2006	●	●	○	●	○						
AASM 2009	●	●	○	○	○						
FNG 2002	●	○	○	○	○						
SRS 2001	●	○	○	○	○						

● Satisfactory
○ Not satisfactory
? Unknown

AGREE instrument consists of 23 items in 6 domains. Each item is rated on a 4-point scale: 1, strongly disagree; 2, disagree; 3, agree; and 4, strongly agree. Domain scores were calculated by dividing the cumulative obtained score by the the maximum possible score.

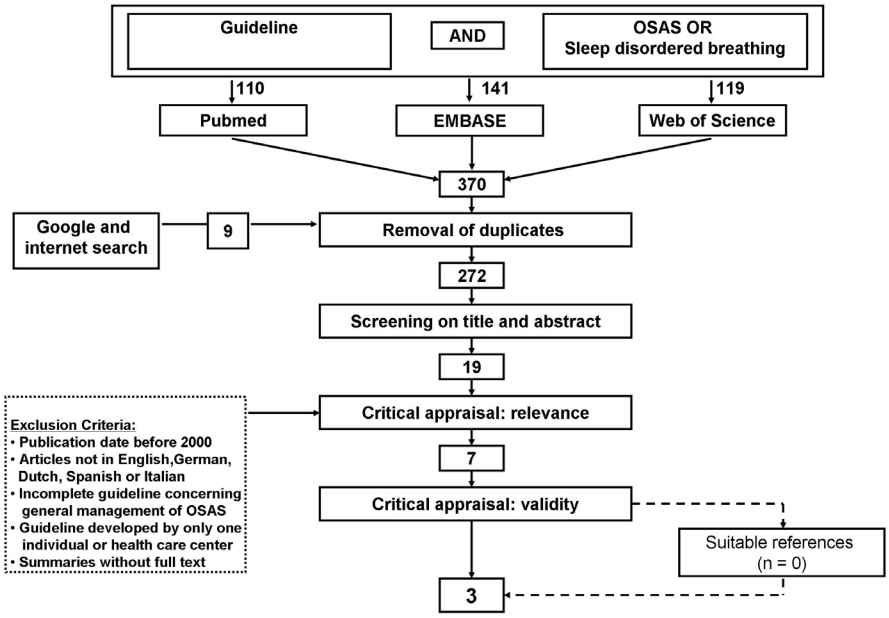

Figure 1: flowchart of the search and appraisal process

During full text screening another 4 guidelines were excluded. The American Academy of Sleep Medicine (AASM) guideline was based on existing evidence-based practice parameters. For areas not covered by these existing practice parameters recommendations were based on consensus instead of evidence, making the guideline not suitable for comparison. The Canadian Thoracic Society (CTS) guideline proved to be an executive summary without full text. The Finnish National Guideline (FNG) and Swiss Respiratory Society (SRS) guidelines were narrative reviews.
The guideline of The Scottish Intercollegiate Guidelines Network (SIGN), The Institute for Clinical Systems Improvement (ICSI) and The Dutch Institute for health care improvement (CBO) were eligible for quality assessment and data extraction.

Quality appraisal – The SIGN, the CBO and the ICSI guideline met the validity criteria: description of development group, performance of literature search, and grading of evidence **(Table 2)**. The CBO guideline described recommendations without

grading. The ICSI guideline reported on a literature search, which, however, could not be reproduced. Nevertheless, all guidelines showed high scores on all domains of the AGREE instrument and were therefore rated high enough to allow further comparison.

Data extraction – The total number of clinical questions with conclusions in the CBO, the SIGN and the ICSI guidelines was 130, 56 and 53, respectively. All three guidelines reported on diagnosis, conservative treatment, surgery and safety. The focus of the guidelines is shown by the number of conclusions drawn. In the ICSI guideline 20 conclusions (38%) concern the diagnosis of OSAHS, in the CBO guideline 42 conclusions concern CPAP (33%) and 37 concern surgery (29%), in the SIGN guideline 16 conclusions concern CPAP (28%) **(Table 3)**.

Table 3: Number of conclusions mentioned in the guidelines per category

Category	ICSI	SIGN	CBO
Diagnosis	20 (38%)	11 (20%)	7 (5%)
Conservative treatment	5 (9%)	6 (11%)	11 (8%)
CPAP	8 (15%)	16 (28%)	42 (33%)
MRA	3 (6%)	12 (22%)	11 (8%)
Surgery	7 (13%)	6 (11%)	37 (29%)
Driving and safety	0 (0%)	2 (3%)	8 (6%)
Other	10 (19%)	3 (5%)	14 (11%)
Total	53 (100%)	56 (100%)	130 (100%)

Evidence filtering – The 3 compared guidelines used different approaches to the assessment and rating of the evidence. To allow comparison of level of evidence of the guidelines we harmonised the different evidence grading classifications into a high, moderate and low quality of evidence **(Table 4)**. The conclusions of the SIGN, CBO and ICSI guidelines were based on high quality levels of evidence in 47%, 20% and 24%, moderate quality in 30%, 49% and 41% and low quality levels of evidence in 23%, 51% and 35% of the conclusions, respectively **(Table 4)**.

The CBO guideline did not provide grades of recommendations, while the ICSI and SIGN guidelines used different approaches to grade recommendations.

Table 4: Levels of evidence of conclusions of SIGN, CBO and ICSI harmonized into high, moderate and low quality of evidence.

Quality of evidence		SIGN		CBO		ICSI
High	1++	11	A1	19	M	5
	1+	15	A2	7	A	8
		26 (47%)		**26 (20%)**		**13 (24%)**
Moderate	1-	1	B	38	B	2
	2++	5			C	20
	2+	11				
	2-	0				
		17 (30%)		**38 (29%)**		**22 (41%)**
Low	3	8	C	64	D	8
	4	5	D	2	RX	11
		13 (23%)		**26 (51%)**		**19 (35%)**
Total		**56 (100%)**		**130(100%)**		**54 (100%)**

Comparison of SIGN and CBO guidelines – The SIGN and CBO guidelines reported on conclusions of 28 similar clinical questions. 5 (18%) of these conclusions were conflicting. The level of evidence of 3 of the 5 conflicting conclusions was similar (twice high and once low). Overall, the level of evidence attached to the 28 conclusions was similar for 13 (46%) and different for 15 (54%) conclusions, of which 23% concerned a high versus a low level of evidence **(Table 5)**. For 15 conclusions with differences in levels of evidence, 3 (20%) could be explained by a distinction in the time period of the search strategy. For the remaining 12 (80%) differences no explanation could be found.

Comparison of SIGN and ICSI guidelines – The conclusions of the SIGN and ICSI guidelines could be compared for 13 similar clinical questions. For 2 (15%) of the 13 similar questions conflicting conclusions were reported, while the remaining 11 (85%) conclusions were similar. For only 1 conflicting conclusion similar level of evidence was attached: low. Overall, the level of evidence of the 13 conclusions was similar for 5 (38%) and different for 8 (62%), of which 14% concerned a high versus a low level of evidence **(Table 5)**. In 2 (25%) of the 8 conclusions with a difference in level of evidence, this could be explained by a distinction in the time period of the search strategy. For the remaining 6 (75%) conclusions, no explanation for the

differences in levels of evidence could be found. The level of evidence of one of the 2 conflicting conclusions was similar (low). The ICSI guideline reported 4 graded recommendations, and the SIGN guideline reported 11 graded recommendations. For one clinical question the recommendation could be compared: the guidelines agreed on this.

Comparison of CBO and ICSI guidelines - The conclusions of the CBO and ICSI guidelines could be compared for 19 similar clinical questions. For 2 (11%) of these conflicting conclusions were reported, while the remaining 17 (89%) conclusions were similar. Overall, the level of evidence of the 19 conclusions was similar in 13 (68%) and different in 6 (32%) conclusions, of which 40% concerned a high versus a low level of evidence **(Table 5)**. None of these differences could be explained. The level of evidence of one of the 2 conflicting conclusions was similar (low). The CBO guideline did not provide grading of recommendations, which hampered such comparison.

Table 5: Comparison of levels of evidence for comparable conclusions in the ICSI, CBO and SIGN guidelines. With similar levels of evidence the proportion of high, moderate and low quality of evidence are presented.
For different levels of evidence the size of the difference is reported.

	SIGN – CBO	SIGN - ICSI	CBO - ICSI
Concordant Conclusions	**23 (82%)**	**11 (85%)**	**17 (89%)**
Similar level of evidence	**10**	**4**	**12**
High	6	3	2
Moderate	2	1	3
Low	2	-	7
Different level of evidence	**13**	**7**	**5**
High - Moderate	3	3	1
Moderate - Low	7	3	2
High - Low	3	1	2
Discordant Conclusions	**5 (18%)**	**2 (15%)**	**2 (11%)**
Similar level of evidence	**3**	**1**	**1**
High	2	-	-
Moderate	-	-	-
Low	1	1	1
Different level of evidence	**2**	**1**	**1**
High - Moderate	-	-	1
Moderate - Low	1	1	-
High - Low	-	-	-

An overview of the conflicting conclusions for the comparison of SIGN versus CBO, ICSI versus SIGN and ICSI versus CBO guidelines is presented in **Table 6**. Five conclusions shared a similar level of evidence and 7 out of 9 conflicting conclusions were based on moderate/low evidence. However, 2 conflicting conclusions were based on high level of evidence. The conflicting conclusions were all based on different references.

Ultimately, the conclusions of the three guidelines (SIGN, CBO and ICSI) could be compared for 8 similar clinical questions. Of these 6 (75%) conclusions were in agreement. Still these 8 conclusions were all based on different references, while the level of evidence was similar for 3 conclusions.

Citation preferences - The CBO guideline was published on the internet in 2009 and did refer to the ICSI and SIGN guidelines which were published in 2008 and 2003 respectively. But the ICSI guideline made no reference to the SIGN guideline.
All three guidelines showed a domestic citation preference concerning the conclusions of the 8 comparable clinical questions **(Table 7)**.
Of the 469 references included in the Dutch CBO guideline 24 (5%) concerned self citations by guideline authors; none of these were included in the ICSI or SIGN guidelines. Of the 158 references included in the SIGN guideline 33 (21%) were self citations, of which 9 were included in the CBO guideline and 1 in the ICSI guideline. Of the 120 references included in the ICSI guideline 4 (3%) were self citations, while 2 of these were cited in the CBO guideline and none in the SIGN guideline.

Table 6: The different conclusions for the comparison of SIGN versus CBO, ICSI versus SIGN and ICSI versus CBO guidelines. The conclusions were all based on different references and 5 conclusions shared a similar level of evidence. 7 out of 9 conflicting conclusions were based on moderate and low evidence. However 2 conflicting conclusions were based on high level of evidence.

	Conclusion	Level of evidence			References
	CBO-SIGN	SIGN	CBO	ICSI	
CBO	MRA and CPAP have a comparable effect on quality of life, however not consistent		A1 **(High)**		Hoekema 2004, Lim 2006
SIGN	CPAP shows a better effect on quality of life than MRA	1++ **(High)**			Ferguson 1997, Engleman 2002, Tan 2002
CBO	Only a high AHI is a negative criterium for UPPP		C **(Low)**		Friedman 2002, Hessel 2003, Hormann 2005
SIGN	UPPP is not recommended for its adverse effect for CPAP	3 **(Low)**			Mortimore 1996
CBO	The quality of life with OSAHS improves with CPAP		A1 **(High)**		Gay 2006, Giles 2006
SIGN	There is no significant effect of CPAP on depression scores and SF36	1++ **(High)**			NHMR 2000
CBO	UPPP is indicated in patients with the palate as only level of obstruction		C **(Low)**		Friedman 2002, Hessel 2003
SIGN	There is no RCT evidence of effect of UPPP for OSAHS (50% IN 50% of patients)	2++ **(Mod)**			Sher 1996, Bridgman 2002
CBO	UPPP is effective in 40% of the patients not evaluated for level of obstruction		C **(Low)**		Sher 1996
SIGN	Effects of surgery on OSAHS could not be proven due to methodological impairments	2+ **(Mod)**			Lojander 1996, Aboussouan 1995, Wilhelmsson 1999

Table 6 (continued):

	Conclusion	Level of evidence			References
	SIGN-ICSI	**SIGN**	**CBO**	**ICSI**	
SIGN	There is some effect of tonsillectomy on OSAHS (supported by case series)	3 **(Low)**			Verse 2000, Boot 2000
ICSI	There are no studies that evaluate the long-term effect of tonsillectomy on OSAHS			X **(Low)**	-
SIGN	There is no RCT evidence of effect of UPPP for OSAHS (50% IN 50% of patients)	2++ **(Mod)**			Sher 1996, Bridgman 2002
ICSI	UPPP has a success rate of four or more years ranging from 31% to 74% on OSAHS			R **(Low)**	Pirsig, 2000
	CBO-ICSI				
CBO	Pharmacological treatment has no clinical important effect on OSAHS		B **(Mod)**		Smith 2006
ICSI	Modafinil has been approved for peristent symptoms of OSAHS despite adequate treatment			B **(Mod)**	Schwartz, 2003 [B]
CBO	A combination of genioglossal advancement and hyoïdsuspension improves OSAHS significantly		B **(Mod)**		Riley 1994a, Riley 1994b, Ramirez 1996, Utley 1997, Bettega 2000, Hsu 2001, Vilaseca 2002, Yin 2007
ICSI	There are no controlled studies evaluating hyoidsuspension for the treatment of OSAHS.			X **(Low)**	-

Table 7: The number of domestic citations of the 16, 24 and 14 references cited by the SIGN, ICSI and CBO guideline respectively compared to the citations by the other guidelines concerning 8 comparable conclusions of the three guidelines.

Guidelines	Country of origin of cited publication						
	UK	US	NL	AUS/NZ	CAN	Other	Total
SIGN (UK)	9 (56%)	2 (13%)	0 (0%)	2	2	1	16 (100%)
ICSI (US)	2 (8%)	7 (29%)	0 (0%)	3	5	7	24 (100%)
CBO (NL)	4 (29%)	7 (50%)	3 (21%)	0	0	0	14 (100%)

Discussion

Our comparison of three evidence-based guidelines regarding the management of OSAHS showed that conflicting conclusions were reported, different levels of evidence used, and other studies referenced. Furthermore, the more recent guidelines did not refer to the other guidelines published before.

Our data show that despite the introduction of several quality criteria e.g. multidisciplinary work groups, transparent search syntax and appraisal criteria, the grading of evidence and recommendations and the appliance of regular updates, differences between the guidelines still remain. Since these guidelines are developed in a transparent way by experienced multidisciplinary work groups with the best intentions without any conflict of interest they should be concerned unprejudiced. However, the domestic citation preference as well as the increased number of "self citations" not cited by the other guidelines poses a serious problem in development of clinical guidelines. As shown in **Table 5**, citation difference can result in conflicting conclusions.

Conflicting recommendations of clinical practice guidelines have been reported earlier[16-18]. Disagreements between guidelines occur for both valid and non-valid reasons and it is well known that guidelines may have different recommendations depending on who wrote or sponsored the guideline[19]. Additionally, the citation preference of national work and cultural aspects as habits, the patient's expectations,

and the structure of the healthcare system have also been reported as influencing factors in developing guidelines[20-22].

Some aspects of the study need further consideration.
First, this study focussed on the comparison of conclusions with their specific level of evidence. As illustrated in **Table 4** guidelines focus on different clinical questions. This limited the number of clinical question that we could compare.
Second, it is highly unlikely that a country by itself will modify the effect of treatment. However, differences in healthcare system, such as organisational structure and financing systems, composition of the patient populations or geographic aspects of the several countries may result in discrepant recommendations. Moreover, such discrepant recommendations will be more likely when they are derived from a limited amount of evidence, than when they are based on consensus or expert opinion. Our study, however, revealed discordant conclusions that are based on high quality evidence.
Third, in this study large differences between guidelines in particular concerning levels of evidence and cited references are revealed. However when this evidence is translated into conclusions and recommendations, most of them do not substantially differ and some of the differences may appear to be mainly due to phrasing rather than substance. The question rises to which extent these reported differences have an actual impact on the eventual care provision and health outcomes. Still, it is striking that personal influences by a guideline workgroup may play such substantial role in the evidence-based guideline developmental process, which was originally developed just to advance objectivity and transparency of the clinical decision making process.

The reported guidelines in our study met the AGREE quality criteria and our additional screening criteria which were directly derived from these. Nevertheless differences in conclusions, levels of evidence and cited references were revealed. Hence, assessing a guideline using these quality criteria alone may result in misleading comfort. The

AGREE criteria proved to be not very helpful for assessing quality of the resulting guidelines since too many different items are added and calculated in a difficult to interpret summary domain score where signal disappears in the rather large noise. In addition, based on this study, the general assumption that clinical guidelines are developed and reported with reasonable quality should be challenged. The reported guidelines show a poor reporting of the approach followed in their construction and main differences in information filtering. Moreover, none of the guidelines were published in peer-reviewed literature.

The 3 compared guidelines used different approaches to appraisal and rating of the evidence, which in order to compare them were harmonised into a classification of high, moderate and low quality of evidence. Although the assessment of levels of evidence is considered to be a quality criterion of guidelines, our study reveals the loss of transparency and false security when evidence is rated. Since rating of evidence may often be performed by consensus of guideline work groups, this might explain the remarkable differences between the levels of evidence. This emphasizes that assessing the quality of cited studies by level of evidence alone can also be misleading[23 24].

Improvement of uniformity of evidence-based guidelines therefore needs more attention. The greatest improvement is needed in the identification, evaluation, and synthesis of the scientific evidence[25]. To be able to handle differences between guidelines the search strategy and appraisal tools have to be presented in a complete transparent way. The question arises if one search strategy for several different clinical questions mentioned in the guideline will suffice or that a custom made search syntax accompanied with appraisal of relevant literature is needed to answer each separate clinical question. In this way physicians can be exactly informed about the strengths and weaknesses of the cited literature and make their own judgement of the quality of the guidelines[19].

Another important aspect in the development of future guidelines has to be a thorough literature search for the existence of earlier published guidelines and related references. The aim of such search is to assess the completeness of the content of the developing guideline concerning clinical aspects, completeness of search strategy and the retrieval of additional references. Furthermore potential omissions of the earlier published guidelines can be corrected. The CBO guideline was the only guideline referring to other existing OSAHS guidelines. Remarkably this could not prevent the presence of differences between these guidelines.

A recently reported method to facilitate the interpretation of the evidence in the guidelines is a systematic guideline review[26]. In this way new guidelines can be derived from existing material and methodological shortcomings and context specific normative issues of guidelines can be taken into account. This enables development of a valid guideline in a resource saving manner. Thereby duplication of effort and inefficient use of resources are prevented and a high-quality product is expected, compared with de novo development of a guideline.

In conclusion: the results of this study show that despite the generally accepted approach and quality criteria regarding Evidence-Based Medicine, remarkable disagreements exist between evidence-based guidelines with the same clinical subject. For similar clinical questions conflicting conclusions, differences in attached levels of evidence, and remarkable discrepancies in cited studies are reported. A plausible reason for this is the citation preference for papers from members of the guideline work group and from own country and the omission of more recent guidelines to cite or correct earlier published guidelines.

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Chapter 4

Evidence-based case report

The diagnostic value of diffusion-weighted magnetic resonance imaging in detecting a residual cholesteatoma

Mark CJ Aarts[1]

Maroeska M Rovers[1,2]

Erwin L van der Veen[1]

Anne GM Schilder[1,2]

Geert JMG van der Heijden[2]

Wilko Grolman[1,3]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

3) Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

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Abstract

In this evidence based case report we addressed the clinical question: what is the predictive value of diffusion-weighted magnetic resonance imaging (DW MRI) for detecting a residual cholesteatoma in patients with chronic otitis media with cholesteatoma who have previously undergone a canal-wall-up procedure. We searched for relevant synonyms for the determinant, being MRI, and for the outcome, being cholesteatoma and retrieved relevant publications in Embase, Pubmed, Cinahl and Web of Science using search terms in title and abstract fields. The search yielded 683 records, of which eleven were relevant and valid for our clinical question. We pooled the data of the MRI findings of the included studies by adding the 2 by 2 tables of the individual studies. For the 8 Echo Planar Imaging (EPI) DW MRI studies this resulted in a pooled sensitivity, specificity, positive and negative predictive value of 68%, 87%, 81% and 78%, respectively. For the 3 Non-Echo Planar (Non-EPI) DW MRI studies the sensitivity, specificity, positive and negative predictive value were 97%, 97%, 97% and 97%, respectively. Diffusion-weighted MRI, especially the Non-EPI DW MRI, appears to be a rather accurate method instead of a standard second look operation for the follow-up of patients who have undergone a canal-wall-up procedure for a chronic otitis media with cholesteatoma and who have no clinical signs of recurrent cholesteatoma.

Clinical case

A 31-year old man who has been operated 6 months ago for chronic otitis media with cholesteatoma on the right side visits your otorhinolaryngology clinic for a planned follow-up. During the operation an epitympanic cholesteatoma was removed and an autologous ossiculoplasty was performed. At this follow-up visit there are no signs of retraction or a mass behind the tympanic membrane and audiometric testing shows a 10 dB HL conductive hearing loss. Routinely you would have planned a second-look operation at this stage, but the patient asks whether it is really necessary for him to have another operation. You consider performing a diffusion-weighted MRI to detect a potential residual cholesteatoma but wonder how strong the evidence is for such an approach.

Searching for evidence

We first formulated an answerable clinical question on the diagnostic accuracy of MRI: what is the predictive value of diffusion-weighted magnetic resonance imaging (DW MRI) to detect or rule out a residual cholesteatoma in patients who have undergone a canal-wall-up procedure for chronic otitis media with cholesteatoma.

We designed a search filter using relevant synonyms for the determinant, being MRI, and for the outcome, being cholesteatoma **(Table 1)**. We retrieved relevant publications in Embase, Pubmed, Cinahl and Web of Science using search terms in title and abstract fields. All titles and abstracts were screened for selection, and subsequently the full-text of eligible studies was screened for a more detailed selection. A study was selected when the following criteria were met: patients who had undergone a canal wall up procedure for a cholesteatoma; a second look operation was performed to rule out residual or recurrent cholesteatoma; a diffusion weighted MRI scan was performed prior to the second look operation. Excluded studies were:

systematic reviews, animal studies, studies detecting primary cholesteatoma only and studies using conventional MRI only. Included studies were critically appraised for quality of their methods and reporting of results using the criteria shown in **Table 1**. Finally, the data of the individual 2 by 2 tables were pooled and overall sensitivity, specificity; positive and negative predictive values were calculated.

Our search yielded 400 publications in Embase, 315 articles in Pubmed, 10 publications in Cinahl and 121 records in Web of Science **(Figure 1)**. A total of 682 unique records was retrieved. Upon screening of the titles and abstracts 17 articles were found eligible. The full text of these 17 selected publications was studied in terms of our domain, determinant and outcome. As a result, 6 publications were excluded. The quality of methods and reporting of results of the remaining 11 articles were critically appraised according to the criteria presented in **Table 2**. The quality of all papers was high enough to be included in our report and imaging techniques reported in the separate papers were similar to each other concerning sequence, slice thickness, TR/TE factor and b-factor, so all relevant data from these 11 articles were extracted and pooled[1-11]. A distinction could be made between 8 studies reporting on Echo Planar Imaging (EPI) DW MRI and another 3 studies reporting on Non-Echo Planar Imaging (Non-EPI) DW MRI. These were analyzed separately[1-11]. We performed unweighted pooling of the included studies by adding the data of the 2 by 2 tables of the individual studies. The overall sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive values (NPV) and additive value of the EPI and Non-EPI DW MRI were calculated including the 95% confidence interval.

Table 1: Search strategy

Database	Search	Hits
Pubmed	(“mr”[tiab] OR “mri”[tiab] OR (“magnetic”[tiab] AND “resonance”[tiab] AND “imaging”[tiab]) OR “magnetic resonance imaging”[tiab] OR “magnetic resonance imaging”[MeSH Terms]) AND (“cholesteatoma”[tiab] OR cholesteatomatous[tiab] OR “cholesteatomas”[tiab] OR “cholesteatoma”[MeSH Terms])	**315**
Embase	See Pubmed	**400**
Cinahl	See Pubmed	**10**
Web of Science	See Pubmed	**121**

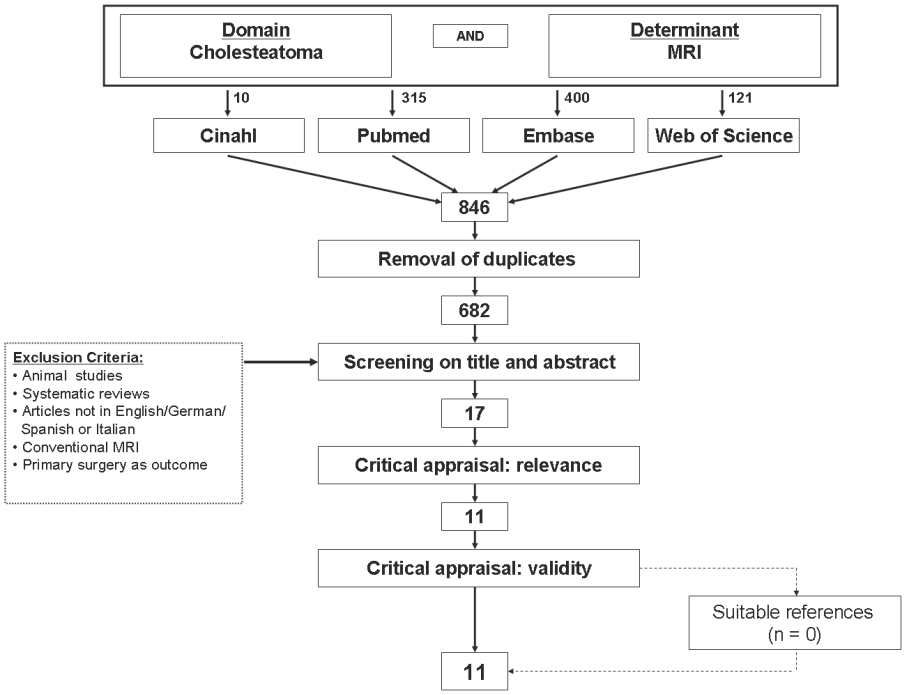

Figure 1: Flow chart

Table 2: Critical Appraisal

Study characteristics			*Validity*			
	MRI type	**N**	**ST**	**BL**	**SB**	**CD**
De Foer et al. 2008	**Non-EPI**	**19**	●	●	○	●
Dhepnorrarat et al. 2009	**Non-EPI**	**23**	●	●	○	●
Dubrulle et al. 2006	**Non-EPI**	**24**	●	●	?	●
Cimsit et al. 2009	**EPI**	**26**	●	●	○	●
Jindal et al. 2009	**EPI**	**35**	●	●	?	●
Venail et al. 2008	**EPI**	**31**	●	●	?	●
De Foer et al. 2007	**EPI**	**23**	●	●	●	●
Jeunen et al. 2008	**EPI**	**32**	●	●	?	●
Vercruysse et al. 2006	**EPI**	**45**	●	●	?	●
Stasolla et al. 2004	**EPI**	**18**	●	●	?	●
Aikele et al. 2003	**EPI**	**17**	●	●	○	●

ST = standardisation of tests ● **= accurate**
BL = blinding ○ **= not accurate**
SB = no selection bias **? = unknown**
CD = complete data **N = Number of patients**

Results

The baseline prevalence of recurrent cholesteatoma in the 8 studies reporting on EPI DW MRI ranged from 9% to 77%[4 8]. As both the positive predictive value, i.e. the proportion of patients with *positive* MRI results who were correctly diagnosed *with cholesteatoma* at surgery, and the *negative* predictive value, i.e. the proportion of patients with a *negative* MRI result who were correctly diagnosed *with no cholesteatoma* at surgery, are known to depend on the baseline prevalence, we plotted these values against each other **(Figure 3)**. The positive predictive value (PPV) ranged from 83% to 100%[2 4 6 7]. The negative predictive value (NPV) decreased with higher prevalences of recurrent cholesteatoma **(Figure 2)**. The pooled sensitivity, specificity, positive and negative predictive values were 68%, 87%, 81% and 78% respectively **(Table 3)**. The added value of the EPI DW MRI for a positive result (PPV minus prevalence) is 37% (95% CI 31; 43%). The added value of EPI DW MRI for a negative result (NPV minus 1-prevalence) is 34% (95% CI 28; 40%). The baseline prevalence of recurrent cholesteatoma in the 3 studies reporting on Non-EPI DW MRI ranged from 30% to 54%[10 11]. Both the positive and negative predictive values ranged from 90 to 100% **(Figure 3)**. The pooled sensitivity, specificity, positive and negative predictive values were 97%, 97%, 97% and 97%, respectively **(Table 4)**. The diameter of the true positive masses varied between 2-24 mm. The diameter of the only reported false negative case was a 2-mm small cholesteatoma pearl[9-11]. The added values of Non-EPI DW MRI for a positive and negative result are 52% (95% CI 40; 64%) and 42% (95% CI 30; 54%), respectively.

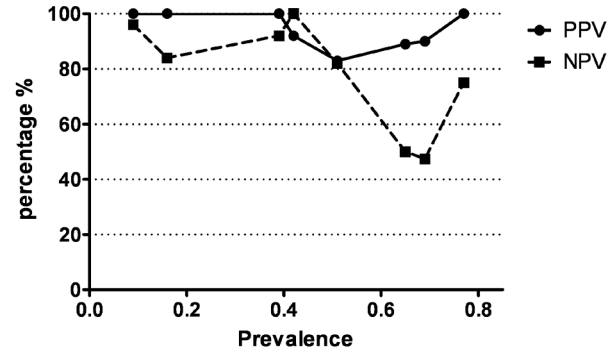

Figure 2: negative and positive predictive values of the separate EPI DW MRI studies

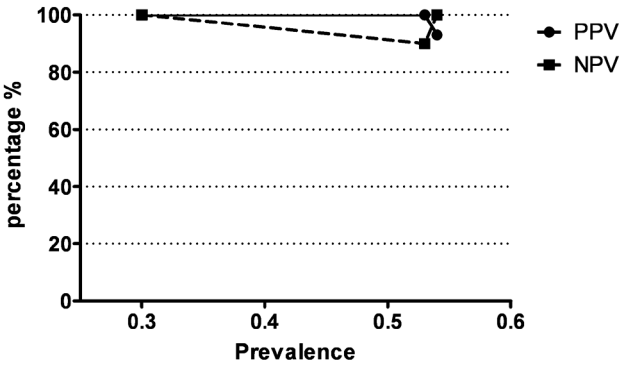

Figure 3: negative and positive predictive values of the separate Non-EPI DW MRI studies

Table 3: pooled data EPI DW MRI studies

	Cholesteatoma +	Cholesteatoma -	Total
EPI DW +	**68**	**16**	**84**
EPI DW -	**32**	**111**	**143**
Total	**100**	**127**	**227**

Sensitivity	**= 68/100**	**= 68% (95% CI 62; 74%)**
Specificity	**= 111/127**	**= 87% (95% CI 85; 89%)**
Positive Predictive Value	**= 68/84**	**= 81% (95% CI 76; 86%)**
Negative Predictive Value	**= 111/143**	**= 78% (95% CI 73; 83%)**

Table 4: pooled data Non-EPI DW MRI studies

	Cholesteatoma +	Cholesteatoma -	Total
Non-EPI DW +	**29**	**1**	**30**
Non-EPI DW -	**1**	**35**	**36**
Total	**30**	**36**	**66**

Sensitivity	**= 29/30 = 97% (95% CI 93; 100%)**
Specificity	**= 35/36 = 97% (95% CI 93; 100%)**
Positive Predictive Value	**= 29/30 = 97% (95% CI 93; 100%)**
Negative Predictive Value	**= 35/36 = 97% (95% CI 93; 100%)**

Translating evidence into practice

The evidence regarding the diagnostic value of diffusion-weighted magnetic resonance imaging indicates that diffusion-weighted MRI, especially the Non-EPI DW MRI, is an accurate method to perform radiological follow-up in patients after a canal-wall-up procedure for a chronic otitis media with cholesteatoma.

Many reports have suggested the improvement in magnetic resonance imaging techniques in diagnosing cholesteatoma with the use of Echo Planar Imaging DW MRI[1-8]. However numerous artefacts can be generated during acquisition of diffusion weighted images, such as eddy current artefacts, susceptibility artefacts, ghosting artefacts, chemical shift and motion artefacts[12]. Non-EPI DW MRI uses turbo or fast spin echo diffusion weighted imaging techniques and permits fast multiplanar imaging in artefact-prone regions such as the petrous bone. Therefore using the EPI DW MRI, cholesteatoma pearls with a minimum diameter of 5 mm can be detected, whereas with Non-EPI DW MRI this minimum is 2 mm[5 6 8]. Hence, in contrast to Non-EPI DW MRI, lesions between 2 and 5mm will be missed by EPI DW MRI, resulting in a higher proportion of false negative scans. More false negative scans lead to a decreased negative predictive value, especially when the “a priori chance” of a recurrent cholesteatoma (prevalence) increases **(Figure 2)**.

Work-up bias cannot be precluded since most studies did not describe the exact process of selection of the patients, i.e. the studies did not report whether all patients who had undergone a canal-wall-up procedure were actually enrolled. The most likely explanation for a possible selection bias could be that only high-risk patients were

operated. This could also explain the high percentage of recurrent cholesteatoma in some studies. The reported pooled negative predictive value may therefore be higher, and the pooled positive predictive value lower in day-to-day practice.
The total number of patients screened with the Non-EPI DW MRI was relatively low (N=66). Nevertheless, we believe that the current evidence is strong enough to justify the use of diffusion-weighted MRI for the follow-up of patient who have undergone a canal-wall-up procedure in day to day otorhinolaryngology practice. Also having in mind the risk of harm of a second-look operation (hearing loss, vertigo, surgical trauma of facial nerve and chorda tympani) and increased costs compared to MRI, there is no reason to postpone radiological follow-up.
It should, however, be emphasized that in clinical practice the scan has to be repeated with a certain interval to rule out a growing cholesteatoma, which is under the detection level of 2mm at time of first measurement.

Answer to our question:

During follow-up of patients who have undergone a canal-wall-up procedure for a chronic otitis media with cholesteatoma diffusion-weighted MRI, especially the Non-Echo Planar Imaging DW MRI, appears to be a rather accurate method instead of a standard second look operation when there are no clinical signs of recurrent cholesteatoma. With our patient we discuss the possibility to perform a diffusion weighted MRI in order to detect a possible residual cholesteatoma. Only when the MRI shows signs of cholesteatoma recurrence a second look operation has to be performed.

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Chapter 5

Evidence-based case report

The value of a mandibular repositioning appliance for the treatment of non-apnoeic snoring

Mark CJ Aarts[1]

Maroeska M Rovers[1,2]

Geert JMG van der Heijden[2]

Wilko Grolman[1,3]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

3) Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

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Abstract

In this evidence based case report we addressed the clinical question: What is the effect of a mandibular repositioning appliance in patients with non-apnoeic snoring on the snoring loudness, partners sleep disturbance and quality of life? We retrieved relevant publications from Embase, Pubmed, Cinahl, CENTRAL and Web of Science. We used title and abstract field searches with relevant synonyms for the domain, being patients with non-apnoeic snoring, and for the determinant, being MRA. The search yielded 499 records. After selection based on relevance and validity, two articles remained for answering our clinical question. We pooled the data for the level of snoring. MRA as compared to placebo resulted in a reduction of snoring loudness in 38% of patients with non-apnoeic snoring, and in an improvement of sleep disturbance in 54% of the partners. No effect on quality of life and daytime sleepiness of the partner was found. Furthermore, evidence for sustained long term effects and complete recovery is lacking.

Clinical case

A 45-year old man visits your clinic with a history of snoring, which recently worsened so much that he sleeps separate from his wife. An earlier performed nocturnal polysomnography revealed an apnoea-hypopnoea index of 6, ruling out obstructive sleep apnoea-hypopnoea syndrome (OSAHS). Dietary measures because of his Body Mass Index (BMI) of 28 had not resulted in a significant decrease of his snoring. Sleep endoscopy showed a collapse of the lateral pharyngeal wall, and some obstruction on the level of the tongue base, which decreased when the mandible was protruded. Additional pulmonary and neurological examination revealed no further abnormalities. Based on the endoscopic results you suggest the fitting of a mandibular repositioning appliance (MRA). However, because there is no health insurance company reimbursement for such a device, the patient asks you about the probability that his snoring will either disappear or decrease to an acceptable level.

Searching for evidence

We formulated the following clinical question: What is the effect of a mandibular repositioning appliance on the snoring loudness, partners sleep disturbance and quality of life in patients with non-apnoeic snoring? We designed a search filter using relevant MeSH and title and abstract synonyms for the domain, being patients with non-apnoeic snoring, and for the determinant, being MRA **(Table 1)**. We retrieved relevant publications in Embase, Pubmed, Cinahl, CENTRAL and Web of Science using search terms in title and abstract fields. Title and abstracts of all retrieved records were screened for relevance of domain, determinant, and outcome. Included were studies reporting on the effects of MRA for complaints of snoring. Exclusion criteria were: systematic reviews, animal studies, articles not in English, German, Spanish or Italian, articles describing patients with obstructive sleep apnoea syndrome, neurological or pulmonary abnormalities and articles describing primary surgery as determinant. After appraisal of their quality of methods and reporting, the absolute risks were extracted from the selected studies.

Table 1: Search strategy

Database	Search (29-04-2010)	Hits
Pubmed	(Snoring[tiab] OR snore[tiab] OR snort[tiab] OR snuffle[tiab] OR wheeze[tiab] OR buzz[tiab] OR ((breathing[tiab] OR respiratory[tiab) AND (sound[tiab] OR sounds[tiab)) OR "sleep disordered breathing"[tiab]) AND (((Mandibular[tiab] AND (reposition[tiab] OR repositioning[tiab] OR advancement[tiab] OR advancing[tiab] OR protrusion[tiab] OR protruding[tiab] OR advancing[tiab])) OR oral[tiab] OR intra-oral[tiab] OR intraoral[tiab] OR prosthetic[tiab] OR snore[tiab] OR dental[tiab]) AND (splint[tiab] OR appliance[tiab] OR appliances[tiab] OR prosthesis[tiab] OR device[tiab]) OR MRS[tiab] OR MRA[tiab] OR MAS[tiab] OR MAA[tiab] OR silensor[tiab] OR silencer[tiab] OR "snore guard"[tiab] OR klearway[tiab] OR "Thornton Adjustable Positioner"[tiab] OR MAD[tiab])	**299**
CENTRAL	See Pubmed	**78**
Embase	See Pubmed	**202**
Cinahl	See Pubmed	**42**
Web of Science	See Pubmed	**209**

Results

Of the 829 studies retrieved, 499 were unique records **(Figure 1)**. Upon screening of title and abstract and full text 10 publications were considered potentially relevant for answering our question. The results of the subsequent appraisal of the quality of methods and reporting by two independent authors is shown in **Table 2**[1-10]. Four studies concerned randomised trials and six studies were case series[1 2 5 7 9 10]. Data were extracted from the 4 randomised controlled trials[3 4 6 8]. The randomised controlled trials comparing different intra-oral devices and MRA with CPAP did not provide direct evidence to answer our question and could therefore be excluded[6 8].

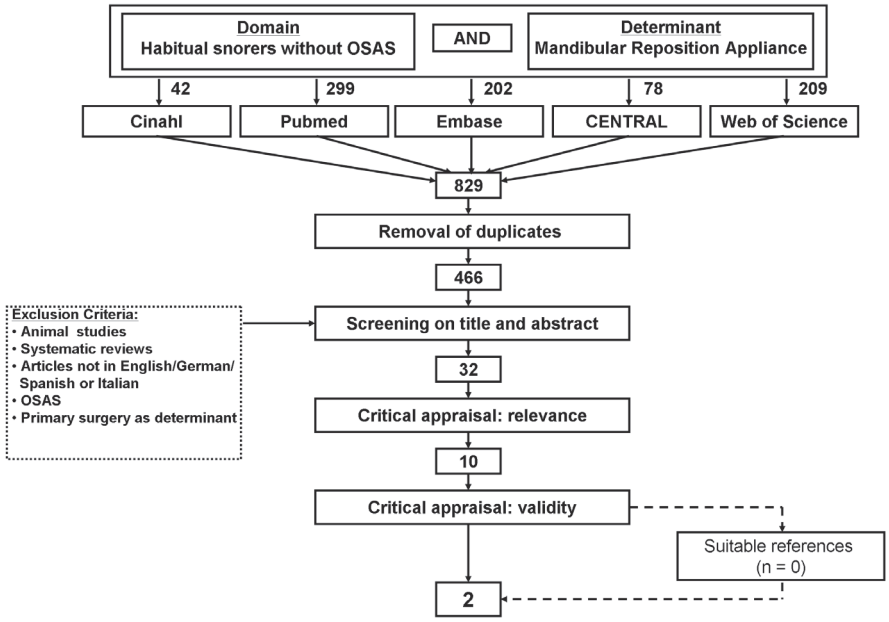

Figure 1: Flowchart

Two randomised cross-over trials provided the best available evidence[3] [4]. They compared MRA with placebo and both used reduction of subjective snoring loudness on a 5 point scale and the Epworth Sleepiness Scale as outcomes. Both defined a reduction of snoring loudness as an improvement of 2 points on this 5 point severity scale. This allowed us to pool their results in a meta-analysis. The pooled risk difference (RD) for reduced snoring loudness after 4-6 weeks favoured MRA and was 38% (95%CI: 20%, 57%) which corresponds with a number needed to treat (NNT) of 3 **(Figure 2)**. Cooke et al. reported that with MRA 68% (95% CI 49%-88%) of the partners reported a clinical important reduction of sleep disturbance, compared to 14% (95% CI 0%-28%) with placebo; hence a RD of 54% (95% CI 26%-74%), and a NNT of 2 (Figure 3)[3]. They also showed a statistically not significant RD of 18% (95% CI -11%-44%) for reduced daytime sleepiness of partners; 63% of the partners (95% CI 44%-84%) with MRA and 45% of the partners (95% CI 25%-66%) with placebo reported a reduction of daytime sleepiness **(Figure 3)**.

Table 2: critical appraisal

Study characteristics				*Relevance*				*Validity*		
	study	N	Follow-up	DO	DE	OU	RA	BL	ST	CD
Cooke 2005 [3]	RCOT	27	12 weeks	●	●	●	●	●	●	●
Johnston 2001 [4]	RCOT	28	12 weeks	●	●	●	●	●	●	●
Marklund 1996 [6]	RCT	15	4 years	●	●	●	●	○	●	●
Robertson 2008 [8]	RCOT	20	3 years	●	●	●	●	○	●	●
Vandervreken 2004 [10]	CS	20	6 months	●	●	●	○	○	●	●
Smith 2004 [9]	CS	35	1 month	●	●	●	○	○	●	●
Cameron 1998 [2]	CS	16	4 weeks	●	●	●	○	○	●	●
Abo-khatwa 2008 [1]	CS	15	4-6 weeks	●	●	●	○	○	●	○
Mahl 2007 [5]	CS	10	?	●	●	●	○	○	●	●
Minhas 2001 [7]	CS	30	22 months	●	●	●	○	○	●	●

N = Number of patients
DO = Domain; included patients with habitual snoring without OSAS
DE = Determinant; mandibular repositioning appliance
OU = Outcome; endpoint was improvement of sleeping disturbance of the partner
RA = Randomization; patients were correctly randomized
BL = Blinding; patients and investigators were blinded for the therapy
ST = Standardisation of treatment; the treatment protocol was the same in all included patients
CD = Complete data; the percentage of missing data does not exceed 20%
RCOT= Randomized cross-over trial
RCT = Randomized controlled trial
CS = Case series
● Satisfactory
○ Not satisfactory
? Insufficient information

Both RCT's also reported on the Epworth Sleepiness Scale, but the reported data did not allow pooling. The average improvement on the ESS of the patients after 5 weeks is too small to be considered as clinically important: 2.7 with MRA and 0.4 with placebo, respectively.

Cooke et al. reported no statistical significant difference regarding quality of life of the patients (SF-36)[3]. Quality of life data of the partners were not reported. Furthermore, they reported side effects, such as muscular discomfort (26% in the MRA versus 13% in the placebo group), temporomandibular joint discomfort (22% in the MRA versus 9% in the placebo group), abnormal bite on waking (17% in the MRA versus 9% in the placebo group) and a dry mouth (70% in the MRA and 52% in the placebo group).

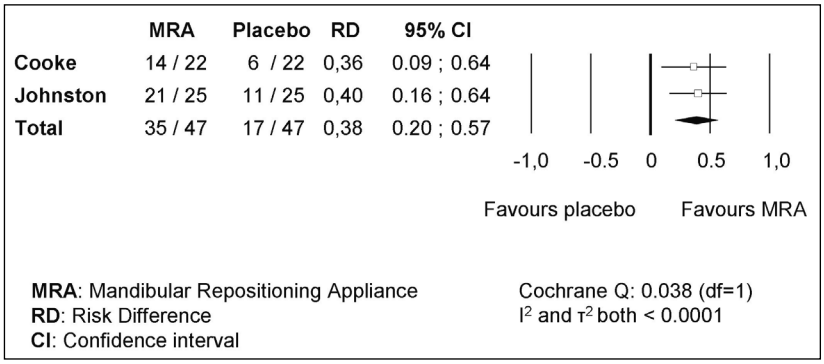

Figure 2: MRA for non-apnoeic snoring: effect as proportion with reduced snoring loudness (at least 2 of 5 points improvement on severity scale)
Meta-analysis of studies of Cooke et al. and Johnston et al [3 4].

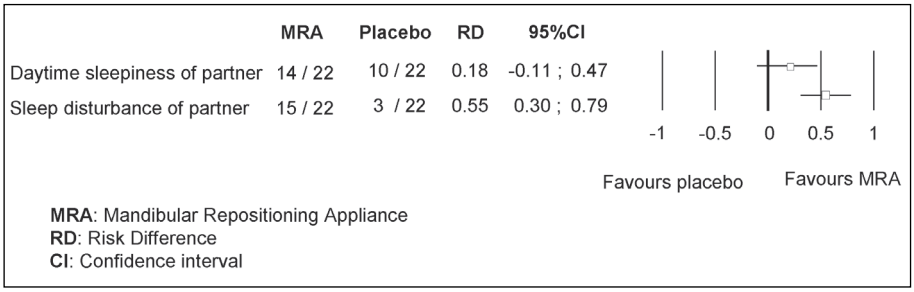

Figure 3: MRA for non-apnoeic snoring: effect as proportion improved (Cooke et al.) [3].

Translating evidence into practice

The evidence of the effect of MRA on patients with non-apnoeic snoring as compared to a placebo suggests improvements of 38% (NNT=3) and 54% (NNT=2) regarding a reduction in snoring loudness and partners sleep disturbance, respectively. Whether these effects sustain at long term is, however, not reported. Data on the quality of life of partners and the number of partners reporting a total disappearance of the snoring are not available.

Since we were interested in patients without OSAHS, we excluded all studies reporting on patients with OSAHS or sleep disordered breathing, which is represented by the reported relatively low ESS scores of the reported patients. Therefore, substantial improvement of the ESS and quality of life scores of the patients were not to be expected. Moreover, our results are not applicable to patients with OSAHS.

Some aspects of the studies need further consideration. First, the aim of this EBCR was to evaluate the effects according to the patient's partner. Many studies report on objective measurements of the level of snoring noise and the apnoea-hypopnoea index (AHI). The partner's evaluation of complaints may not be connected directly to such objective effect measurement of snoring. Second, the mean BMI score of the patients reported in the two pooled randomised trials was 27.5. BMI is likely to increase the likelihood of snoring but may also have an impact on the effect of MRA. However, data to distinguish their independent effect of BMI on snoring are currently not available. Third, when patients suffer from snoring which is not reduced after mandibular advancement during sleep endoscopy, MRA is less likely to be effective[11]. Therefore Cooke et al excluded such patients[3]. Remarkably Cooke et al. reported similar effects of MRA as Johnston et al. who did not exclude such patients[4].

Answer to our question

We informed our patient that the evidence regarding the effect of MRA on the level of snoring loudness and sleep disturbance of the partners of patients who suffer from non-apnoeic snoring suggest that 7 out of 10 partners will notice a reduction of complaints from heavy to moderate or from moderate to very mild. We also inform our patient that no data were found regarding complete recovery or long term effects.

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Chapter 6

Evidence based case report:

Salvage laryngectomy after primary radiotherapy:

what are prognostic factors for the development of pharyngocutaneous fistulae?

Mark CJ Aarts[1]

Maroeska M Rovers[1,2]

Cai Grau[3]

Wilko Grolman[1,4]

Geert JMG van der Heijden[2]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

3) Department of Oncology, Aarhus University Hospital, Denmark

4) Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

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Abstract

In this evidence based case report we addressed the clinical question: which factors predict the occurrence of a pharyngocutaneous fistula after total laryngectomy in patients that already were treated with radiotherapy for a squamous cell carcinoma of the larynx? We searched for relevant synonyms for the domain, being patients earlier treated with radiotherapy for a squamous cell carcinoma of the larynx and having a recurrence for which a salvage total laryngectomy is necessary, with the outcome being the development of a post-operative pharyngocutaneous fistula. We searched for relevant publications in Embase, Pubmed and Web of Science using search terms in title and abstract fields. The search yielded 1764 records, of which three were relevant and valid for our clinical question. Our results show that the absolute risk of a pharyngocutaneous fistula after total laryngectomy in patients earlier treated with radiotherapy for a squamous cell carcinoma of the larynx mainly depends on characteristics and site of the primary tumour. In patients who have a primary glottic laryngeal T1 or T2 tumour the absolute risk of developing a fistula is 11% (95% CI 6; 15%), whereas the risk of developing a fistula in patients with a T3 or T4 extra laryngeal tumour is 35% (95% CI 25; 46%). Other patient and surgical characteristics can however not be ruled out as important prognostic factors since many of them have to date not been studied, e.g. diabetes mellitus, alcohol consumption, smoking, suture materials and surgical technique used.

Clinical case

A 54 year old male who has been treated with 35 doses of 2 Gray during 7 weeks for a T3NOMO squamous cell carcinoma of the right vocal cord 6 months ago, recently underwent a biopsy because he was suspected to have a recurrence. The patient is known with non insulin dependent diabetes mellitus and hypertension. Currently, he smokes 10 cigarettes per day, but that was 25 cigarettes per day before he was diagnosed with laryngeal cancer. He consumes about four beers per day. The histopathological examination showed a residual tumour and after discussion in the multidisciplinary oncology board we recommended salvage surgery by means of a total laryngectomy. We discussed potential complications, with our patient such as a pharyngocutaneous fistula, which is likely to increase the time for recovery and length of hospital stay. The patient asked about his risk of a fistula. We know that earlier meta-analysis has shown that pre-operative radiotherapy considerably increases the risk of post-operative wound complications with a relative risk of 2.28[1]. Since our patient has been irradiated before we want to know if other potential risk factors are of importance. So we searched the literature for available evidence whether the risk of a pharyngocutaneous fistula depends from, for example, age, gender, tumour stage, smoking status, diabetes mellitus, alcohol consumption, radiotherapy protocol, suture materials and surgical technique.

Searching for evidence

We first formulated a prognostic clinical question: which factors predict the occurrence of a pharyngocutaneous fistula after total laryngectomy in patients that already were treated with radiotherapy for a squamous cell carcinoma of the larynx?

We designed a search filter using relevant synonyms for the domain, being patients earlier treated with radiotherapy for a squamous cell carcinoma of the larynx and having a recurrence for which a salvage total laryngectomy is necessary, with the outcome being the development of a post-operative pharyngocutaneous fistula. We

searched for relevant publications in Embase, Pubmed and Web of Science using search terms for salvage laryngectomy, squamous cell carcinoma, radiotherapy, recurrence and pharyngocutaneous fistula and all possible synonyms in title and abstract fields. We finalised our search by tracking citations of selected relevant papers for missing publications. Our search yielded 936 articles in Pubmed, 803 publications in Embase, and 1140 records in Web of Science **(Table 1)**. After removing the retrieved duplicates there were 1764 records left which were screened on title and abstract. The following inclusion criteria were used: patients who had received radiotherapy for a squamous cell carcinoma of the larynx and who suffered from a recurrence for which a salvage total laryngectomy was performed. The following studies were excluded: systematic reviews, animal studies, studies reporting on radiotherapy as possible prognostic factor, studies reporting on prognostic factors following other oncological procedures than total laryngectomy, studies reporting on patients earlier treated with chemoradiotherapy and studies with other languages than English, French, German, Italian or Spanish. After title and abstract screening 15 articles remained for full text screening **(Figure 1)**[2-16]. We studied the full-text of these selected publications in detail for relevance in terms of domain, determinants and outcomes. As a result of this, 12 publications eventually did not match our inclusion criteria and were excluded. The quality of methods and reporting of results of the remaining 3 articles were critically appraised by two authors in a separate manner, using the criteria shown in **Table 2**[14-16]. The 3 studies satisfied all our validity criteria. The original raw data of Grau et al. were re-analysed in order to calculate absolute risks of the separate and combined risk factors, which were not published before.

Table 1: Search strategy

Database	Search	Hits
Pubmed	((((Laryngectomy[tiab] OR (salvage[tiab] AND surgery[tiab]) OR (larynx[tiab] AND extirpation[tiab]) OR (salvage[tiab] AND therapy[tiab]) AND (squamous[tiab] AND cell[tiab] AND carcinoma[tiab]) OR tumour[tiab] OR neoplasm[tiab] OR cancer[tiab] OR tumor[tiab]) AND recurrence[tiab] OR recurrent[tiab] OR relaps[tiab] OR relapse[tiab] OR ((post[tiab] OR prior[tiab]) AND (radiotherapy[tiab] OR irradiation[tiab]))) AND radiotherapy[tiab] OR radiation[tiab] OR irradiation[tiab]) AND Prognos*[tiab] OR cohort[tiab] OR (follow[tiab] AND up[tiab] AND studies[tiab]) OR complication[tiab] OR complications[tiab] OR fistula[tiab] OR fistulae[tiab] OR dehiscence[tiab] OR defect[tiab] OR pharyngocutaneous[tiab] OR cutaneus[tiab])	**936**
Embase	See Pubmed	**803**
Web of Science	See Pubmed	**1140**

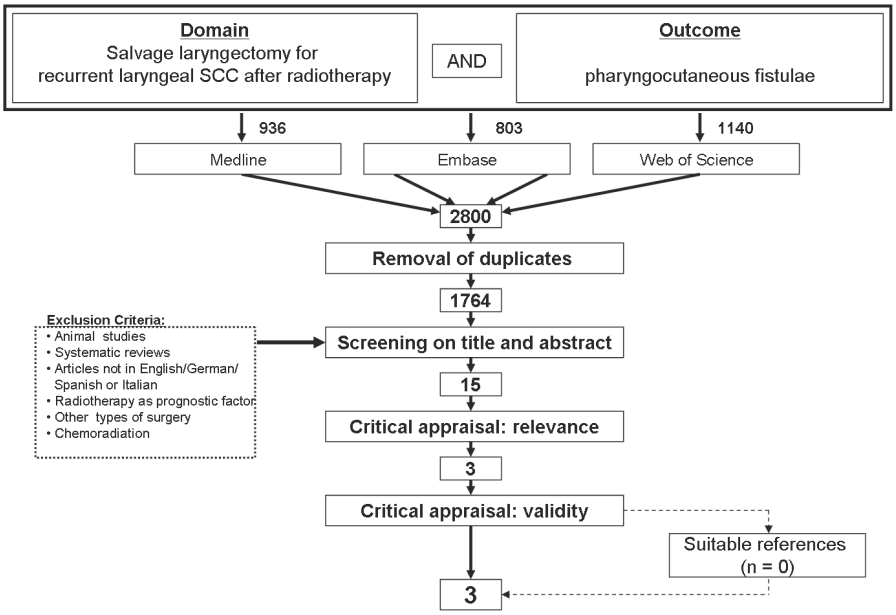

Figure 1: Flow chart

Table 2: Critical Appraisal

Study characteristics			*Relevance*			*Validity*	
	study	**N**	**DO**	**DE**	**OU**	**ST**	**CD**
Dirven 2009 [15]	**RC**	**38**	●	●	●	●	●
Grau 2003 [14]	**PC**	**415**	●	●	●	●	●
Spriano 1989 [16]	**RC**	**79**	●	●	●	●	●
Wakisaka 2008 [2]	**PC**	**63**	○	●	●		
Saki 2008 [3]	**RC**	**146**	○	●	○		
Qureshi 2005 [4]	**PC**	**143**	○	●	●		
Dequanter 2004 [5]	**RC**	**75**	○	●	**?**		
Agra 2003 [6]	**RC**	**124**	○	●	●		
Aguilar 2001 [7]	**RC**	**183**	○	●	○		
Lavertu 1998 [8]	**RC**	**100**	○	●	○		
Tomkinson 1996 [9]	**RC**	**50**	○	○	○		
Mc Combe 1993 [10]	**RC**	**357**	○	●	●		
Mendelsohn 1985 [11]	**RC**	**100**	○	●	○		
Vd Bogaert 1984 [12]	**RC**	**60**	○	●	○		
Robbins 1972 [13]	**RC**	**22**	○	●	○		

DO **Domain; included patients undergo a salvage total laryngectomy for a residual laryngeal carcinoma**
DE **Determinant; possible prognostic factors for a fistula were clearly described**
OU **Outcome; endpoint was fistula**
CD **Complete data; the percentage of missing data does not exceed 20%**
ST **Standardisation of treatment; the treatment protocol was the same in all included patients**
RC **Retrospective cohort**
PC **Prospective cohort**
● **Satisfactory**
○ **Not satisfactory**
? **Insufficient information**

Results

All 3 remaining studies reported on possible risk factors for the occurrence of a fistula after salvage total laryngectomy. Dirven et al. showed that patients who also received a neck dissection or flap reconstruction had an increased risk of a pharyngocutaneous fistula[15]. Spriano et al reported on 60 patients treated for a recurrence of a laryngeal carcinoma during 24 years and studied the following prognostic factors of a pharyngocutaneous fistula: surgery within 6 months after radiotherapy, radiotherapy

on positive lymph nodes, the performance of a neck dissection, level of haemoglobin and albumin and blood transfusion[16].

Grau et al. performed a prospective cohort study during 10 years on prognostic risk factors of a pharyngocutaneous fistula in patients who have undergone a total laryngectomy after recurrence of a laryngeal or pharyngeal carcinoma after earlier radiotherapy. Advanced primary tumour (T3 or T4), extra laryngeal tumour site, age below 63 years, tumour positive lymph nodes, resection of hyoid bone, radiation dose of more than 66 gray, radiation field size of more than 49 cm^2 and surgery within 6 months after radiotherapy were identified as potential prognostic factors for developing a fistula (Table 3)[14]. Additional multivariate logistic regression analysis, however, showed that only initial tumour stage and tumour site remained as independent prognostic factors of a pharyngocutaneous fistula. The reported odds ratio (OR) for tumour stage was 2.08 (95% confidence interval (CI) 1.26-3.45) of tumour stage T3-4 in comparison to T1-2 for developing a fistula. The OR for tumour site was 2.08 (95% CI 1.25-3.45) of non-glottic tumours in comparison to glottic tumours.

Using the original raw data, which were provided by the authors, we were able to calculate independent absolute risks for the occurrence of a pharyngocutaneous fistula for either one or a combination of both prognostic factors. **Table 4** shows that in patients who have a primary glottic laryngeal T1 or T2 tumour the absolute risk of developing a pharyngocutaneous fistula is 11% (95% CI 6; 15%), whereas the risk of developing a fistula in patients with a T3 or T4 extra laryngeal tumour is 35% (95% CI 25; 46%).

Table 3: Patient and disease characteristics and their absolute (univariate) risk (with confidence intervals) of a fistula

Prognostic factors	*Univariate analysis*	
	Grau et al. [14]	Dirven et al. [15]
Advanced primary tumour (T3 or T4)	**26% (95%CI 19 ; 32)**	
Extra laryngeal tumour site	**24% (95%CI 19 ; 30)**	
Patient younger than the age of 63	**23% (95%CI 18 ; 29)**	
Tumor positive lymph nodes	**29% (95%CI 17 ; 40)**	
Resection of hyoid bone	**24% (95%CI 18 ; 30)**	
Radiation dose > 66 gray	**24% (95%CI 19 ; 30)**	
Field size > 49 cm2	**22% (95%CI 17 ; 26)**	
Salvage surgery < 6 months after radiotherapy	**22% (95%CI 14 ; 29)**	
Neck dissection performed		**39% (95%CI 21 ; 57)**
Flap reconstruction		**25% (95%CI 13 ; 37)**

Table 4: Multivariate prognostic factors and absolute risks at 10 year follow-up (with confidence intervals) of a fistula based on the data of Grau et al.

Prognostic factors	*Multivariate analysis* Grau et al. [14]
T1 or T2 tumour and laryngeal tumor site	**11% (95%CI 6 ; 15)**
T3 or T4 tumour and laryngeal tumor site	**20% (95%CI 11 ; 29)**
T1 or T2 tumour and extra laryngeal tumor site	**21% (95%CI 13 ; 29)**
T3 or T4 tumour and extra laryngeal tumor site	**35% (95%CI 25 ; 46)**

Translating evidence into practice

Our results show that the absolute risk of a pharyngocutaneous fistula after total laryngectomy in patients earlier treated with radiotherapy for a squamous cell carcinoma of the larynx mainly depends on characteristics and site of the primary tumour. The risk of a fistula is 3 times higher in patients with a glottic T3 or T4 extra laryngeal tumour as compared to patients with a primary glottic laryngeal T1 or T2 tumour (35 versus 11%, respectively). This implies that one out of every three patients with a T3 or T4 extra laryngeal tumour develops a fistula.

During the last decades radiotherapy has become the main primary treatment modality for patients with a small to moderate squamous cell laryngeal carcinoma. When salvage surgery is performed after earlier radiotherapy, it should be considered that patients have an increased risk of developing a pharyngocutaneous fistula post-operatively. The next clinically interesting challenge therefore is to identify other possible prognostic factors for the occurrence of fistulae in patients who have been irradiated before, which we aimed with this evidence-based case report.

All studies included in this paper reported on tumour specific risk factors increasing the risk of a fistula. Other patient and surgical characteristics can however not be ruled out as important prognostic factors since many of them have to date not been studied, e.g. diabetes mellitus, alcohol consumption, smoking, suture materials and surgical technique used. Moreover, a multivariate prediction rule for fistula risk has not been derived. Therefore further studies investigating the other potentially relevant factors using such a multivariate approach are needed before final conclusions can be drawn.

All the included studies use absolute risks to report on their longitudinal prognostic data. In general absolute risks are preferable above odds-ratios when interpreting clinical data. Although Grau et al. reported a multivariate analysis they presented the outcomes as odds. To facilitate a translation of these data to clinical practice, we used their data to re-calculate the absolute risks.

The included studies failed to report sufficient information about the initial radiotherapy protocol, so we could not judge whether all patients had indeed undergone the same intervention. So we obtained additional information from the authors, from which it appeared that the initial radiotherapy protocols were quite similar. It should be noted that in a multivariate approach to constructing a prediction model for fistula risk, the features of the initial radiotherapy should also be considered.

In conclusion: the absolute risk of developing a pharyngocutaneous fistula after total laryngectomy in patients earlier treated with radiotherapy for a squamous cell carcinoma of the larynx can rise to 35% in certain cases. Since salvage surgery is

the only remaining treatment option for these patients, a benefit-harm analysis is difficult to make. Hence the data reported in this EBCR will not result in a change of therapy management, but the relatively high risk of fistula and the effect on quality of life and cost analysis in certain patients have to be taken into account when salvage surgery is considered, and should be discussed with patients.

Answer to our patient

We told our patient that we can only partly answer his question.

We informed him that there is sufficient evidence that original high tumour stage and extra laryngeal tumour site are independent prognostic factors for the occurrence of a pharyngocutaneous fistula in patients who have been treated with radiotherapy before. Since our patient originally had a T3 tumour in a glottic region according to our current knowledge he seems to have a risk of 20% of developing a fistula. We however were unable to appropriately inform our patient about the impact of other potentially important prognostic factors such as diabetes mellitus, alcohol consumption and smoking due to lack of adequate data from research.

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Chapter 7

Evidence-based case report

No evidence for diagnostic value of Mallampati score in patients suspected of having OSAHS*

Mark CJ Aarts[1]

Sander Bins[1]

Theodoor D Koster[1]

Albert H de Heij[1]

Akkeline C de Vries[1]

Anouk B van Pelt[1]

Maroeska M Rovers[1,2]

Geert JMG van der Heijden[1,2]

1) Department of Otorhinolaryngology, University Medical Centre Utrecht, The Netherlands

2) Julius Centre for Health Sciences and Primary Care, Utrecht, The Netherlands

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*** Since this publication was part of a medical student teaching programme it was publicated in a slightly different form**

Abstract

To analyse whether the Mallampati score is reliable as a simple diagnostic test for predicting obstructive sleep apnoea-hypopnoea syndrome (OSAHS).

A literature search was performed using Pubmed, Embase, Scopus, Cochrane and Cinahl. Studies were ranked by their relevance and validity in a critical appraisal table. Positive and negative predictive values were obtained or recalculated from the selected articles. A comparison was made for subgroups of the Mallampati score. Eight relevant articles met our inclusion criteria. Three studies reported predictive values for Mallampati score 3 to 4. Our results show that the prevalence (or prior probability) of OSAHS in these three studies was 58% (95% CI: 50 ; 67), 76% (95% CI: 72 ; 79) and 82% (95% CI: 80 ; 84), respectively. With a Mallampati score 1 to 2 the risk of OSAHS decreases to 45% (95%CI: 33 ; 58), 74% (95%CI: 70 ; 78) and 81% (95%CI: 77 ; 86), respectively. With a Mallampati score 3 to 4 the risk of OSAHS is 69% (95%CI: 59 ; 80), 82% (95%CI: 74 ; 89) and 82% (95%CI: 79 ; 85), respectively. The differences between the prior and the posterior probabilities are rather small and do not reach statistical significance. There is no evidence to maintain that the Mallampati score has added value for ruling in or ruling out a diagnosis of OSAHS in patients suspected of having OSAHS. Current clinical guidelines on the diagnosis of OSAHS should be revised accordingly.

Introduction

Obstructive sleep apnoea-hypopnoea syndrome (OSAHS) is a common disorder in the general population with an estimated prevalence of 4% in men and 2% in women between 30 and 60 years of age[1]. It is associated with partial or complete pharyngeal obstruction. The reference test for diagnosing OSAHS is night time polysomnography[2]. An apnoea-hypopnoea-index (AHI) of 5 or more apnoeas per hour confirms the presence of OSAHS[2]. The Mallampati test was originally designed to predict a difficult intubation. It is also considered to be predictive for diagnosing OSAHS[2].

Some guidelines for management of OSAHS mention that macroglossia is a predisposing factor[2-5]. Guidelines of the Dutch CBO and the American Academy of Sleep Medicine both recommend assessing the Mallampati score in the diagnostic process, since a score of 3 or 4 enlarges the risk of having OSAHS[6]. This information is based on studies of Nuckton et al. and Friedman et al.[7 8]. We aimed to evaluate whether the Mallampati score is of diagnostic value in patients suspected of having OSAHS.

Clinical question

What is the diagnostic value of the Mallampati score in patients suspected of having OSAHS? That is, given the prior probability (or prevalence) of OSAHS, does the risk of OSAHS change with a positive or negative Mallampati score?

Searching for evidence

Search strategy and selection - A literature search was performed using Pubmed, Embase, Scopus, Cinahl and Cochrane. We combined Mallampati or its synonyms as determinant, and OSAHS or its synonyms as outcome in our search **(Appendix A)**. All OSAHS synonyms could be reduced to the MESH-term “apnea”, for our other search terms no appropriate MESH-terms were available. Many similar articles were retrieved from different bibliographic platforms. The selection of studies is based on full consensus of two authors who applied the inclusion and exclusion criteria **(Figure 1)** during screening of titles and abstracts. A related articles search in Pubmed and

cross reference checking was used to retrieve relevant articles missed and to identify additional useful search terms.

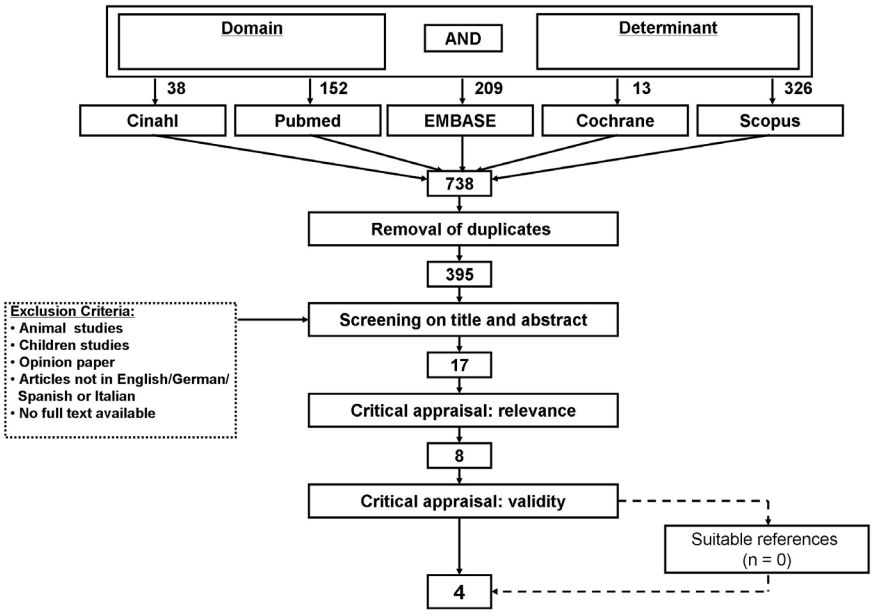

Figure 1: Flow chart on selection of studies on the diagnostic value of the Mallampati score in patients suspected of having OSAHS

Critical appraisal - Five authors independently appraised the relevance and validity of the selected articles. Discordant judgements were resolved by consensus discussion. Studies were ranked by their relevance and validity **(Table 1)**.

Data extraction - The prevalence (or prior probability), the positive and negative predictive values of OSAHS and their corresponding confidence intervals were obtained or recalculated from the selected articles. For this we used OpenEpi v2.3.1[9]. When the prevalence and predictive values were not reported, we assessed other outcomes (likelihood ratio, odds ratio, relative risks and correlations). Only predictive values were further analysed. The positive posterior probability is defined as the risk on OSAHS with a Mallampati score 3 to 4; the negative predictive probability is defined as the risk on OSAHS with a Mallampati score 1 to 2.

Table 1: Characteristics of studies on the diagnostic value of the Mallampati score in patients suspected of having OSAHS

First author	*n*	*Missing data (%)*	*Assessment Mallampati*	*Limit OSAHS in AHI*	*Determinant*
Nuckton [7]	**137**	**ND**	**Tongue protruded**	**5**	**Mallampati 3 to 4 Mallampati 4**
Ramachandran [9]	**511**	**ND**	**Tongue protruded**	**5**	**Mallampati 3 to 4**
Hukins [15]	**953**	**ND**	**Tongue protruded**	**5**	**Mallampati 3 to 4 Mallampati 4**
Dahlqvist [10]	**801**	**9.5**	**Tongue protruded**	**15**	**Mallampati 3 to 4**
Lam [13]	**239**	**ND**	**Tongue protruded**	**5**	**Mean Mallampati**
Liistro [14]	**202**	**ND**	**Tongue protruded**	**15**	**Mallampati 3 to 4**
Tsai [11]	**75**	**ND**	**No protrusion**	**10**	**Mean Sampsoon-Young 1-4**
Herzog [12]	**131**	**16**	**No protrusion**	**5**	**Mean Mallampati**

Abbreviations: n = number of patients; ND = Not described; AHI = Apnoea-Hypopnoea Index

The following subject areas were not distinguishing between study populations:
Domain: Subjects suspected of having OSAHS
Design: Cross-sectional
Work-up bias: Reference test was not performed based on Mallampati outcome
Reference test: Polysomnography was used as reference test
Standardisation: Mallampati was standardised and can be replicated (not specified for Ramachandran and Herzog).

There is a discrepancy between the results described in the text by Hukins and recalculated values from the tables. The tables represent the accurate data.

Results

Selection - We retrieved 395 unique article titles related to our clinical question. After applying inclusion and exclusion criteria, we selected 17 relevant articles. Neither with the related articles search in Pubmed nor with the cross reference checking were additional relevant titles or search terms found. After screening the full-text of the 17 articles only 8 articles met our inclusion criteria[7 10-16].

Determinant - Mallampati scores were determined in patients suspected of having OSAHS. In 2 of the selected papers the average Mallampati score was used while in 6 papers the Mallampati scores were categorised and contrasted **(Table 1)**. Four of the 8 papers reported predictive values or data that could be used to recalculate these[7 10 11 16].

Outcome – The criterion standard for diagnosing OSAHS is polysomnography (PSG). Nuckton et al., Ramachandran et al. and Hukins et al. used an AHI of 5 or higher as cut-off point for the diagnosis of OSAHS while Dahlqvist et al. used an AHI of 15 or higher[7 10 11 16].

Prevalences – We calculated the overall risk in all study populations to determine prior probabilities on having OSAHS, which was 58% (95% CI: 50 ; 67) for Nuckton et al., 76% (95% CI: 72 ; 79) for Ramachandran et al. and 82% (95% CI: 80 ; 84) for Hukins et al[7 10 16].

Predictive values - Nuckton et al. calculated a positive and negative posterior probability of Mallampati score 4 in predicting OSAHS, reporting values of 70% (95% CI: 42 ; 98%) and 57% (95% CI: 49 ; 66%), respectively. For Mallampati score 3 to 4 these values were 69% (95 CI: 58 ; 79%) and 45% (95% CI: 33 ; 57%), respectively[7]. According to Ramachandran et al. positive and negative probabilities of Mallampati score 3 to 4 in predicting OSAHS were 82% (95% CI: 74 ; 89%) and 74% (95% CI: 70 ; 78%), respectively[10]. Hukins et al. described positive and negative probabilities of Mallampati score 3 to 4 in predicting OSAHS of 82% (95% CI: 79 ; 85%) and 80% (95% CI: 76-85%)[16]. Dahlqvist et al. measured predictive values for an AHI of ≥ 15 with a positive predictive value (PPV) of 21% and a negative predictive value (NPV) of 66% in men and a PPV of 14% and a NPV of 82% in women[11].

In the other eligible papers, predictive values were not reported and could not be recalculated either. Liistro et al. found a significant association between Mallampati score 3 to 4 and the presence of OSAHS[15]. Four studies showed a higher risk of OSAHS with a higher predictor status, which Herzog et al. failed to show[7 10 12-14].

Discussion

We report the prior probability (prevalence) of having OSAHS ranging between 58 and 81 percent. With a Mallampati score 3 to 4 the posterior probability of having OSAHS increased between 0% and 11%, while with a Mallampati score 1 to 2 it decreased between 1 and 13 percent. However, none of the reported differences between prevalence and posterior probabilities were statistically significantly **(Table 2)**. As shown in **Figure 2** the differences in prior and posterior probabilities are negligible in studies with a high prevalence of OSAHS[10 16]. The largest effect of the Mallampati score was seen in where OSAHS has a low prevalence, i.e. when it is less common[7]. We consider our approach and results robust enough to conclude that there is no evidence that the Mallampati score has added value in diagnosing OSAHS.

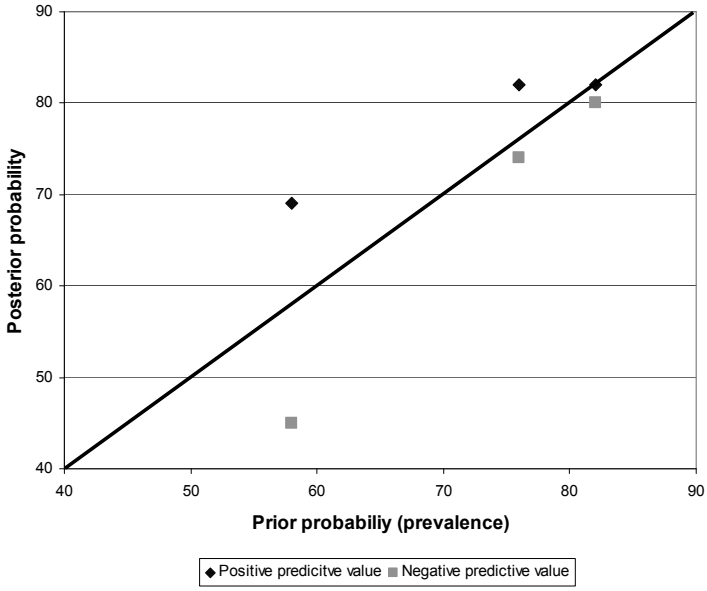

Figure 2: Positive and negative predictive value of Mallampati score 3 to 4 compared to prior probabilities (prevalences) of having OSAHS.
Diagonal indicates no added value of Mallampati score.

Table 2: Predictive values of Mallampati score 3 to 4 for diagnosing OSAHS.

First author	Prior probability of OSAHS		Risk on OSAHS if Mallampati = 3-4			Risk on OSAHS if Mallampati ≠ 3 -4		
	n / N	% (95%CI)	n / N	% (95%CI)	Δ %	n / N	% (95%CI)	Δ %
Nuckton [7]	80 / 137	58 (50 ; 67)	52 / 75	69 (59 ; 80)	+11	28 / 62	45 (33 ; 58)	-13
Ramachandran [9]	387 / 511	76 (72 ; 79)	81 / 99	82 (74 ; 89)	+6	306 / 412	74 (70 ; 78)	-1
Hukins [15]	781 / 953	82 (80 ; 84)	550 / 668	82 (79 ; 85)	0	231 / 285	81 (77 ; 86)	-1

OSAHS = Obstructive Sleep Apnoea-Hypopnoea Syndrome
n = Number of patients with OSAHS
N = Total group
Δ= Difference between risk and prior probability

Our findings deserve some comments. First, despite their adequate design meeting our selection criteria, the studies of Herzog et al, Lam et al, Liistro et al. and Tsai et al. criteria could not be analysed, because prior probabilities and positive predictive values could not be recalculated from the published data[12-15]. Hence, a total of 647 patients could not be included in this study.

Second, Dahlqvist et al. used a cut-off point for AHI of 15 or higher[11]. Therefore their results do not satisfy to answer our clinical question. Moreover, this cut-off point may lead to an underestimation of the positive predictive value. Furthermore, Dahlqvist only described predictive values and did not provide sufficient data to perform recalculations.

Third, the study by Nuckton et al. was the only to use both home monitoring and in-laboratory polysomnography as gold standards to diagnose OSAHS, whereas the other 2 studies used in-laboratory polysomnography only[10 16]. Although Collop mentioned that there is little difference between both tests under specific conditions, the lower prevalence in the population studied by Nuckton et al. might be explained by the use of home monitoring[25]. Fourth, the studies that reported predictive values of the Mallampati score, assessed the score with the tongue protruding. Hence, our conclusions and recommendations are based on studies assessing the Mallampati score with a protruded tongue.

Translating evidence into recommendations

Although guidelines of the Dutch CBO and the AASM state that the Mallampati score has additional value in the diagnosis of OSAHS, we show that the differences between the prior and the posterior probabilities are rather small and do not reach statistical significance[2, 6]. We conclude that there is no evidence that the Mallampati score has added value in diagnosing OSAHS. We therefore do not recommend that clinicians use the Mallampati score in diagnosing OSAHS.

Notes

SB, TDK, AHdH, ACdV and ABvP are medical master students. They contributed equally to this paper.

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Appendix A: Search strategies for PubMed, Embase, Scopus, Cinahl and Cochrane

Pubmed (search 22-01 to 2011)	
#1	Search mallampati OR mallampati* OR malampati OR malampatti OR mallampatti OR malampati* OR malampatti* OR mallampatti* OR mmp OR ems OR Friedman OR (Samsoon AND Young) OR (Sampsoon AND Young) OR (High AND tongue) OR (Height AND of AND tongue) Field: Title/Abstract
#2	Search OSAHS OR (obstructive AND sleep AND apnea) OR (sleep AND apnea) OR sleepapnea OR apnea OR (obstructive AND sleep AND apneas) OR (obstructive AND sleep AND apneic) OR (obstructive AND sleep AND apnoe) OR (obstructive AND sleep AND apnoea) OR (obstructive AND sleep AND apnoeas) OR (obstructive AND sleep AND apnoeic) OR (obstructive AND sleep AND breathing AND disorder) OR (obstructive AND sleep AND disorder) OR (obstructive AND sleep AND disordered) OR (obstructive AND sleep AND disturbance) OR (obstructive AND sleep AND related) OR (obstructive AND sleep AND hypopnea) OR (obstructive AND sleep AND hypopneic) OR (obstructive AND sleep AND hypopnoe) OR (obstructive AND sleep AND hypopnoea) OR (obstructive AND sleep AND hypopnoeas) OR (obstructive AND sleep AND hypopnoeic) OR (obstructive AND snor*) OR osahs Field: Title/Abstract
#3	#1 AND #2
Embase (search 22-01 to 2011)	
#1	mallampati:ab,ti OR mallampati*:ab,ti OR malampati:ab,ti OR malampatti:ab,ti OR mallampatti:ab,ti OR malampati*:ab,ti OR malampatti*:ab,ti OR mallampatti*:ab,ti OR mmp:ab,ti OR ems:ab,ti OR friedman:ab,ti OR (samsoon:ab,ti AND young:ab,ti) OR (sampsoon:ab,ti AND young:ab,ti) OR (high:ab,ti AND tongue:ab,ti) OR (height:ab,ti AND of:ab,ti AND tongue:ab,ti)
#2	OSAHS:ab,ti OR (obstructive:ab,ti AND sleep:ab,ti AND apnea:ab,ti) OR (sleep:ab,ti AND apnea:ab,ti) OR sleepapnea:ab,ti ORapnea:ab,ti OR (obstructive:ab,ti AND sleep:ab,ti AND apneas:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND apneic:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND apnoe:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND apnoea:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND apnoeas:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND apnoeic:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND breathing:ab,ti AND disorder:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti ANDdisorder:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND disordered:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti ANDdisturbance:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND related:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti ANDhypopnea:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND hypopneic:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti ANDhypopnoe:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND hypopnoea:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti ANDhypopnoeas:ab,ti) OR (obstructive:ab,ti AND sleep:ab,ti AND hypopnoeic:ab,ti) OR (obstructive:ab,ti AND snor*:ab,ti) ORosahs:ab,ti
#3	#1 AND #2
Scopus (search 22-01 to 2011)	
#1	TITLE-AB-KEY(mallampati OR mallampati* OR malampati OR malampatti OR mallampatti OR malampati* OR malampatti* OR mallampatti* OR mmp OR ems OR Friedman OR (Samsoon AND Young) OR (Sampsoon AND Young) OR (High AND tongue) OR (Height AND of AND tongue))

#2	TITLE-ABS-KEY(OSAHS OR (obstructive AND sleep AND apnea) OR (sleep AND apnea) OR sleepapnea OR apnea OR (obstructive AND sleep AND apneas) OR (obstructive AND sleep AND apneic) OR (obstructive AND sleep AND apnoe) OR (obstructive AND sleep AND apnoea) OR (obstructive AND sleep AND apnoeas) OR (obstructive AND sleep AND apnoeic) OR (obstructive AND sleep AND breathing AND disorder) OR (obstructive AND sleep AND disorder) OR (obstructive AND sleep AND disordered) OR (obstructive AND sleep AND disturbance) OR (obstructive AND sleep AND related) OR (obstructive AND sleep AND hypopnea) OR (obstructive AND sleep AND hypopneic) OR (obstructive AND sleep AND hypopnoe) OR (obstructive AND sleep AND hypopnoea) OR (obstructive AND sleep AND hypopnoeas) OR (obstructive AND sleep AND hypopnoeic) OR (obstructive AND snor*) OR osahs)
#3	#1 AND #2
Cinahl (search 22-01 to 2011)	
#1	mallampati OR mallampati* OR malampati OR malampatti OR mallampatti OR malampati* OR malampatti* OR mallampatti* OR mmp OR ems OR Friedman OR (Samsoon AND Young) OR (Sampsoon AND Young) OR (High AND tongue) OR (Height AND of AND tongue) Field: Title/Abstract
#2	OSAHS OR (obstructive AND sleep AND apnea) OR (sleep AND apnea) OR sleepapnea OR apnea OR (obstructive AND sleep AND apneas) OR (obstructive AND sleep AND apneic) OR (obstructive AND sleep AND apnoe) OR (obstructive AND sleep AND apnoea) OR (obstructive AND sleep AND apnoeas) OR (obstructive AND sleep AND apnoeic) OR (obstructive AND sleep AND breathing AND disorder) OR (obstructive AND sleep AND disorder) OR (obstructive AND sleep AND disordered) OR (obstructive AND sleep AND disturbance) OR (obstructive AND sleep AND related) OR (obstructive AND sleep AND hypopnea) OR (obstructive AND sleep AND hypopneic) OR (obstructive AND sleep AND hypopnoe) OR (obstructive AND sleep AND hypopnoea) OR (obstructive AND sleep AND hypopnoeas) OR (obstructive AND sleep AND hypopnoeic) OR (obstructive AND snor*) OR osahs Field: Title/Abstract
#3	#1 AND #2
Cochrane (search 22-01 to 2011)	
#1	mallampati OR mallampati* OR malampati OR malampatti OR mallampatti OR malampati* OR malampatti* OR mallampatti* OR mmp OR ems OR Friedman OR (Samsoon AND Young) OR (Sampsoon AND Young) OR (High AND tongue) OR (Height AND of AND tongue) Field: Title/Abstract
#2	OSAHS OR (obstructive AND sleep AND apnea) OR (sleep AND apnea) OR sleepapnea OR apnea OR (obstructive AND sleep AND apneas) OR (obstructive AND sleep AND apneic) OR (obstructive AND sleep AND apnoe) OR (obstructive AND sleep AND apnoea) OR (obstructive AND sleep AND apnoeas) OR (obstructive AND sleep AND apnoeic) OR (obstructive AND sleep AND breathing AND disorder) OR (obstructive AND sleep AND disorder) OR (obstructive AND sleep AND disordered) OR (obstructive AND sleep AND disturbance) OR (obstructive AND sleep AND related) OR (obstructive AND sleep AND hypopnea) OR (obstructive AND sleep AND hypopneic) OR (obstructive AND sleep AND hypopnoe) OR (obstructive AND sleep AND hypopnoea) OR (obstructive AND sleep AND hypopnoeas) OR (obstructive AND sleep AND hypopnoeic) OR (obstructive AND snor*) OR osahs Field: Title/Abstract
#3	#1 AND #2

Chapter 8

General discussion

Background

Nowadays, clinicians and patients expect high quality of care according to latest findings of research, taking into account the needs and wishes of individual patients. Clinicians therefore need skills to retrieve and critically review information from research to identify, use and translate valid evidence into their practice[1]. This is in contrast to the approach used in the past, i.e. combining clinical experience and patho-physiological reasoning with expert opinion and tradition. However, can practitioners retrieve the best evidence, and subsequently use it in their decision making? Searching for relevant evidence that is of sufficient quality and applies to the individual patient is complicated by the tasks and time pressure at point of care. The focus of the EBM community has therefore shifted from persuading clinicians to practice according to the principles of EBM, to addressing how a busy clinician might be able to identify and apply best evidence at point of care[2].

One of the major instruments to facilitate this point of care is the introduction of evidence-based guidelines. Over the last decade many guideline organizations have been established, e.g. the National Institute for Health and Clinical Excellence (NICE) in the UK, the Agency for Healthcare Research & Quality (AHRQ) in the United States, the Institute for Healthcare Improvement (CBO) in the Netherlands, and the Scottish Intercollegiate Guideline Network (SIGN) in Scotland[3-6]. Subsequently, the number of available guidelines has increased tremendously, and validated methods, such as the AGREE instrument and the GRADE classification were developed to improve the quality and effectiveness of clinical practice guidelines[7-11].

Limitations of guidelines

So far, several evidence-based guidelines have been developed within otorhinolaryngology[12-17]. These guidelines are based on explicit and transparent criteria including instructions for guideline work group composition, searching and appraising evidence, rating conclusions, grading recommendations and updating

guidelines[8 9]. The aim of these guidelines is to provide a comprehensive overview of diagnostic and therapeutic management options based on the most recent evidence. Such evidence-based guidelines have become powerful instruments in current healthcare, making patient care safer and more effective, and improving its quality[18]. However, potential limitations have also been reported.

First, guidelines do either only focus on therapeutic clinical questions, i.e. they often fails to include pertinent prognostic questions from clinical practice. Some even mix up prognostic clinical questions with diagnostic or etiologic questions.

Second, recommendations in guidelines are often vague and absolute risks or predictive values are not reported. Lack of explicitness may on the one hand limit the applicability to individual patients, and on the other hand allows variability in diagnostic and therapeutic management options. Thereby more variation between doctors than between patients may be seen **(Chapter 2)**.

Third, many guidelines are not comprehensive. They include many primary clinical questions which may result in a huge volume with a large number of pages. This will impede their use as a quick reference guide for answering clinical questions at point of care. A limited number of focussed questions and an executive summary of the practice guidelines may help to overcome the above limitations.

Fourth, due to the long period of time needed to complete and publish guidelines they quickly run out of date; often new evidence that should be included is available before a guideline is published.

Fifth, guidelines on a similar topic may show dissimilarities regarding conclusions, levels of evidence, and citations used. We have shown that more recent guidelines do not include references used in guidelines published before. Moreover, guidelines may show domestic citation preference and a high number of "self citations" **(Chapter 3)**. These limitations may reduce the utility and influence of evidence-based guidelines. The main effort of the EBM community therefore has to be to further improve practicality, transparency and applicability of evidence-based guidelines.

Evidence-based case reports

We therefore introduce a novel approach of potential additive value i.e. evidence-based case reports (EBCR's)[19 20]. An EBCR starts with a knowledge gap identified in daily practice regarding diagnosis, prognosis, or intervention. It follows an explicit and transparent approach, and provides practical best evidence summaries that are applicable to specific patient management issues.

The aim of EBCR's is to (re)produce absolute risks, to enable extrapolation of this evidence to clinical practice, and make the evidence accessible for and applicable to individual patient care. An answer on *diagnostic, therapeutic and prognostic* questions is provided based on the following criteria:

1. A specific clinical question related to an acute and realistic decision on individual patient management for which a knowledge gap existed, is identified in daily clinical practice.
2. A search for all studies of appropriate relevance to the three part question, (i.e. the domain, determinant, and outcome) is performed.
3. Among the retrieved studies, those with the lowest risk of bias, i.e., those with the most appropriate design(s) are selected.
4. For each of the selected studies, the numerical outcomes, notably their direction, magnitude, and precision are tabulated.
5. The consistency of the outcomes across studies is judged and interpreted and a conclusion on the strength of the evidence (strong or weak) for both the benefit and harm is drawn.
6. On the basis of the conclusion, the clinical question should be answered and a clinical recommendation on how to apply the evidence in patient management can be included.

Application of EBCR's

EBCR's may play a role in guideline development since evidence is transparently separated from judgement. EBCR's can be used to assist guideline panel consensus sessions. An apparent definition of knowledge gaps and a formal system for rating

the evidence can be used. Subsequently, recommendations can be progressively formed by the guideline panel using a considered judgement approach during a group decision making process, instead of being based on so-called “expert discussion”.

Although EBCR’s can be of additional value in the development of evidence-based guidelines, some aspects may need further consideration:
First, in otorhinolaryngology trials and cohort studies with high quality of methods are yet sporadic[21 22]. This implies that the evidence used to answer clinical questions is often weak. In addition, omission of the outcome of interest, enrolled participants being different from one’s patient, or both, may result in too indirect evidence. Both weakness of evidence and indirectness of evidence preclude strong recommendations for individual patient management decisions. Nevertheless, a well-planned, transparent and explicit approach may help to retrieve the best available evidence to meet information needs and inform individual patient management. Such approach, at the same time, may help to identify important gaps in the knowledge and evidence in otorhinolaryngology, and may thereby assist in compiling and prioritising topics for research in otorhinolaryngology[23 24].
Second, in answering the clinical question separating evidence from judgement is very important. This in particular when the studies show methodological flaws, study outcomes become less direct, and when observed effects are smaller, less precise and show more heterogeneity. Circumstantial and indirect evidence of lower methodological quality can often be the most appropriate and most valid evidence to answer the relevant clinical questions in EBCR’s. Accuracy of the evaluation process has to be taken into account when making the translation of this kind of evidence into practice to prevent invalid recommendations.
Third, there are an infinite number of clinical topics which have to be answered and updated to construct a guideline. Since the performance of an EBCR is time consuming, it is considered impossible to create all these EBCR’s in our daily practice. In 2004, however, an evidence-based medicine module was established at our medical school at the University Medical Center Utrecht. Nowadays, all medical

students at our medical school learn to make EBCR's according to a predefined structure, including an informative title, a structured abstract, main text (maximum 1200 words), the date and syntax of searches, a flow chart for the results of retrieval, evidence tables for relevance and validity, including numerical outcomes, a graded clinical recommendation, and research priorities. Thereby a high quality of the EBCR's can be warranted. Each student has to write three EBCR's, implying that per year about 300 of such best-evidence summaries are written. If this module is adopted by other Dutch and international universities, this can lead to a potential 2500 EBCR's per year in the Netherlands and an infinite number of EBCR's worldwide.

In daily practice, EBCR's can assist otorhinolaryngologists to answer specific clinical questions for which general guidelines are missing. Assisted by medical students or residents, clinical questions can be answered in a systematic way. Such EBCR's can also assist in formulating or revising local diagnostic and treatment protocols. EBCR's may also play a role in the development of more interactive media. For example, they can assist current interactive web-based databases like Best Bets, CATS, the database of abstracts of reviews of effect (DARE) and the Dutch WIKI ENT website to further improve evidence-based practice[25 26]. In addition, EBCR's may also play a role in locating important gaps in knowledge needed for patient care, and therefore assist in prioritising novel research.

Conclusion

EBCR's can be of additive value to further improve the current development of evidence-based guidelines, i.e. they may assist guideline panel consensus sessions. Furthermore, EBCR's can also be used in the formation or adjustment of local diagnostic and treatment protocols, and assist in developing interactive media, to further improve evidence and guidelines in otorhinolaryngology.

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Scottish Intercollegiate Guidelines Network
73
Management of Obstructive Sleep Apnoea/Hypopnoea Syndrome in Adults
A national clinical guideline
Summary
RESEARCH
Pilot study of a semi-flexible intra-oral appliance for the control of snoring
Pharyngolaryngectomies des cancers et récidivants : étude des facteurs de risque et complications
Pharyngolaryngectomy for advanced and recurrent cancer: Prognostic factors and complications
Mallampati Class is Not Useful in the Clinical Assessment of Sleep Clinic Patients

In **Chapter 1** a general introduction and the aim and outline of this thesis are presented. In this chapter we address whether the current otorhinolaryngology guidelines sufficiently serve the effectiveness, safety and quality of patient care in terms of uptake of new medical knowledge.

Since clinical uptake of clinical guidelines is of high importance, we describe a survey among Dutch otorhinolaryngologists in **Chapter 2**. We aim to study their current awareness, knowledge, and opinion of evidence-based otorhinolaryngology guidelines. We also use two clinical scenarios to assess their adherence to guidelines. Our results show that 70% of the otorhinolaryngologists report to be influenced by guidelines: for 32% they guide daily practice and for 62% they support daily practice. Confidence in the accuracy of guidelines is 77% average. While deviation from guidelines in daily practice is reported in 45%, younger ENT physicians less often do so. In case of a severe OSAHS patient the treatment by Dutch otorhinolaryngologists shows a homogenous pattern, which is in accordance with the strict recommendations of the guideline. For the scenario with less well-defined disease features the guidelines include less strict recommendations and allow multiple treatment options. And so, in accordance with the guidelines an increased variation in the chosen treatment is found. We conclude that Dutch otorhinolaryngologists are familiar with available guidelines and a majority uses them in daily practice. Most choose treatment consistent with the OSAS guideline. The lack of strict recommendations in guidelines can be difficult to use directive.

In **Chapter 3** we compare the evidence-based Scottish (SIGN), Dutch (CBO) and American (ICSI) guideline on diagnosis and treatment of obstructive sleep apnoea-hypopnoea syndrome (OSAHS). If guidelines are constructed on similar scientific evidence, they will produce similar conclusions and recommendations. Our comparison of these guidelines, however, shows that the three guidelines focus on different aspects of the management of OSAHS. Furthermore, for similar clinical questions these 3 guidelines show differences in attached levels of evidence (32%-

62%), and remarkable discrepancies in cited studies. A plausible reason for these differences is the citation preference for papers from members of the guideline work group and from own country. Despite different publication dates, more recent guidelines fail to cite earlier published guidelines. As a result of this, conflicting conclusions between guidelines are reported: 18% (5/28) for the comparison of CBO and SIGN, 11% (2/19) for CBO and ICSI and 15% (2/13) for SIGN and ICSI. We come to the conclusion that, despite the generally accepted approach regarding the development of evidence-based guidelines, remarkable differences exist between guidelines from different countries on the same clinical subject.

In **Chapter 4** we introduce a novel approach to provide answers to questions on common clinical problems in otorhinolaryngology as a response to differences between guidelines: the "evidence-based case report" (EBCR). We provide an answer on the *diagnostic* question: "what is the diagnostic value of diffusion-weighted magnetic resonance imaging (DW MRI) in detecting a residual cholesteatoma?" The evidence of this EBCR reveals a pooled positive and negative predictive value of 97% and 97%, respectively and added values of 52% and 42% for a positive and negative result, respectively. This evidence is strong enough to justify the use of DW MRI for the follow-up of patients who have undergone a canal-wall-up procedure in day to day otorhinolaryngology practice. Nowadays follow-up of patients with cholesteatoma will be performed by DW MRI if the surgical conditions allow this. Furthermore, DW MRI is more and more used as instrument in the detection of primary or congenital cholesteatoma.

In **Chapter 5** we use this systematic approach to answer a question on *intervention*: "What is the value of a mandibular repositioning appliance (MRA) for the treatment of non-apnoeic snoring?" The evidence of this EBCR exposes that a MRA results in a reduction of snoring loudness in one out of three patients with non-apnoeic snoring, and in an improvement of sleep disturbance of the partner in one out of two patients. No effect on quality of life and daytime sleepiness of the partner is

found. Furthermore, evidence for sustained long term effects and complete recovery is lacking. In daily practice we are now able to hand over this evidence to our patient. Since treatment of patients with non-apnoeic snoring is no longer reimbursed, these data facilitate the choice for our patient whether to spend his money on a MRA or not. He can make this balancing together with his partner, since partner's sleep disturbance and daytime sleepiness have also been included in the outcome parameters.

In **Chapter 6** we reply on the *prognostic* question: "Salvage laryngectomy after primary radiotherapy: what are prognostic factors for the development of pharyngocutaneous fistulae?" Multivariate logistic regression analysis shows that only initial tumour stage and tumour site remain as independent prognostic factors of a pharyngocutaneous fistula. We are also able to re-calculate that in patients who have a primary glottic laryngeal T1 or T2 tumour the absolute risk of developing a pharyngocutaneous fistula is one out of ten, whereas the risk of developing a fistula in patients with a T3 or T4 extra laryngeal tumour is one out of three. These data are of importance when we discuss the post-operative risks of a salvage laryngectomy with our patients since this is likely to increase the time for recovery and length of hospital stay.

In **Chapter 7** we give an example of an EBCR in response to differences between guidelines. We answer the diagnostic question: What is the value of the Mallampati score in diagnosing OSAHS in patients suspected for OSAHS? The Dutch and American OSAHS guideline mention the diagnostic value of such classification, while the Scottish SIGN guideline does not mention it at all. This EBCR reveals that the positive predictive values (risk of OSAHS with Mallampati grade 3-4) are 69%, 82% and 81% and the negative predictive values (risk of OSAS with Mallampati grade 1-2) are 55%, 26% and 19%. Since the prevalence (or prior probability) of OSAHS is 58%, 75% and 81% respectively, the risk of the diagnosis OSAHS is reported to increase maximally 11% with a Mallampati grade 3-4 and to decrease between 3% to 62%

with a Mallampati grade 1-2. Therefore the Mallampati score offers little for ruling in or ruling out the diagnosis of OSAHS in patients suspected for OSAHS.

In **Chapter 8** we emphasize the potential additive value of EBCR's to earlier reported limitations of the current evidence based guideline development. An EBCR starts with a knowledge gap identified in daily practice regarding diagnosis, prognosis, or intervention. An explicit and transparent approach is followed, and practical best evidence summaries are provided that are applicable to specific patient management issues. EBCR's may play a role in guideline development since evidence is transparently separated from judgement. EBCR's can be used to assist guideline panel consensus sessions. An apparent definition of knowledge gaps and a formal system for rating the evidence can be used. Subsequently, recommendations can be progressively formed by the guideline panel using a considered judgement approach during a group decision making process, instead of being based on so-called "expert discussion". Furthermore, EBCR's can also be used in the formation or adjustment of local diagnostic and treatment protocols, and assist in developing interactive media, to further improve "evidence and guidelines" in otorhinolaryngology.


Dutch summary

In **hoofdstuk 1** worden een algemene inleiding, het doel en de hoofdlijnen van dit proefschrift gepresenteerd. De vraag die in dit hoofdstuk centraal staat is of de huidige KNO richtlijnen voldoende invloed hebben op medisch handelen in de praktijk. Hierbij wordt in het bijzonder gekeken naar de beoogde toename van de effectiviteit, veiligheid en kwaliteit van de patiëntenzorg.

Omdat het van groot belang is dat medisch specialisten richtlijnen in de dagelijkse praktijk ook daadwerkelijk volgen, beschrijven we in **hoofdstuk 2** een enquête onder Nederlandse KNO-artsen. Bestudeerd wordt in hoeverre zij bekend zijn met de richtlijnen en in hoeverre zij deze volgen. We gebruiken ook twee klinische scenario's om te beoordelen in hoeverre men handelt volgens de richtlijnen. Het blijkt dat voor 70% van de KNO-artsen het medisch handelen wordt beïnvloed door de richtlijnen. Voor 32% zijn de richtlijnen een leidraad en voor 62% een ondersteuning in hun dagelijkse praktijk. Het vertrouwen in de juistheid van richtlijnen is gemiddeld 77%. Respondenten geven aan in 45% van hun dagelijkse praktijk van richtlijnen af te wijken; jongere KNO-artsen doen dat minder vaak. In het geval van een ernstige OSAS patiënt toont behandeling van de Nederlandse KNO-artsen een homogeen patroon dat in overeenstemming is met de aanbevelingen van de richtlijn. Conform de aanbevelingen in de richtlijn zijn bij het scenario met minder scherp omschreven ziekte kenmerken meerdere behandelingen mogelijk; variatie in gekozen behandeling neemt hierdoor toe. Onze conclusie is dat Nederlandse KNO-artsen bekend zijn met beschikbare richtlijnen en deze gebruiken ter ondersteuning van hun dagelijkse praktijk. Bij de keuze van behandeling is er grote overeenkomst met de aanbevelingen van de OSAS richtlijn. Het ontbreken van strikte aanbevelingen in richtlijnen kan het gebruik echter lastig maken.

In **hoofdstuk 3** evalueren we in hoeverre de Engelse (SIGN) Nederlandse (CBO), en Amerikaanse (ICSI) richtlijnen voor de diagnostiek en behandeling van patiënten met het obstructieve slaap apneu syndroom (OSAS) overeenkomen. Indien richtlijnen met dezelfde wetenschappelijke studies onderbouwd worden, zullen zij doorgaans

vergelijkbare conclusies trekken en overeenkomstige aanbevelingen formuleren. Onze vergelijking laat echter zien dat de richtlijnen zich richten op verschillende aspecten van OSAS. Voor overeenkomstige klinische vragen tonen deze drie richtlijnen in veel gevallen verschillen in genoemde “levels of evidence” (32%-62%) en opmerkelijke verschillen in geciteerde studies. Belangrijke citaties uit eerder gepubliceerde richtlijnen worden in later gepubliceerde richtlijnen niet gebruikt. Citaties uit eigen land en van richtlijn auteurs blijken favoriet. Als gevolg van deze verschillen worden doorslaggevende tegenstrijdige conclusies geformuleerd: 18% (5/28) voor de vergelijking van CBO en SIGN, 11% (2/19) voor CBO en ICSI en 15% (2/13) voor SIGN en ICSI.
Concluderend kan gesteld worden dat ondanks de algemeen aanvaarde ontwikkelingsmethode van “evidence-based” richtlijnen, er vandaag de dag nog steeds opmerkelijke verschillen bestaan tussen de richtlijnen van diverse landen over hetzelfde klinische onderwerp

In **hoofdstuk 4** introduceren we een nieuwe benadering als aanvulling op de verschillen tussen richtlijnen: het “evidence-based case report” (EBCR). EBCR’s geven antwoord op vragen over veelvoorkomende klinische problemen in de KNO-heelkunde. We geven in dit hoofdstuk een antwoord op de *diagnostische* vraag: “wat is de diagnostische waarde van diffusie-gewogen MRI (DW MRI) bij het opsporen van een residuaal cholesteatoom?” Het bewijs van dit EBCR toont een gepoolde positief en negatief voorspellende waarde van 97% en 97% en een toegevoegde waarde van 52% en 42%, respectievelijk, voor een positief en negatief resultaat. Dit bewijs is sterk genoeg om het gebruik van diffusie gewogen MRI in de dagelijkse KNO-praktijk voor de follow-up van patiënten na een “canal-wall-up” procedure te rechtvaardigen. Vandaag de dag wordt deze follow-up met behulp van DW MRI standaard uitgevoerd indien de chirurgische voorwaarden dit toelaten. Bovendien wordt DW MRI steeds meer gebruikt als instrument voor de opsporing van primaire of aangeboren cholesteatomen

In **hoofdstuk 5** gebruiken we deze systematische aanpak om een *therapeutische* vraagstelling te beantwoorden: “Wat is de waarde van een mandibulair repositionerings apparaat (MRA) voor de behandeling van snurken zonder apneus. Dit EBCR toont aan dat het gebruik van een MRA resulteert in een klinisch relevante verlaging van het snurkgeluid in één op de drie patiënten en een afname van de slaap verstoring van de partner in één op de twee patiënten. Er wordt geen effect gevonden op de kwaliteit van leven en slaperigheid overdag van de partner. Bovendien ontbreken gegevens ten aanzien van lange termijn effecten en volledig verdwijnen van het snurken. In de dagelijkse praktijk kunnen we deze informatie met onze patiënt bespreken. Dit is relevant, aangezien de behandeling van snurken zonder apneus niet meer wordt vergoed door de zorgverzekeraar. Deze gegevens vergemakkelijken de keuze voor onze patiënt of hij zijn geld wil besteden aan een MRA of niet. Hij kan dit samen met zijn partner beslissen aangezien verstoring van de slaap en slaperigheid overdag van de partner ook zijn meegenomen in de uitkomst parameters

In **hoofdstuk 6** geven we met een EBCR antwoord op de *prognostische* vraagstelling: “Salvage laryngectomie” na primaire radiotherapie: wat zijn prognostische factoren voor het ontstaan van pharyngocutane fistels?” Uit een multivariate logistische regressie-analyse blijkt dat slechts het oorspronkelijke tumor stadium en de tumor plaats onafhankelijke prognostische factoren zijn voor het ontstaan van een pharyngocutane fistel. Op basis van originele data zijn we ook in staat de absolute risico’s opnieuw te berekenen: indien een patiënt aanvankelijk behandeld was voor een primair T1 of T2 glottisch larynxcarcinoom ontstaat een fistel bij één op de tien patiënten. Echter indien patiënten eerder een primaire T3 of T4 extra-laryngeale tumor hadden, stijgt het risico op een fistel en treedt dit postoperatief op bij één op de drie patiënten. Deze gegevens zijn van belang ten aanzien van het inschatten van de post-operatieve risico’s van een “salvage laryngectomie”, omdat deze de tijd van het post-operatieve herstel en het ziekenhuisverblijf verlengen

In **hoofdstuk 7** geven we een voorbeeld van een EBCR als antwoord op verschillen tussen richtlijnen. We beantwoorden de *diagnostische* vraag: Wat is de waarde van de Mallampati score voor het diagnosticeren van OSAS bij patiënten verdacht voor OSAS? In de Nederlandse en Amerikaanse OSAS richtlijn wordt melding gemaakt van de diagnostische waarde van de Mallampati classificatie. In de Schotse SIGN richtlijn wordt deze echter niet genoemd. De positief voorspellende waarde (risico van OSAS met Mallampati graad 3-4) is 69%, 82% en 81% en de negatief voorspellende waarde (kans op OSAS met Mallampati graad 1-2) is 55%, 26% en 19%, respectievelijk. Omdat de prevalentie (priorkans) van OSAS 58%, 75% en 81% is, is de aanvullende waarde van de Mallampati graad 3-4 op het detecteren van OSAS maximaal 11% en de aanvullende waarde van de Mallampati graad 1-2 op het uitsluiten van OSAS 3% tot 62%. Daarom draagt de Mallampati score weinig bij aan het diagnosticeren van OSAS bij patiënten verdacht voor OSAS.

In **hoofdstuk 8** benadrukken we de potentiële toegevoegde waarde van EBCR's ten aanzien van de eerder genoemde beperkingen van de huidige "evidence-based" richtlijnontwikkeling. Een EBCR begint met een kennislacune in de dagelijkse praktijk met betrekking tot diagnose, prognose, of therapie. Door een expliciete en transparante aanpak wordt het beste bewijs bondig samengevat. Zodanig dat dit van toepassing is op klinische vragen over specifieke patiënten in de dagelijkse praktijk. EBCR's kunnen een rol spelen bij richtlijnontwikkeling, omdat het bewijs transparant is en niet gebaseerd op vooroordelen of opinie. EBCR's kunnen worden gebruikt om de richtlijn panel consensus sessies te ondersteunen. Een heldere definitie van de kennislacunes en een gestructureerd systeem voor de beoordeling van het bewijs kan worden gebruikt. Hiermee kunnen heldere en transparante aanbevelingen worden gevormd door de richtlijn werkgroep. Door middel van een weloverwogen beoordeling van het bestaande bewijs worden aanbevelingen geformuleerd. Dit staat in contrast met de huidige "expert discussie" waarbij aanbevelingen worden gevormd op basis van consensus. Daarnaast kunnen EBCR's ook worden gebruikt bij de vorming of aanpassing van lokale diagnostische en behandelprotocollen en helpen bij de ontwikkeling van interactieve media. Hierdoor kunnen ze bijdragen aan een verdere verbetering van "evidence en richtlijnen" in de KNO-heelkunde.

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Curriculum Vitae

Mark Aarts werd geboren op 29 november 1978 in Waalwijk. In 1997 werd het eindexamen Gymnasium behaald aan het dr. Mollercollege te Waalwijk. Hierna bepaalde het lot dat hij geneeskunde mocht gaan studeren aan de Universiteit Utrecht. De eerste kennismaking met de KNO-heelkunde vond plaats tijdens een coschap in het St. Elisabeth ziekenhuis te Curaçao wat gevolgd werd door een keuze coschap op de afdeling KNO-heelkunde in het Universitair Medisch Centrum Utrecht. Hier werd onder Prof. Dr. G.J. Hordijk de basis gelegd voor de eerste wetenschappelijke publicatie. In 2004 behaalde hij zijn artsenbul en kreeg hij van David Kupperman en Paul Struyvenberg vervolgens de mogelijkheid om ervaring in het vak op te doen als AGNIO op de afdeling KNO-heelkunde van het Centraal Militair Hospitaal Utrecht. Prof. Dr. G.J. Hordijk nam hem vervolgens aan voor de opleiding tot KNO-arts die uiteindelijk in 2006 na nog een AGNIO-stage van 8 maanden onder Prof. Dr. F.W.J. Albers werd aangevangen en via Dr. A.F. van Olphen en B-opleider Dr. P.P.G. van Benthem in Apeldoorn onder Prof. Dr. W. Grolman in 2011 werd afgerond. Tijdens de opleiding werd de rotsbeendissectieprijs veroverd in 2008 en de 1^{e}-jaars prijs in 2006. Na enkele korte wetenschappelijke projecten binnen de Hoofd-hals oncologie, Kinder KNO-heelkunde en elektrofysiologie werd hem in 2009 de kans geboden om promotieonderzoek te doen, wat uiteindelijk heeft geleid tot dit proefschrift. Hij is thans werkzaam in het Centraal Militair Hospitaal en in het UMC Utrecht. Hij is getrouwd met Ilja Panis.