Criteria for the diagnosis of extra nodal extension detected on radiological imaging in head and neck cancer

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Title page

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HNCIG international consensus recommendations

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Abstract: Extranodal extension of tumour on histopathology (pENE) is known to be a negative prognostic factor in head and neck cancer (HNC). Compelling evidence suggests that extranodal extension detected on radiological imaging (imaging-detected ENE; iENE) is also a negative prognostic factor. Furthermore, if iENE could be identified reliably before start of treatment, it could be used to guide treatment selection, as patients with iENE may be better managed with non-surgical approaches to avoid the toxicity and cost of trimodality therapy. There are many aspects of iENE that remain unresolved or which lack consensus – such as the criteria to best diagnose iENE and the associated terminology. The Head and Neck Cancer International Group conducted a five-round modified Delphi process with a group of 18 international radiology experts, representing 14 national clinical research groups.

We generated consensus recommendations on the terminology and diagnostic criteria for iENE to harmonize clinical practice and research. These recommendations have been endorsed by 19 national organisations, representing 34 countries. We propose a new classification system to aid diagnosis, which was supported by the majority of participating experts over existing systems, and which will require validation in the future. Additionally, we have created an online educational resource for grading iENE.

Keywords: extranodal extension, extracapsular spread, radiology, head and neck cancer, squamous cell carcinoma

Manuscript

INTRODUCTION

Despite improvements in cure rates for head and neck squamous cell carcinoma (HNSCC) seen with the increasing proportion of HPV-mediated disease and with treatment advances, outcomes remain poor in locally advanced cases. Up to 30-40% of HNSCC patients relapse following curative-intent treatment, and consequently have dismal chances of cure[8].

In recent years, our ability to identify patient groups based on differential prognosis has resulted in refinements to the staging system for HNSCC and more appropriately tailored treatments. One of the most notable changes between the latest editions of the AJCC/UICC stage classifications for HNSCC was the incorporation of clinical extranodal extension (ENE) into the staging system for HPV-negative disease[9]. ENE is the growth of nodal metastatic disease beyond the capsule of that lymph node. ENE reflects tumor aggressiveness and presents as a spectrum, ranging from early stages that can only be detected microscopically on histopathology (pENE), to intermediate stages detected on radiologic imaging (imaging-detected ENE; iENE), to the most advanced stages which are identified overtly on clinical examination (cENE).

In locally advanced HNSCC, the presence of pENE constitutes a high-risk feature for disease progression and metastasis.[10,11] In surgically-treated patients with pENE, evidence from randomized trials supports the addition of concurrent chemotherapy to adjuvant radiotherapy to reduce relapse and improve overall survival.[10] Compelling evidence suggests that iENE also carries prognostic importance in both HPV-negative and HPV-positive HNSCC.[1,12-15] Studies show that iENE demonstrates a sensitivity of 60-80% and specificity of 72-96% to predict pENE.[2-4] Recent systematic reviews and meta-analyses show that iENE is also associated with poorer prognosis, with a higher hazard ratio for mortality compared to pENE in patients with HPV-mediated oropharyngeal cancer[1,2].

In the case of iENE, the diagnosis relies on clinical or radiological examination without histopathological confirmation. The ability to diagnose iENE accurately on radiologic assessment has the potential to result in significant changes in management. For example, patients with oropharyngeal cancer with a high risk of ENE based on diagnostic imaging may

be treated with primary chemoradiation rather than upfront surgery and postoperative chemoradiotherapy, thereby avoiding the excessive toxicity associated with trimodality therapy, and preserving patients' quality of life.

As iENE is a relatively new concept for the radiology community, there is no expert consensus on or standardisation of the diagnostic criteria by which to define iENE, or on the best classification system to describe the extent of iENE. For this reason, we assembled a group of international HNSCC radiology experts representing 14 national clinical research bodies spanning 29 countries, to generate consensus on terminology and criteria for iENE and provide a framework for decision-making.

Methods

Participant selection

A study steering group was established by the Head and Neck Cancer International Group (HNCIG), a consortium of 21 national head and neck oncology research groups. The steering group comprised expert head and neck radiologists, surgeons, and oncologists, who led the overall study design and execution (names provided in the appendix - **Table A, p1**).

All 21 member groups of the HNCIG were invited to nominate a head and neck radiologist representative to join the consensus panel. Nominees had to be currently practicing head and neck radiologists, considered to be a national or international expert, and be willing to complete all rounds of the online modified Delphi process. Fourteen of the 21 invited organizations provided nominations, all of whom participated in the process and were included in the manuscript authorship. The participating organizations were: the Danish Head and Neck Cancer Group (DAHANCA), the Dutch Head and Neck Society (NWHHT), the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN), the French Head and Neck Cancer Group (GORTEC), Fudan University Shanghai Cancer Center (FUSCC), the German Interdisciplinary Working Group for Head and Neck Tumors (IAG-KHT), the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG), the Hellenic Cooperative Oncology Group (HeCOG), Hong Kong Nasopharyngeal Cancer Study Group (HKNPCSG), the Latin American Cooperative Oncology Group (LACOG), the National Cancer Centre Singapore (NCCS), the National Cancer Research Institute UK (NCRI), NRG Oncology, and the Spanish Head and Neck Cancer Cooperative Group (TTCC).

Consensus process and data collection

To achieve consensus, a modified Delphi process was conducted online over five rounds using methods described previously[16]. In brief, the nominated expert head and neck radiologists were invited to complete an online questionnaire, delivered by the Qualtrics online survey platform (Qualtrics, Provo, UT, USA). The survey included four main sections: Criteria for iENE, inter-observer agreement for iENE criteria, the impact of core biopsy on iENE diagnosis, and classification systems for iENE reporting. An overview of the modified Delphi process is shown in **Figure 1**. Questions were selected by

the steering group and were revised or amended iteratively over subsequent rounds. In rounds two and three, some new questions were also introduced to add granularity to particularly nuanced topics. In rounds four and five, we identified the classification most preferred by the experts, and refined that proposed new classification system. Before each round, the questions were piloted on an independent group of expert head and neck radiologists for readability, and face and content validity.

In questions on the criteria for diagnosing iENE, participants were asked about the degree with which these proposed criteria correlated with pENE. They were given the following options: consistent with = >90% correlation; suspicious for = 60-90%; possible = 30-60%, and unlikely <30% correlation. For questions on the degree of interobserver agreement, respondents were given the following scale: 1 = very low likelihood of interobserver agreement between radiologists; 2 = low likelihood; 3 = average likelihood; 4 = good likelihood; and 5 = very high likelihood. Respondents were instructed that they could use the same grade for more than one criterion if deemed necessary; in other words, they did not have to rank each criterion with reference to the other criteria.

Each survey round was open for 7-14 days. A reminder email was sent three days before the deadline. After each round, data was collated and analyzed, and predetermined criteria for agreement were applied. These criteria were extrapolated from the RAND methodology[17]: Consensus of 80% and above indicated strong agreement for a statement; 67-79% indicated agreement; 21-66% indicated no agreement; and 20% or less of responses in agreement indicated strong agreement against a statement (i.e. rejection of a statement). A statement was removed from the next round either when strong agreement for or against was reached, or after completion ofall rounds, whichever occurred first.[18]

Results were shared back with the respondents after each round. When making their recommendations, participants were asked to consider that while imaging will never be as sensitive as pathologic assessment for the detection of ENE, the goal of the project was to recognize the utility of iENE in its own right as an independent predictive and prognostic entity that could inform staging and treatment recommendations. As part of the Delphi process, respondents were reminded that they could change their response to a question in the next round, if they wished, depending on the results and emerging consensus of the previous rounds, and there was a “free text” option to elaborate on certain points.

This study was granted a research ethics waiver from the Research Ethics Department at the University of Birmingham (Birmingham, UK), application number ERN_0910-1.

FINDINGS

Process

Eighteen expert nominees representing 14 research groups, spanning 29 countries, participated in this study, as the Dutch, Fudan, Japanese, and the Spanish groups had two representatives each. The full list is provided in the appendix (**Table B, p 1**). In total, 15/18 (83.3%) participants completed all five rounds. One participant withdrew after the first round and was not substituted as their group was already represented by a second nominee. One participant was unable to complete the third round and was substituted by their group.

In total, 45 questions were asked in the first round; 38 questions in the second round; and 18 questions in the third round. Twenty out of forty-five and 31 of 38 questions were removed after the first and second rounds respectively, after reaching strong agreement for (≥80%) or against (≤20%). Only 8 of the 18 questions asked in the third round failed to achieve any form of agreement (21-66%). The reported rates of agreement reflect when the item first reached one of the agreement thresholds, which might have been after one or morerounds of questioning. Full results and agreement levels of the questions asked in all rounds are provided in the appendix (**Table C, pp 2-9**).

The final recommendations were endorsed by 19 national head and neck cancer clinical research groups, representing 34 countries (**Panel 1**).

Criteria for extranodal extension on imaging

A summary of the consensus findings for extranodal extension on imaging is provided in **Table 1**.

Indistinct or irregular nodal margin or border

Experts agreed unanimously that "*indistinct or irregular nodal margin or border*" should be considered a criterion for iENE (17/17, 100%). Most respondents (14/16, 87·5%) agreed that this finding correlates with "*suspicious for*" pENE (60-90% correlation with pENE) as opposed to "*consistent with*", *"possible*", or "*unlikely*". Experts reached strong agreement that this criterion can be applied when using CT scans (17/17, 100%) and MRI scans (16/17, 94·1%), and there was agreement that this criterion *cannot* be applied when interpreting ultrasound images, with 11/16 (68·8%) advising against. The panel did not reach agreement regarding the interobserver agreement of irregular or ill-defined nodal margins on imaging. However, half of the respondents (8/16, 50%) thought this criterion might have a "*good likelihood*" for interobserver agreement.

There was unanimous agreement (16/16, 100%) that *indistinct or irregular nodal margin or border*" can be applied as a criterion for the diagnosis of iENE in both HPV-associated oropharyngeal carcinoma, and for all non-HPV related HNSCCs, including HPV-negative oropharyngeal and nasopharyngeal carcinoma (16/16, 100%).

Based on feedback from the expert respondents, we added a question in rounds two to four regarding whether there is a difference between "*indistinct (ill-defined)*" versus "*irregular*" nodal contour or margin. The participants could reached strong agreement against there being a difference between these two terms, with only 2/15 (13.0%) reporting there was a difference. Importantly, there was agreement (12/16, 75%) that these two features should be combined together and should not be considered as two independent criteria for iENE.

Extension into perinodal fat

Experts reached agreement (12/16, 75%) that the finding of "*extension into perinodal fat*" on imaging denotes "*consistent with*" pENE (i.e. >90% confidence). Experts were in strong agreement that this criterion can be applied when using CT scans (17/17, 100% agreement) and MRI (17/17, 100% agreement). Experts also reached strong agreement *against* using this criterion when interpreting ultrasound images (2/16, 12·5%). There was also strong agreement *against* taking "*distance of invasion into perinodal fat*" into account when diagnosing iENE, with only 2/16 (12·5%) of respondents answering in favor. There was strong agreement (13/16, 81.3%) that extension into perinodal fat has *at least* "*good*

likelihood" of interobserver agreement between radiologists, with 11/16 (68.8%) reporting "*good*" and 2/16 (12.5%) reporting "*very high likelihood*".

There was strong agreement that this criterion can be applied for the diagnosis of iENE in both HPV-associated oropharyngeal carcinoma (13/16, 81.3%), and for all non-HPV related HNSCCs, including HPV-negative oropharyngeal and nasopharyngeal carcinoma (16/16, 100%).

Extension into adjacent structures such as muscle, skin, glands, neurovascular bundle

Experts unanimously agreed (17/17, 100%) that "*extension into adjacent structures such as muscle, skin, glands, or neurovascular bundle*" should be considered a criterion for diagnosing iENE. They indicated strong agreement (15/17, 88·2%) that this finding is "*consistent with*" pENE, indicating that it would give them >90% confidence in presence of pENE. There was strong agreement that this criterion could be applied when using CT scans (17/17, 100%) and MRI scans (17/17, 100%), *as well as* ultrasound (15/16, 93·8%). There was strong agreement that the site or number of sites of involved adjacent structures (such as muscle, skin, glands, etc.) should *not* be taken into account when determining presence or absence of iENE (15/16, 93·8%). Experts agreed unanimously (16/16, 100%) that the criterion of "*extension into adjacent structures*" is associated with *at least* "*good likelihood*" of interobserver agreement including 11/16 (68.8%) "*very high likelihood*" and 5/16 (31.3%) "*good likelihood*".

There was strong agreement that this criterion can be applied for the diagnosis of iENE in both HPV-associated oropharyngeal carcinoma (15/16, 93.8%), and for all non-HPV related HNSCCs, including HPV-negative oropharyngeal and nasopharyngeal carcinoma (16/16, 100%).

Conglomerate/matted/coalescent nodes

Experts agreed strongly (14/16, 87·5%) that "*conglomerate/matted/coalescent*" nodes (defined as effacement of the capsules of two or more adjoining lymph nodes, fusing into one another with loss of the intervening internodal planes) should be considered a criterion for iENE. There was agreement (11/16, 68·7%) that this finding is "*suspicious for*" pENE, indicating 60-90% confidence in this criterion. There was strong agreement that this criterion can be applied when using

CT scans (15/17, 88·2%) and MRI scans (15/17, 88·2%) for the diagnosis of iENE, and there was agreement (11/16, 68·7%) that this criterion can also be applied to ultrasound scans.

Experts were in strong agreement (13/14, 92·9%) that if extension between nodes is seen, the number of nodes involved does *not* need to be taken into account for the diagnosis. There was strong agreement (14/16, 87.5%) that this criterion indicated *at least* "*good likelihood*" of interobserver agreement including 9/16 (56.3%) "*very high likelihood*" and 5/16 (31.3%) "*good likelihood*".

They were also in strong agreement that the criterion of "*conglomerate/matted/coalescent*" nodes can be applied for the diagnosis of iENE in HPV-associated oropharyngeal carcinoma (16/16, 100%) and for all non-HPV related primary head and neck carcinoma (12/14, 85.7%).

The participants also reached strong agreement (14/15, 93.3%) that there is not difference between the three terms "*conglomerate*", "*matted*", and "*coalescent*" to describe "effacement of the capsules of two or more adjoining lymph nodes, fusing into one another with loss of the intervening internodal planes" for the diagnosis of iENE.There was no agreement on which of these three terms would be the most preferred to be used in that context, with 7/16 (43.7%) favouring *'conglomerate*', 5/16 (31.3%) '*matted*', and 4/16 (25%) '*coalescent'*.

Capsular thickening

Experts agreed strongly *against* the use of "*capsular thickening*" as a criterion by which to diagnose iENE (3/16, 18·7%).

Central nodal necrosis

Experts agreed strongly against "*central nodal necrosis*", also known as significant "*intranodal heterogeneity*", being a criterion for iENE (15/16, 93·8%).

Additional criteria for consideration

Only 6/17 (35.3%) of the respondents in the first round, and 1/16 (5.9%) in the second round proposed additional criteria to be considered for the iENE diagnosis, including lymph node size, and increased avidity on positron emission tomography (PET). These criteria were deemed by the steering group as not particularly specific to iENE diagnosis and were not considered for subsequent rounds.

Impact of recent core biopsy on interpretation of iENE

Respondents were in strong agreement (15/16, 93·8%) that a history of a recent core biopsy from the same area would influence their interpretation of early iENE in that area. 56.2% (11/16) of the expert radiology panel indicated they would *not* be able to make an accurate diagnosis and report of iENE if the history of recent core biopsy was not available, but that statement did not reach agreement level. In figure 2, we show an example that demonstrates how a core biopsy can confound the determination of iENE in a lymph node (**Figure 2**).

Classification systems for iENE reporting

Standardized classification systems and synoptic reporting

The respondents unanimously (17/17, 100%) supported the use of a standardized classification system for iENE, and all would be willing to use standardized synoptic reporting for iENE in their routine practice (17/17, 100%).

When asked if they are aware of any existing classification systems for iENE diagnosis, only 35.3% (6/17) of the participants indicated that they are aware of the classification system proposed by Hoebers *et al.*[7], 11.8% (2/17) indicated that they are aware of the classification system described by Ai *et al.*[19], and 5.9% (1/17) were aware of the classification systems described by Lu *et al.*[20]; Chai *et al.*[21] and Elsholtz *et al.*[22]. The Steering group removed the systems described by Chai *et al.*[21] and Elsholtz *et al.*[22] from subsequent rounds as these were not considered to be true classification systems for iENE.

The three remaining published systems were then anonymized, and then presented in random order to the respondents to rank in relation to each other with regards to their usefulness for undertaking the diagnosis and reporting of iENE in routine clinical practice and research (**Table 2**). Ai *et al.*[19] (System A) was ranked first with weighted average score of 77.1%

(37/48), while Hoebers *et al.*[7] (system C) and Lu *et al.*[20] (system B) scored 62.5% (30/48) and 60% (29/48) and were ranked second and third respectively.

Based on the emerging consensus and the findings of this Delphi process, the steering group proposed a new classification system for iENE diagnosis. The goal of introducing a new, consensus-based system is to enhance iENE pickup rate without increasing false positive diagnoses. The respondents were then asked to compare this new system (system 1) to the two systems that received the highest ranks in the previous round- Ai *et al.*[19] (system 2) and Hoebers *et al.*[7] (system 3)- with regards to their usefulness for the diagnosis and reporting of iENE in routine clinical practice and research. These three systems were anonymized and then presented in random order to the respondents who were asked to choose only one preferred system or none. None of the three systems reached agreement in the first three rounds, but the majority of the participants (9/16, 56.3%) preferred the new system (system 1), while 31.2% (5/16) and 12.5% (2/16) preferred system 2 (Ai *et al.*[19]) and system 3 (Hoebers *et al.*[7]) respectively. We received feedback from our expert radiologist respondents as well as from the radiologists on our steering committee that there was concern about grading irregular/ill-defined nodal margins as iENE, which could then be used to determine treatment selection. Therefore, the proposed 5-tier classification system was converted into a 4-tier classification system, with irregular/ill-defined nodal margins and extension into perinodal fat amalgamated into one grade. On completing two more rounds of the Delphi process focused on selecting a classification system. strong agreement (13/15, 86%) on the new four-tier classification was achieved (Table 3, Figure 2).

Reasons for preferred classification systems

In the first 3 rounds, we asked the respondents to give reasons for their choice of classification system. They were provided with a list of the six features selected by the steering group, and they could select more than one option. For those who preferred the new system 1, 66.7% (6/9) thought it may improve interobserver agreement between radiologists (increase standardization and consistency of reporting), and 55.6% (5/9) indicated it will likely be a more descriptive/comprehensive system to cover all relevant iENE features. Furthermore, 55.6% (5/9) of the respondents felt system 1 was more likely to be specific (more able to identify cases with *no* ENE compared to other systems). Respondents who chose system 2 (a 3-

tier system) indicated that it is potentially easier to apply or use in clinical practice (5/5, 100%), and also more likely to have high interobserver agreement between radiologists (4/5, 80%).

Discussion

Histopathology is the gold standard for diagnosing ENE. Though iENE is known to be prognostic, it has not yet been integrated into any staging systems or into routine clinical practice in HNSCC. That is in large part due to a lack of consensus around diagnostic imaging features, and lack of an accepted standardized classification system. In these guidelines, using a modified Delphi process, experts from 14 leading national clinical research groups representing 29 countries reached consensus on the definitions and diagnostic criteria of iENE in HNSCC. They also unanimously supported synoptic reporting and the need for a classification system for iENE and the large majority favour a new classification system that we developed based on the results of the consensus achieved here.

We have also developed an atlas which serves as an educational resource for grading iENE using the new HNCIG classification system, which is available for access and download online (www.hncig.org) and which offers detailed and specific guidance using real-life examples. The atlas provides examples of orthogonal views in multiple planes for each of the Grades of iENE. The atlas demonstrates extension into perinodal fat (Grade1 iENE) where one can appreciate spiculated foci of tissue extending clearly beyond the margin of the node. The key to diagnosing Grade 2 iENE is to identify the presence of two or more nodes that have lost any intervening separating tissue planes. The atlas also highlights that coalescent nodes (Grade 2 iENE) are best evaluated by scrolling through images on a PACS system, ideally using multiple orthogonal planes. Whilst they may still have partially visible planes, at least a portion of the periphery has been lost (i.e. is not visible), indicating where the nodes have come together into a common mass. These characteristics are difficult to demonstrate with a solitary axial slice.

Randomised studies have shown that surgically-treated patients who have pENE benefit from postoperative adjuvant chemoradiotherapy, which improves outcomes but also adds significant toxicity[10]. iENE has the potential to determine treatment. If it were possible to reliably and consistently identify iENE before start of treatment, patients with iENE could be offered non-surgical primary chemoradiotherapy, and so avoid the toxicity and cost of tri-modality therapy[23,24]. Alternatively, they may actually benefit from treatment escalation, and so it may be used as an indication for induction chemotherapy or tri-modality treatment.

Furthermore, iENE may have prognostic power in the non-surgical setting. Using images from a randomized controlled trial, a recent study evaluated the prognostic value of iENE diagnosed on CT scans in patients with locally advanced HNSCC treated with concurrent chemoradiotherapy and found pre-treatment iENE to be independently prognostic for clinical response (HR 1.71, 95%CI 1.054-2.786). The authors concluded that it is possible to use iENE as a predictive marker by which to stratify patients into responders versus non-responders and to better tailor therapy[25]. Another study investigated the importance of iENE in HPV-mediated HNSCC and showed that it is a strong prognostic factor (HR for OS= 3.86, $p < 0.001$), so may help better identify patients who are not suitable for deintensification trials. That study proposed a TNM staging system for HPV-mediated HNSCC incorporating iENE, which outperformed the current TNM (8th edition) system[15]. Several other studies have demonstrated prognostic power of iENE in nasopharyngeal cancer, where the presence of a "conglomerate/matted/coalescent" nodal mass has been shown to be an independent prognostic factor for distant metastasis-free survival[26] as well as overall survival (OS)[12]. Other studies have also demonstrated that utilizing iENE to upstage patients with nasopharyngeal cancer and iENE to stage N3 results in better and more accurate staging compared to the current 8th edition of AJCC TNM staging system [20,27,28].

However, despite this plethora of data, iENE is still not implemented in routine clinical practice. That is partly because, in contrast to pENE, there is currently no level I trial evidence for the efficacy of iENE as a determinant of treatment. Furthermore, due to a lack of standardization, existing studies have often used different criteria and definitions, making it difficult to generalize or compare findings. Additionally, there remains wide variability regarding the diagnostic accuracy of pre-treatment imaging in the detection of iENE in HNSCC[2-6]. Several recent systematic reviews and meta-analyses have assessed this. Taken together, the literature suggests that CT, MRI and ultrasound are appropriate methods for identifying iENE, but that they differ in sensitivity and specificity, and that interobserver concordance would likely benefit from more defined classification systems. Furthermore, a multi-centre radiology study demonstrated that a learning curve exists for iENE assessment, and that reliability can therefore be augmented by strategies including consolidated operating definitions and sharing experience among radiologists[7].

The expert radiologists were supportive of using a classification system. The consensus on definitions during this process gave rise to a new classification, which was supported by the majority of experts, reaching strong agreement. We also

provided a template for a synoptic report (**panel 2**). Experts favoured this new classification because it was more likely to have interobserver agreement, more likely to be specific and may be easier to implement in clinical practice. This new classification would need to be validated before its widespread adoption into clinical practice. Specifically, the following characteristics of the new classification system would need to be defined: sensitivity and specificity of detecting pENE, interrater agreement and reproducibility, and the prognostic power of the different grades. If validated, it may lead to trials assessing its utility in determining treatment selection, and especially escalation or de-escalation of treatment according to iENE status.

This study has limitations. Fifteen of the 18 experts completed all five rounds of the process. These experts are academics who are more likely to be cognizant of diagnostic criteria and have higher levels of experience and expertise. Therefore, the generalizability of their views to routine clinical practice remains to be determined. The new four-tier classification system that we proposed will need to be validated in terms of diagnostic accuracy, discrimination, and reproducibility, before wider clinical implementation. However, the strong consensus reached regarding the classification provides for the first time an international consensus that identifies a classification system for international evaluation and routine use if validated.

Conclusion

An essential prerequisite for implementation of iENE into clinical practice is the availability of widely accepted, reliable and consistent definitions and diagnostic criteria, which for the first time is now available through these international guidelines. The experts in our consensus process agreed strongly on the following as criteria for the diagnosis of iENE: Indistinct or irregular nodal margin or border; extension into perinodal fat; extension into adjacent structures such as muscle, skin, glands, neurovascular bundle; and conglomerate/matted/coalescent nodes. Experts also agreed strongly against the use of capsular thickening and central nodal necrosis as criteria. The least agreement between the experts occurred around the naming of features of iENE. Long standing and ingrained labels like matted and conglomerate, or indistinct and irregular, along with the somewhat nebulous nature of the names, meant that there was no agreement on

the best terms to use. However, there was agreement that they should be used interchangeably when it comes to iENE. The expert radiologists also supported and are willing to utilize a standardized classification system and synoptic reporting in their routine clinical practice. Based on this Delphi consensus and existing data, these guidelines will serve to standardize definitions and classifications to aid reporting in both clinical practice and research. We have also proposed a new classification system for the diagnosis of iENE that requires validation before wider clinical implementation.

Contributors

HM, CH and AKA-F conceived the study concept and initiated the study design. HM, CH, AKA-F, **CG, SHH, ADK, WML, LM, AAN, PCN, BO, RR, YX, and EY** were involved in study development, data analysis, and data interpretation of this Policy Review. All authors participated in data collection, manuscript preparation, and approved the final manuscript. HM is a senior investigator for the National Institute for Health Research (NIHR). The views expressed in this Policy Review are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Declaration of interests

HM is the director and a shareholder of Warwickshire Head and Neck Clinic; chair of the Head and Neck Cancer International Group (HNCIG); and past president of the British Association of Head and Neck Oncologists. HM also reports receiving honoraria from AstraZeneca; Speakers Bureau on MSD, Sanofi Pasteur, Merck; research Funding from GSK Biologicals, MSD, Sanofi Pasteur, GSK Plc, AstraZeneca; travel Accommodation Expenses from Sanofi, Pasteur, MSD, Merck. CG received royalties from Elsevier for authoring and editing books and chapters for Elsevier-Amirsys. **WL** declares he is the chair of American Joint Committee on Cancer (AJCC) 9th Version head and neck task force. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [HM], upon reasonable request.

Search strategy and selection criteria

To identify areas of uncertainty in clinical practice regarding the diagnostic features of extranodal extension on imaging (iENE) in head and neck cancer, as well as the available classification systems for iENE reporting, we did a literature search of PubMED, Embase, Medline, and Google that included grey literature, and relevant published guidelines. We used the main search terms ‘head neck cancer’ and (‘radiological extranodal extension’ OR ‘extranodal

extension on imaging' OR 'radiological extracapsular spread' OR 'extracapsular spread on imaging' OR 'radiological extranodal spread' OR 'extranodal spread on imaging' OR 'radiological extracapsular extension' OR 'extracapsular extension on imaging'), and searched for articles published between January 1, 1980, to April 15, 2023. We limited our search to peer-reviewed papers published in English, including systematic reviews, large series papers, and guidelines published by national or international bodies. Discussions between the members of a multidisciplinary steering committee highlighted areas of uncertainty identified in the literature, along with controversies and challenges to clinical practice. All issues were then collated into initial domains and questions formulated by the multidisciplinary steering group. All questions were piloted by expert radiologists for readability, as well as face and content validity. Survey questions and the results of all five rounds are provided in the appendix (**PP 2-9**).

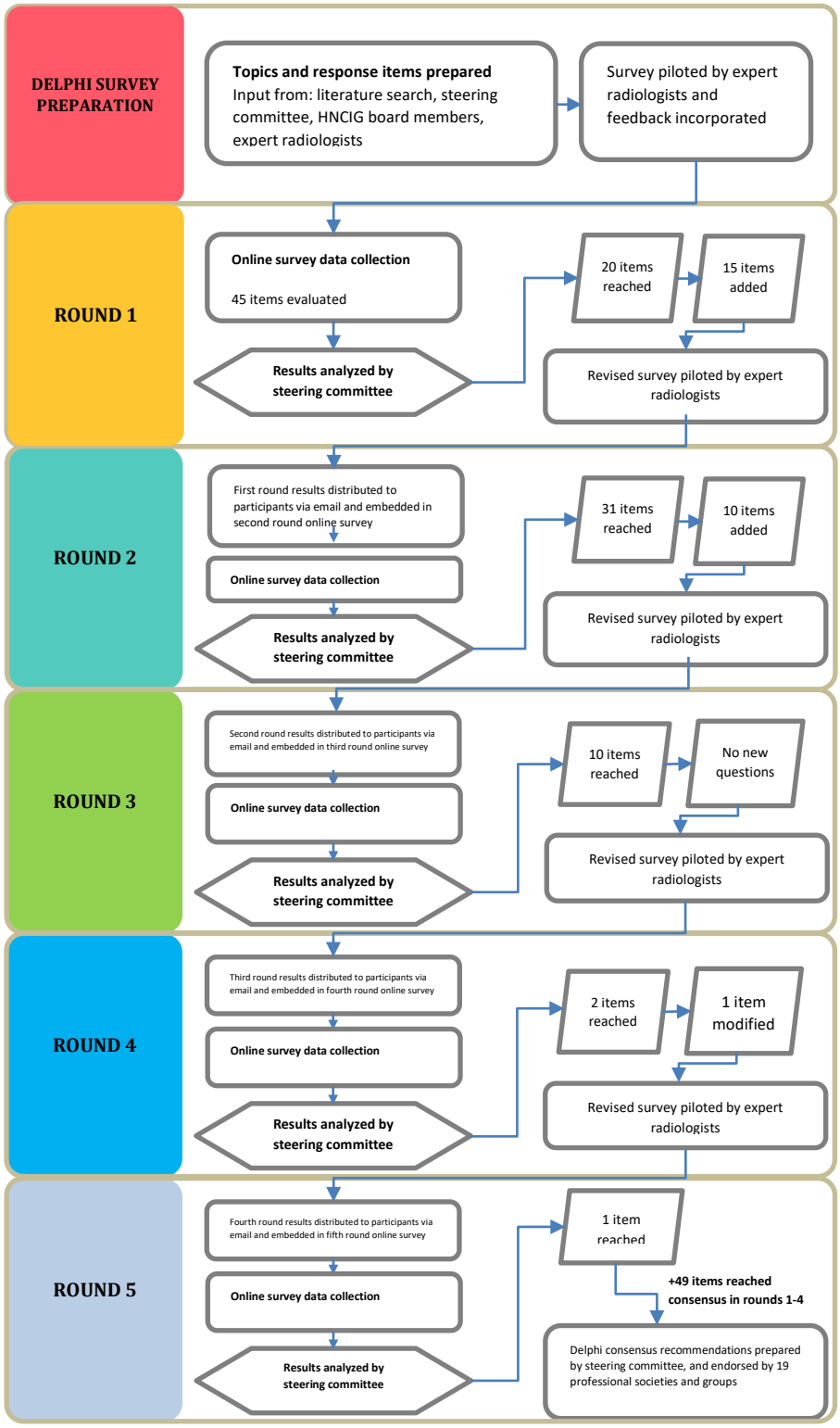


Figure 1: Schematic of the modified Delphi process used to generate these guidelines.

Panel 1: National research groups endorsing the recommendations, in alphabetical order

The Canadian Cancer Trials Group (CCTG)

Cancer Trials Ireland (CTI)

The Danish Head and Neck Cancer Group (DAHANCA)

The Dutch Head and Neck Society (NWHHT)

The Eastern Cooperative Oncology Group & the American College of Radiology Imaging Network (ECOG-ACRIN), USA

The French Head and Neck Cancer Group (GORTEC)

Fudan University Shanghai Cancer (FUSCC), China

The German Interdisciplinary Working Group for Head and Neck Tumours (IAG-KHT)

The Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG)

The Hellenic Cooperative Oncology Group (HeCOG), Greece

Hong Kong Nasopharyngeal Cancer Study Group (HKNPCSG)

The Latin American Cooperative Oncology Group (LACOG)

The National Cancer Centre Singapore (NCCS)

The National Cancer Research Institute-UK (NCRI)

Northwest Italian Oncology Group (GONO)

NRG Oncology, USA

The Spanish Foundation for the Treatment of Head and Neck Tumours Group (FETTCC)

TATA medical centre (TMC), India

Trans-Tasman Radiation Oncology Group (TROG), Australia and New Zealand

Figure 2. Example of the impact of prior core needle biopsy on interpretation of iENE

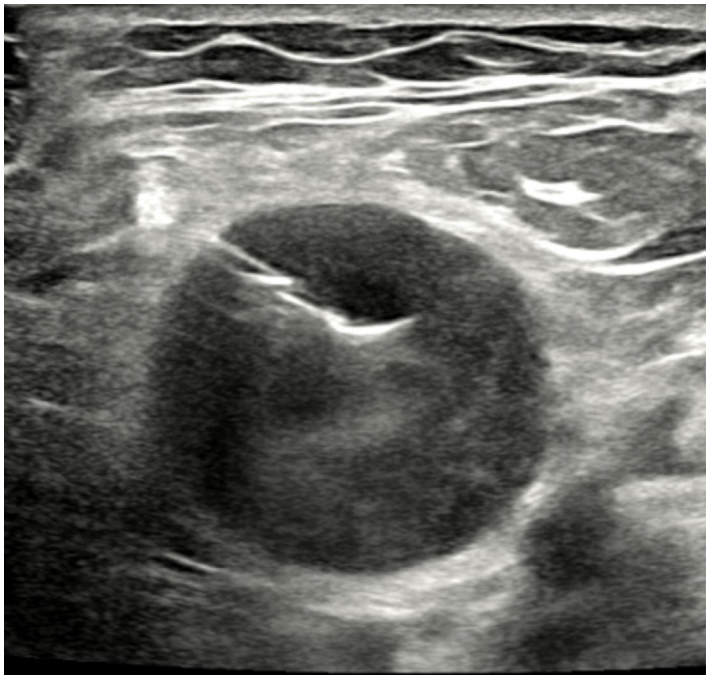
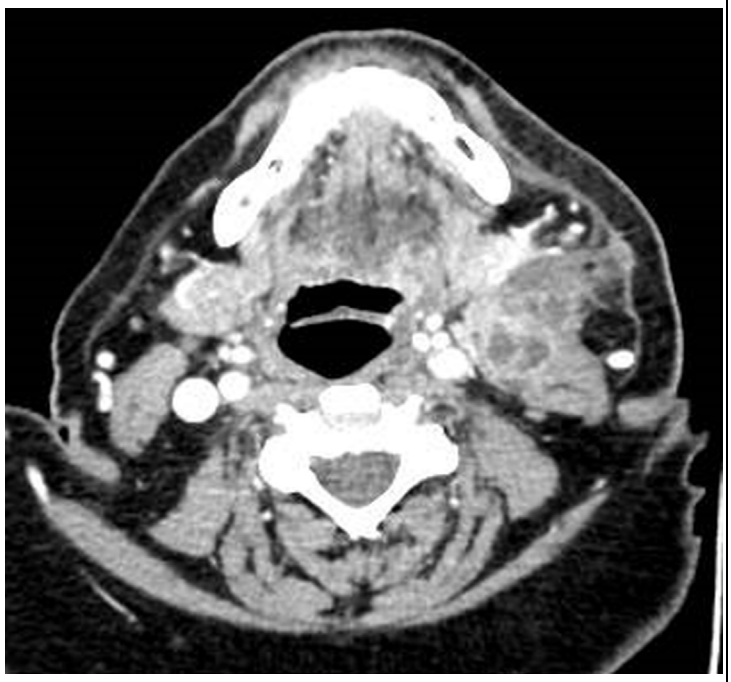
Left level II transverse ultrasound during core needle biopsy, with node showing no evidence of iENE. This patient bled following the procedure.	CT neck with contrast 72 hours later. The appearance of the Left neck node and surrounding tissue changes could easily be mistaken for Grade 3 iENE.
	

Table 1. Consensus recommendations for extranodal extension on imaging

	Agreement Level
Indistinct or irregular nodal margin or border	
Should be used as a criterion by which to identify iENE	Strong agreement
Correlates with 'suspicious for'(60-90% likelihood of) pENE	Strong agreement
Can be applied to CT and MRI interpretation	Strong agreement
Should **not** be applied to ultrasound interpretation	Agreement
Can be applied to both HPV-mediated and non-HPV related cancers	Strong agreement
"Indistinct" and "irregular" nodal margins do **not** describe different iENE features	Strong agreement
"Indistinct" and "irregular" nodal margins should **not** be used as two independent criteria for iENE	Agreement
Extension into perinodal fat	
Should be used as a criterion by which to identify iENE	Strong agreement
Correlates with "consistent with" (>90%) likelihood of pENE	Agreement
Can be applied to CT and MRI interpretation	Strong agreement
Should **not** be applied to ultrasound interpretation	Strong agreement
Can be applied to both HPV-mediated and non-HPV related cancers	Strong agreement
Distance of invasion into perinodal fat should **not** be taken into account to diagnose iENE	Strong agreement
Extension into adjacent structures such as muscle, skin, glands, neurovascular bundle	
Should be used as a criterion by which to identify iENE	Strong agreement
Correlates with "consistent with" (>90%) likelihood of pENE	Strong agreement
Can be applied to CT and MRI interpretation	Strong agreement
Can be applied to ultrasound interpretation	Strong agreement

Type or number of sites of involved adjacent structures (such as muscle, skin, glands, etc.) should **not** be taken into account when determining presence or absence of iENE	Strong agreement
Can be applied to both HPV-mediated and non-HPV related cancers	Strong agreement
Conglomerate / matted / coalescent nodes	
Should be used as a criterion by which to identify iENE	Strong agreement
Correlates with "suspicion for" (60-90%) likelihood of pENE	Agreement
Can be applied to CT and MRI interpretation	Strong Agreement
Can be applied to ultrasound interpretation	Agreement
The specific number of nodes involved does **not** need to be taken into account to diagnose iENE	Strong agreement
Can be applied to both HPV-mediated and non-HPV related cancers	Strong agreement
"Conglomerate", "matted", and "coalescent" do **not** describe different things	Strong Agreement
One of these three terms preferred over the others.	No agreement
Central nodal necrosis	
Should **not** be used as a criterion by which to identify iENE	Strong agreement
Capsular thickening	
Should **not** be used as a criterion by which to identify iENE	Strong agreement
Core biopsy effect on reporting	
History of recent core biopsy from same area influences interpretation of early iENE	Strong agreement
Can **not** make an accurate diagnosis and report of iENE if the history of recent core biopsy was not available	No agreement
Use of classification systems and synoptic reporting	
Support use of a standardized classification system for iENE	Strong agreement

Willing to utilize standardized synoptic reporting for iENE in routine clinical practice	Strong agreement

HPV= Human papillomavirus.
Strong agreement indicates a threshold of 80% and above. Agreement indicates a threshold of 67% and above after the third round for statements not considered to have reached a strong agreement.

Table 2: Published classification systems for grading likelihood of iENE

System A **(**Ai *et al.*[19] **)**	3-tier system: Grade 0: node without iENE Grade 1: node with ENE infiltrating surrounding fat Grade 2: node with ENE infiltrating adjacent muscle and/or skin and/or salivary glands
System B (Lu *et al.*[20]**)**	4-tier system: ENE Grade 1: overt LN with infiltration into surrounding fat plane only ENE Grade 2: coalescent LNs (comprised of ≥2 LNs) with clear evidence of iENE) ENE Grade 3: tumor invading beyond LN capsule into adjacent structures (i.e. muscles, nerves, parotid glands, etc.) ENE negative: All other cases with none of these radiological features of iENE or those that are Equivocal/uncertain cases
System C (Hoebers *et al.*[7]**)**	4-tier system: Grade 1 iENE: Tumor invasion through the nodal capsule of an individual LN with unambiguous ill-defined nodal border(s), but confined to perinodal fat Grade 2 iENE: Tumor invasion through the nodal capsules of two or more inseparable adjoining nodes exhibiting unambiguous effacement of any component of their internodal plane(s) (implying replacement by tumor, that is, extranodal extension), which invariably produces a lobulated appearing nodal mass Grade 3 iENE: Tumor invading beyond perinodal fat to overtly invade or encase adjacent structures, for example, skin, muscle, neurovascular structures, etc. ENE negative: All other cases with none of these radiological features of iENE, or cases which are equivocal or uncertain

Table 3: The new HNCIG classification system for iENE

iENE negative (Grade 0): None of the radiological features of iENE below

iENE Grade 1: Clearly irregular or ill-defined nodal margins and/or extension into and confined to perinodal fat

iENE Grade 2: Clear invasion through two or more inseparable adjoining lymph nodes, also known as conglomerate or matted or coalescent nodes +/- grade 1 features

iENE Grade 3: Clear extension into adjacent structures such as muscle, skin, glands, neurovascular bundle +/- grade 1 or 2 features

Notes: In your textual report, please indicate all features that are clearly present, and any features that are equivocal. Then please indicate the highest overall grade of features that are clearly present.

If a feature is equivocal – then it is considered as '*absent*' in terms of grade.

E.g., if a case has clear extension into perinodal fat but equivocal presence of coalescent nodes, then the case is assigned Grade 1, not Grade 2

Criterion / **iENE Grade**	**Clearly irregular or ill-defined nodal margins**	**Clear extension into perinodal fat**	**Clear invasion through two or more inseparable adjoining nodes- conglomerate/matted/ coalescent nodes**	**Clear extension into adjacent structures such as muscle, skin, glands, neurovascular bundle**
iENE grade 0	-	-	-	-
iENE grade 1	**+**	+/-	-	-
iENE grade 1	+/-	**+**	-	-
iENE grade 2	+/-	+/-	**+**	-
iENE grade 3	+/-	+/-	+/-	**+**

+ means feature clearly present

- means feature absent *or equivocal*

+/- presence not essential for diagnosis of that grade

Panel 2: Template for a proposed synoptic report

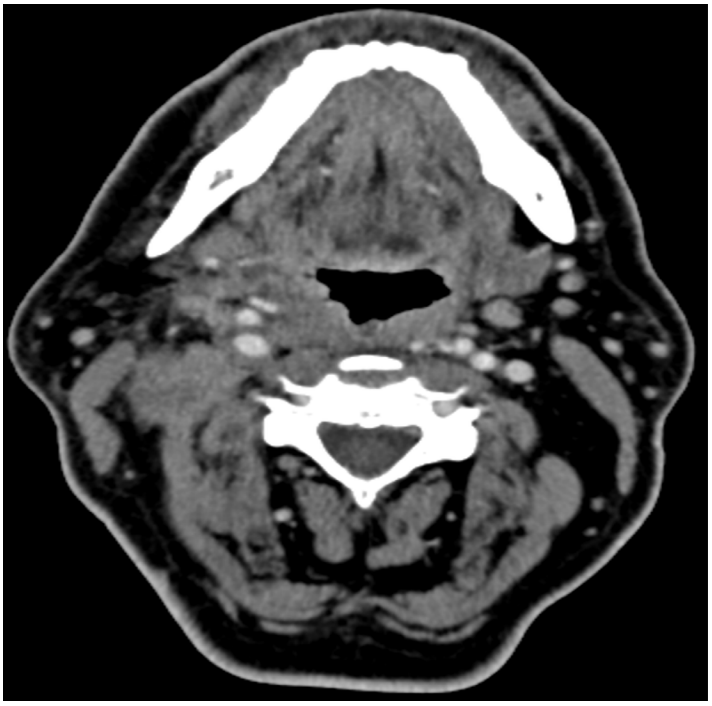
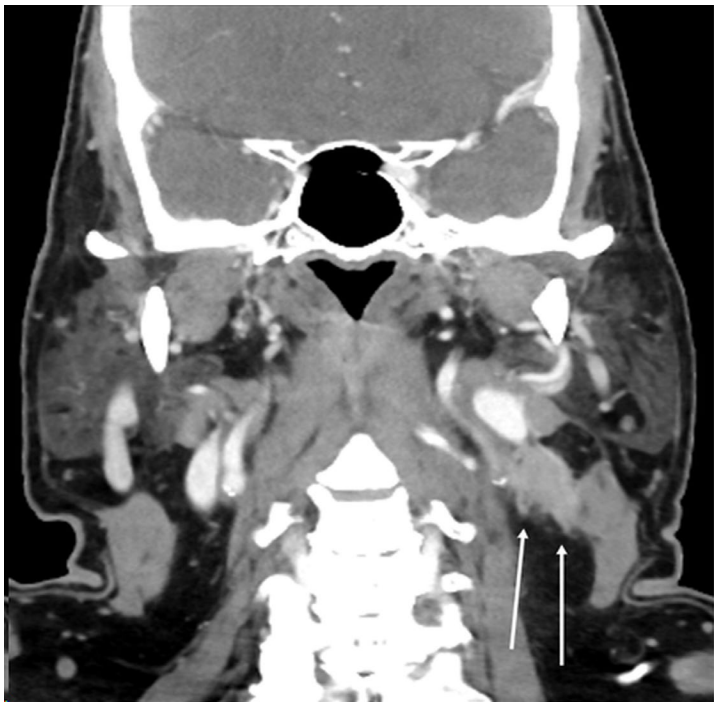
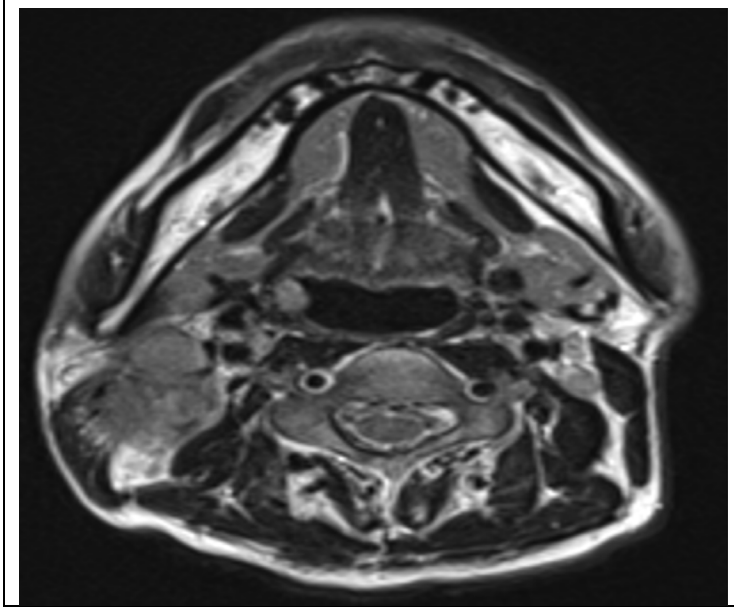
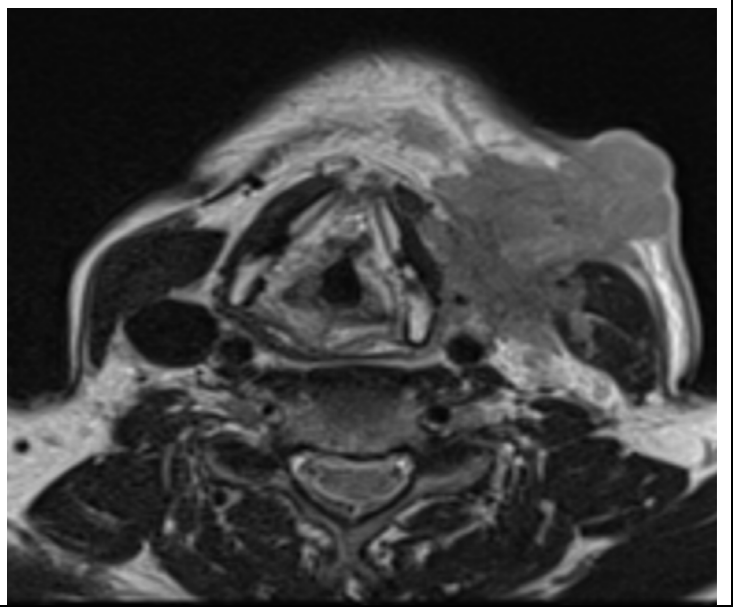
HNCIG iENE Synoptic reporting form template

Was a core biopsy done? Yes/no/not known If yes, date:

	Present/ absent /equivocal
Clearly irregular or ill-defined nodal margins	
Clear extension into perinodal fat	
Clear invasion through the capsules of two or more adjoining nodes, fusing into one another with loss of the intervening nodal capsules and planes, also known as conglomerate or matted or coalescent nodes	
Clear extension into adjacent structures such as muscle, skin, glands, neurovascular bundle	
Overall HNCIG iENE grade (0-3)	

Textual description (including any equivocal or other features):

Figure 3: Examples of criteria included in the HNCIG iENE classification (Images courtesy of Dr. Eugene Yu, Toronto, Canada and Dr. Alex Nagelschneider, Rochester, USA)

iENE Grade 1: Clearly irregular or ill-defined nodal margins (axial CT with contrast)	**iENE Grade 1:** Clear extension into perinodal fat (coronal CT with contrast)
	
iENE Grade 2: Conglomerate/matted/coalescent nodes – effacement of the capsules of two or more adjoining lymph nodes, fusing into one another with loss of the intervening internodal planes (axial T2-weighted MRI)	**iENE Grade 3:** Clear extension into adjacent structures such as muscle, skin, glands, neurovascular bundle (axial T2-weighted MRI)
	

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