Head and Neck Cancer Consensus Recommendations 2

Criteria for the diagnosis of extranodal extension detected on radiological imaging in head and neck cancer: Head and Neck Cancer International Group consensus recommendations

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Extranodal extension of tumour on histopathology is known to be a negative prognostic factor in head and neck cancer. Compelling evidence suggests that extranodal extension detected on radiological imaging is also a negative prognostic factor. Furthermore, if imaging detected extranodal extension could be identified reliably before the start of treatment, it could be used to guide treatment selection, as patients might be better managed with non-surgical approaches to avoid the toxicity and cost of trimodality therapy (surgery, chemotherapy, and radiotherapy together). There are many aspects of imaging detected extranodal extension that remain unresolved or are without consensus, such as the criteria to best diagnose them 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 imaging detected extranodal extension to harmonise clinical practice and research. These recommendations have been endorsed by 19 national and international organisations, representing 34 countries. We propose a new classification system to aid diagnosis, which was supported by most of the participating experts over existing systems, and which will require validation in the future. Additionally, we have created an online educational resource for grading imaging detected extranodal extensions.

Introduction

Despite improvements in cure rates with treatment advances for head and neck squamous cell carcinoma with the increasing proportion of human papillomavirus (HPV)-mediated disease, outcomes remain poor in locally advanced cases. Up to 30–40% of patients relapse following curative-intent treatment, and consequently have a low chance of cure.[1]

In recent years, our ability to identify patient groups on the basis of differential prognosis has resulted in refinements to the staging system for head and neck squamous cell carcinoma and more appropriately tailored treatments. One of the most notable changes between the latest editions of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer stage classifications for head and neck squamous cell carcinoma was the incorporation of clinical extranodal extension to the staging system for HPV-negative disease.[2] Extranodal extension is the growth of nodal metastatic disease beyond the capsule of the specific lymph node. Extranodal extension reflects tumour aggressiveness and presents as a spectrum, ranging from early stages that can only be detected microscopically on histopathology, to intermediate stages detected on radiological imaging, to the most advanced stages, which are identified overtly on clinical examination.

In locally advanced head and neck squamous cell carcinoma, the presence of histology detected extranodal extension constitutes a high-risk feature for disease progression and metastasis.[3,4] In surgically treated patients with histology detected extranodal extension, evidence from randomised trials supports the addition of concurrent chemotherapy to adjuvant radiotherapy to reduce relapse and improve overall survival.[3] Compelling evidence suggests that imaging detected extranodal extension also carries prognostic importance in both HPV-negative and HPV-positive head and neck squamous cell carcinoma.[5–9] Studies show that imaging detected extranodal extension exhibits a sensitivity of 60–80% and specificity of 72–96% to predict histological extranodal extension.[10–12] Systematic reviews and meta-analyses show that imaging detected extranodal extension is also associated with poorer prognosis, with a higher hazard ratio (HR) for mortality compared with histology detected extranodal extension in patients with HPV-mediated oropharyngeal cancer.[5,10]

For imaging detected extranodal extension, diagnosis relies on clinical or radiological examination without histopathological confirmation. The ability to diagnose

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extranodal extensions accurately from radiologic assessment has the potential to result in considerable changes in management. For example, patients with oropharyngeal cancer with a high risk of extranodal extension on the basis of diagnostic imaging might 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 imaging detected extranodal extension is a new concept for the radiology community, there is no expert consensus on or standardisation of the diagnostic criteria by which to define imaging detected extranodal extension, or on the best classification system to describe the extent of the extranodal extension. For this reason, we assembled a group of international head and neck squamous cell carcinoma radiology experts representing 14 national clinical research bodies spanning 29 countries, to generate consensus on terminology and criteria for imaging detected extranodal extension 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 consisted of expert head and neck radiologists, surgeons, and oncologists, who led the overall study design and execution (names provided in the appendix p 53).

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 practising head and neck radiologists, a national or international expert, and be willing to complete all rounds of the online modified Delphi process. 14 of the 21 invited organisations provided nominations, all of whom participated in the process and were included in the manuscript authorship. The participating organisations were: the Danish Head and Neck Cancer Group, the Dutch Head and Neck Society, the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network, the French Head and Neck Cancer Group, Fudan University Shanghai Cancer Center, the German Interdisciplinary Working Group for Head and Neck Tumors, the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group, the Hellenic Cooperative Oncology Group, Hong Kong Nasopharyngeal Cancer Study Group, the Latin American Cooperative Oncology Group, the National Cancer Centre Singapore, the National Cancer Research Institute UK, NRG (National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group, and the Imaging and Radiation Oncology Core) Oncology, and the Spanish Head and Neck Cancer Cooperative Group. The names of the representatives for each of these groups is provided in the appendix (p 53).

Consensus process and data collection

To achieve consensus, a modified Delphi process was conducted online over five rounds using methods described previously.[13] In brief, the nominated expert head and neck radiologists were invited to complete an online questionnaire, delivered by the Qualtrics online survey platform. The survey included four main sections: criteria for diagnosing extranodal extension by imaging, inter-observer agreement for the criteria, the effect of core biopsy on the diagnosis, and classification systems for 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 preferred most by the experts and refined the 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 validity and content validity.

For questions on the criteria for diagnosing imaging detected extranodal extension, participants were asked about the degree with which these proposed criteria correlated with histology detected extranodal extension. They were given the following options: consistent correlation with histology detected extranodal extension (more than 90% correlation), suspicious for histology detected extranodal extension (60–90%), and possible (30–60%) and unlikely correlation with histology detected extranodal extension (<30%). For questions on the degree of inter-observer agreement, respondents were given the following scale: 1 (very low likelihood of inter-observer 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 3 days before the deadline. After each round, data were collated and analysed, and predetermined criteria for agreement were applied. These criteria were extrapolated from the RAND methodology:[14] consensus of 80% and above indicated strong agreement for a statement, 67–79% suggested agreement, 21–66% signified no agreement, and 20% or less signified strong agreement against a statement (ie, rejection of a statement). A statement was removed from the next round either when strong agreement for or against was reached, or after completion of all rounds, whichever occurred first.[15]

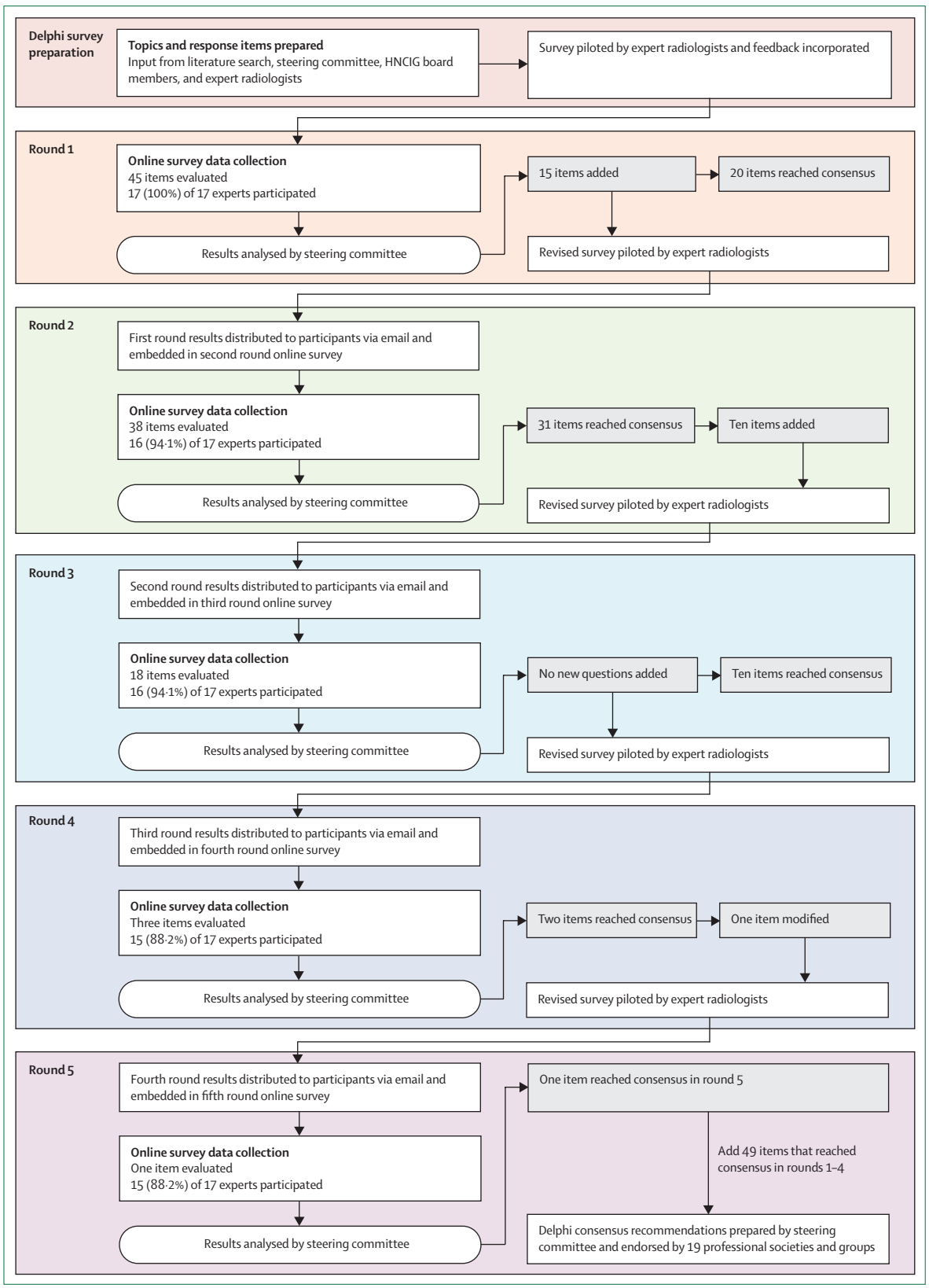

Figure 1: **Schematic of the modified Delphi process used to generate the guidelines**
HNCIG=Head and Neck Cancer International Group.

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See **Online** for appendix

For the **Qualtrics online survey platform** see https://www.qualtrics.com/uk/?rid=ip&prevsite=en&newsite=uk&geo=GB&geomatch=uk

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 pathological assessment for the detection of extranodal extensions, the goal of the project was to recognise the use of imaging based detection 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 specific 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.

Results

Process

18 expert nominees representing 14 research groups, spanning 29 countries, participated in this study, as the Dutch, Fudan, Japanese, and Spanish groups had two representatives each. The full list is provided in the appendix (p 53). In total, 15 (83·3%) of 18 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 an alternative from their group. One person was missing from the fourth and fifth rounds and was not replaced.

In total, 45 questions were asked in the first round, 38 questions in the second round, and 18 questions in the third round. 20 of 45 questions were removed from the first round and 31 of 38 questions from the second round, after reaching strong agreement for or against. Only eight of the 18 questions asked in the third round failed to achieve any form of agreement (ie, 21–66% agreement). The reported rates of agreement reflect when the item first reached one of the agreement thresholds, which might have been after one or more rounds of questioning. Full results and agreement levels of the questions asked in all rounds are provided in the appendix (pp 54–61). The final recommendations were endorsed by 19 national and international head and neck cancer clinical research groups, representing 34 countries (panel 1).

***Panel 1*: National and international research groups endorsing the recommendations**

- 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 Center (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), Singapore
- The National Cancer Research Institute (NCRI), UK
- 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

Criteria for extranodal extension on imaging

A summary of the consensus findings for ENE on imaging is provided in panel 2.

Indistinct or irregular nodal margin or border

All 17 experts agreed unanimously that "indistinct or irregular nodal margin or border" should be considered a criterion for imaging detected extranodal extension. 14 (87·5%) of 16 respondents agreed that this finding could be considered as "suspicious for" on histology detected extranodal extension (60–90% correlation) rather than "consistent with", "possible", or "unlikely" to be on histology detected extranodal extension. All 17 (100%) experts reached strong agreement that this criterion can be applied when using CT scans and 16 (94·1%) agreed with MRI scans, and there was agreement that this criterion cannot be applied when interpreting ultrasound images, with 11 (68·8%) of 16 experts advising against. The panel did not reach agreement regarding the inter-observer agreement of irregular or ill-defined nodal margins on imaging. However, eight (50%) of the 16 respondents thought this criterion might have a "good likelihood" for inter-observer agreement.

There was unanimous agreement of all 16 (100%) experts that "indistinct or irregular nodal margin or border" can be applied as a criterion for the diagnosis of imaging detected extranodal extension in both HPV-associated oropharyngeal carcinoma, and for all non-HPV related head and neck cancers, including HPV-negative oropharyngeal and nasopharyngeal carcinoma.

Based on feedback from the expert respondents, we added a question in rounds two to four regarding whether

***Panel 2*: Consensus recommendations for extranodal extension on imaging**

Strong agreement indicates a threshold of 80% and above. Agreement indicates a threshold of 67% and above for statements that did not reach a strong agreement after the fifth round.

Indistinct or irregular nodal margin or border

- Strong agreement: should be used as a criterion by which to identify imaging-detected extranodal extension
- Strong agreement: indistinct or irregular nodal margin correlates with "suspicious for" extranodal extension of tumour on histopathology (60–90% likelihood of correlation)
- Strong agreement: can be applied to CT and MRI interpretation
- Agreement: should not be applied to ultrasound interpretation
- Strong agreement: can be applied to both HPV-mediated and non-HPV-related cancers
- Strong agreement: "indistinct" and "irregular" nodal margins do not describe different features
- Agreement: "indistinct" and "irregular" nodal margins should not be used as two independent criteria for imaging detected extranodal extension

Extension into perinodal fat

- Strong agreement: should be used as a criterion by which to identify imaging detected extranodal extension
- Agreement: extension into perinodal fat is considered "consistent with" histology detected extranodal extension (>90% likelihood of correlation)
- Strong 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 imaging detected extranodal extension

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

- Strong agreement: should be used as a criterion by which to identify imaging detected extranodal extension
- Strong agreement: extension into adjacent structures is considered "consistent with" histology detected extranodal extension (>90% likelihood of correlation)
- 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 (eg, muscle, skin, glands, etc) should not be taken into account when determining presence or absence of imaging detected extranodal extension
- Strong agreement: can be applied to both HPV-mediated and non-HPV-related cancers

Conglomerate, matted, and coalescent nodes

- Strong agreement: should be used as a criterion by which to identify imaging detected extranodal extension
- Strong agreement: conglomerate, matted, and coalescent nodes correlate with "suspicion for" histology detected extranodal extension (60–90% likelihood of correlation)
- Strong agreement: can be applied to CT and MRI interpretation
- Agreement: can be applied to ultrasound interpretation
- Strong agreement: the specific number of nodes involved does not need to be taken into account to diagnose imaging detected extranodal extension
- 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
- No agreement: one of these three terms preferred over the others

Central nodal necrosis

- Strong agreement: should not be used as a criterion by which to identify imaging detected extranodal extension

Capsular thickening

- Strong agreement: should not be used as a criterion by which to identify imaging detected extranodal extension

Core biopsy effect on reporting

- Strong agreement: history of recent core biopsy from the same area influences interpretation of early imaging detected extranodal extension
- No agreement: cannot make an accurate diagnosis and report of imaging detected extranodal extension if the history of recent core biopsy was not available

Use of classification systems and synoptic reporting

- Strong agreement: support use of a standardised classification system for imaging detected extranodal extension
- Strong agreement: willing to utilise standardised synoptic reporting for imaging detected extranodal extension in routine clinical practice

there is a difference between "indistinct (ill-defined)" versus "irregular" nodal contour or margin. The participants reached strong agreement against there being a difference between these two terms, with only two (13%) of 15 reporting a difference. Importantly, 12 (75%) of 16 agreed that these two features should be combined and not be considered as two independent criteria for imaging detected extranodal extension.

Extension into perinodal fat

12 (75%) of 16 experts reached agreement that the finding of "extension into perinodal fat" on imaging denotes "consistent with" histology detected extranodal extension (ie, denotes >90% confidence in the presence of histology detected extranodal extension). All 17 (100%) experts were in strong agreement that this criterion can be applied when using CT scans and MRI. 14 (87·5%) of 16 experts also reached strong agreement against using this criterion when interpreting ultrasound images. There was also strong agreement against taking "distance of invasion into perinodal fat" into account when diagnosing imaging detected extranodal extension, with only two (12·5%) of 16 respondents answering in favour. 13 (81·3%) of 16 respondents were in strong agreement that extension into perinodal fat has at least "good likelihood" of inter-observer agreement between radiologists, with 11 (68·8%) reporting "good" and two (12·5%) reporting "very high likelihood". 13 (81·3%) of 16 respondents were in strong agreement that this criterion can be applied for the diagnosis of imaging detected extranodal extension in HPV-associated oropharyngeal carcinoma, and all 16 respondents agreed this for all non-HPV related HNSCCs, including HPV-negative oropharyngeal and nasopharyngeal carcinoma.

Extension into adjacent structures

All 17 (100%) experts unanimously agreed that "extension into adjacent structures such as muscle, skin, glands, or neurovascular bundle" should be considered a criterion for diagnosing imaging detected extranodal extension. 15 (88·2%) of 17 experts indicated strong agreement that this finding is "consistent with" histology detected extranodal extension, indicating that it would give them more than 90% confidence in the presence of histological evidence. All 17 (100%) respondents were in strong agreement that this criterion could be applied when using CT scans and MRI scans, and 15 (93·8%) of 16 experts agreed for its use for ultrasound. 15 (93·8%) of 16 experts strongly agreed that the site or number of sites of involved adjacent structures (eg, muscle, skin, glands, etc) should not be considered when determining the presence or absence of imaging detected extranodal extension. All 16 (100%) experts agreed unanimously that the criterion of "extension into adjacent structures" is associated with at least "good likelihood" of inter-observer agreement, including 11 (68·8%) agreeing on "very high likelihood" and five (31·3%) agreeing on "good likelihood".

15 (93·8%) of 16 experts strongly agreed that this criterion can be applied for the diagnosis of imaging detected extranodal extension in HPV-associated oropharyngeal carcinoma, and 16 (100%) agreed for all non-HPV related head and neck squamous cell carcinomas, including HPV-negative oropharyngeal and nasopharyngeal carcinoma.

Conglomerate, matted, and coalescent nodes

14 (87·5%) of 16 experts agreed strongly 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 imaging detected extranodal extension. 11 (68·7%) of 16 experts agreed that this finding is "suspicious for" histology detected extranodal extension, indicating 60–90% correlation in this criterion. 15 (88·2%) of 17 experts strongly agreed that this criterion can be applied when using CT scans and 15 (88·2%) agreed for MRI scans, and 11 (68·7%) agreed that this criterion can also be applied to ultrasound scans.

13 (92·9%) of 14 experts were in strong agreement that if extension between nodes is seen, the number of nodes involved does not need to be considered for the diagnosis. 14 (87·5%) of 16 strongly agreed that this criterion indicated at least "good likelihood" of inter-observer agreement, including nine (56·3%) deciding "very high likelihood" and five (31·3%) choosing "good likelihood". All 16 (100%) were also in strong agreement that the criterion of "conglomerate/matted/coalescent" nodes can be applied for the diagnosis of imaging detected extranodal extension in HPV-associated oropharyngeal carcinoma and 12 (85·7%) of 14 agreed for all non-HPV related primary head and neck carcinoma.

14 (93·3%) of 15 participants also reached strong agreement that there is no 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 imaging detected extranodal extension. There was no agreement on which of these three terms would be the most preferred to be used in that context, with seven (43·7%) of 16 participants favouring "conglomerate", five (31·3%) favouring "matted", and four (25%) favouring "coalescent".

Capsular thickening and central node necrosis

13 (81·3%) of 16 experts agreed strongly against the use of "capsular thickening" as a criterion by which to diagnose imaging detected extranodal extension. 15 (93·8%) experts agreed strongly against "central nodal necrosis", also known as significant "intranodal heterogeneity", being a criterion for imaging detected extranodal extension.

Additional criteria for consideration

Only six (35·3%) of the 17 respondents in the first round and one (5·9%) of 16 in the second round proposed additional criteria to be considered for imaging detected extranodal extensiondiagnosis, including lymph node size and increased avidity on PET. These criteria were deemed by the steering group as not particularly specific to imaging detected

extranodal extension diagnosis and were not considered for subsequent rounds.

Effects of recent core biopsy on the interpretation of imaging detected extranodal extension

15 (93·8%) of 16 respondents were in strong agreement that a history of a recent core biopsy from the same area would influence their interpretation of early imaging detected extranodal extension in that area. 11 (56·2%) of 16 on the expert radiology panel indicated they would not be able to make an accurate diagnosis and report of imaging detected extranodal extension if the history of recent core biopsy was not available, but that statement did not reach agreement. In figure 2, we provide an example that shows how a core biopsy can confound the identification of extranodal extension in a lymph node.

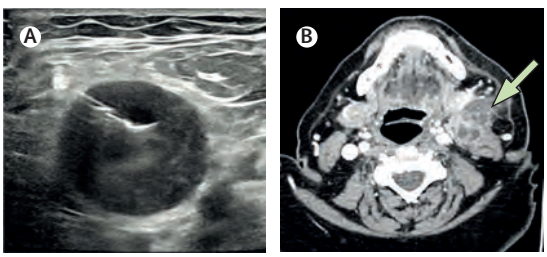

Figure 2: **Example of the effect of previous core needle biopsy on the interpretation of imaging detected extranodal extension**
(A) Left level II transverse ultrasound during core needle biopsy, with node showing no evidence of extranodal extension. This patient bled following the procedure. (B) CT neck with contrast 72 hours later. The appearance of the left neck node and surrounding tissue changes could easily be mistaken for grade 3 imaging detected extranodal extension.

Classification systems for imaging detected extranodal extension reporting

Standardised classification systems and synoptic reporting

All 17 (100%) respondents unanimously supported the use of a standardised classification system for imaging detected extranodal extension, and all 17 (100%) said they would be willing to use standardised synoptic reporting for imaging detected extranodal extensions in their routine practice. When asked if they are aware of any existing classification systems for imaging detected extranodal extension diagnosis, only six (35·3%) of 17 participants indicated that they are aware of the classification system proposed by Hoebers and colleagues,[16] two (11·8%) stated that they are aware of the classification system described by Ai and colleagues,[17] and one (5·9%) person was aware of the classification systems described by Lu and colleagues,[18] Chai and colleagues,[19] and Elsholtz and colleagues.[20] The steering group removed the systems described by Chai and colleagues[19] and Elsholtz and colleagues[20] from subsequent rounds as these were not considered to be true classification systems for imaging detected extranodal extension.

The three remaining published systems were anonymised, then presented in a random order to the respondents to rank in relation to each other with regards to their usefulness for undertaking the diagnosis and reporting of imaging detected extranodal extension in routine clinical practice and research (panel 3). Ai and colleagues[17] (system A) was ranked first with a weighted average score of 37 (77·1%) of 48, while Hoebers and colleagues[16] (system C) was second and scored 30 (62·5%), and Lu and colleagues[18] (system B) ranked third and scored 29 (60%).

On the basis of the emerging consensus and the findings of this Delphi process, the steering group proposed a new classification system for imaging detected extranodal extension diagnosis. The goal of introducing a new, consensus-based system is to enhance detection of extranodal extension by imaging 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 and colleagues[17] (system 2) and Hoebers and colleagues[16] (system 3)—with regards to their usefulness for the diagnosis and reporting of imaging detected extranodal extension in routine clinical practice and research. These three systems were anonymised and then presented in

Panel 3: **Published classification systems for grading likelihood of imaging detected extranodal extension**

System A: Ai et al (2019)[17]
- Three-tier system
- Grade 0: node without imaging-detected extranodal extension
- Grade 1: node with extranodal extension infiltrating surrounding fat
- Grade 2: node with extranodal extension infiltrating adjacent muscle, skin, or salivary glands

System B: Lu et al (2019)[18]
- Four-tier system
- Grade 1: overt lymph node with infiltration into surrounding fat plane only
- Grade 2: coalescent lymph nodes (comprised of ≥2 lymph nodes with clear evidence of imaging detected extranodal extension)
- Grade 3: tumour invading beyond lymph node capsule into adjacent structures (ie, muscles, nerves, parotid glands, etc)
- Negative: all other cases with none of the radiological features of imaging detected extranodal extension or those that are equivocal or uncertain cases

System C: Hoebers et al (2022)[16]
- Four-tier system
- Grade 1: tumour invasion through the nodal capsule of an individual lymph node with unambiguous ill-defined nodal border, but confined to perinodal fat
- Grade 2: tumour invasion through the nodal capsules of two or more inseparable adjoining nodes exhibiting unambiguous effacement of any component of their internodal planes (implying replacement by tumour, that is, extranodal extension), which invariably produces a lobulated appearing nodal mass
- Grade 3: tumour invading beyond perinodal fat to overtly invade or encase adjacent structures; for example, skin, muscle, neurovascular structures, etc
- Negative: all other cases with none of these radiological features of imaging detected extranodal extension, or cases that are equivocal or uncertain

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

The four-tier classification was developed by the Delphi process. In the textual report, all features that are clearly present, and any features that are equivocal should be indicated. The highest overall grade of features that are clearly present should also be noted. If a feature is equivocal, it is considered as absent in terms of grade. For example, if a case has clear extension into perinodal fat, but there is equivocal presence of coalescent nodes, then the case is assigned grade 1 and not grade 2. +=feature clearly present. –=feature absent or equivocal. +/–=presence not essential for diagnosis of that grade. Grade 0=negative, none of the radiological features of imaging detected extranodal extension from grades 1–3. Grade 1=clearly irregular or ill-defined nodal margins or extension into and confined to perinodal fat, or both. Grade 2=clear invasion through two or more inseparable adjoining lymph nodes, also known as conglomerate or matted or coalescent nodes +/– grade 1 features. Grade 3=clear extension into adjacent structures, such as muscle, skin, glands, and the neurovascular bundle +/– grade 1 or 2 features.

Table: **Proposed four-tier classification system for imaging detected extranodal extension**

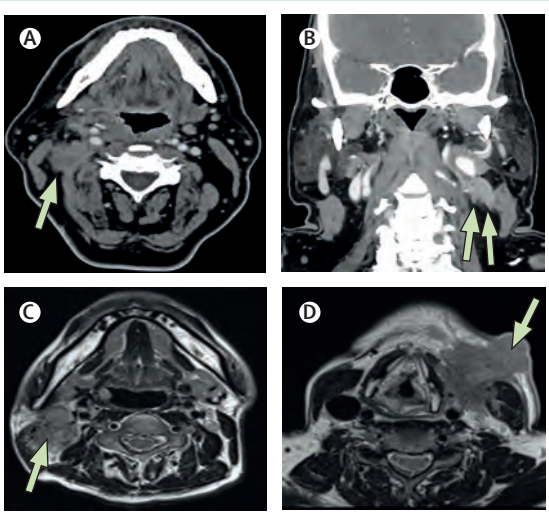

Figure 3: **Examples of criteria included in the classification of imaging detected extranodal extension by the Head and Neck Cancer International Group**
(A) Grade 1: clearly irregular or ill-defined nodal margins (axial CT with contrast). (B) Grade 1: clear extension into perinodal fat (coronal CT with contrast). (C) Grade 2: conglomerate, matted, or 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). (D) Grade 3: clear extension into adjacent structures such as muscle, skin, glands, or the neurovascular bundle (axial T2-weighted MRI). Images provided by EY and AAN.

random order to the respondents who were asked to choose one preferred system only or none. No agreement was reached in the first three rounds, but nine (56·3%) of 16 participants preferred the new system (system 1), while five (31·2%) preferred system 2 and two (12·5%) preferred system 3. We received feedback from our expert radiologist respondents and from the radiologists on our steering committee that there was concern about grading irregular or ill-defined nodal margins as imaging detected extranodal extension, which could then be used to decide treatment selection. Therefore, the proposed five-tier classification system was converted into a four-tier classification system, with irregular and 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, there was strong agreement with 13 (86%) of 15 experts agreeing on the new four-tier classification (table, figure 3).

Reasons for preferred classification systems

In the first three 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 could select more than one option. For those who preferred the new system 1, six (66·7%) of nine thought the system might improve inter-observer agreement between radiologists (increase standardisation and consistency of reporting), and five (55·6%) indicated that it will likely be a more descriptive and comprehensive system to cover all relevant imaging detected extranodal extension features. Furthermore, five (55·6%) of the respondents felt that system 1 was more likely to be specific (ie, more able to identify cases with no extranodal extension compared with other systems). All five (100%) respondents who chose system 2 (a three-tier system) indicated that it is potentially easier to apply or use in clinical practice, and four (80%) agreed that it is more likely to have high inter-observer agreement between radiologists. Both respondents who selected system 3 (a four-tier system) indicated that it was more likely to result in higher inter-observer agreement between radiologists.

Discussion

Histopathology is the gold standard for diagnosing extranodal extensions. Although imaging detected extranodal extension is known to be prognostic, it has not yet been integrated into any staging systems or into routine clinical practice for head and neck squamous cell carcinoma partly because of the lack of consensus on

diagnostic imaging features and absence of an accepted standardised 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 imaging detected extranodal extension in head and neck squamous cell carcinoma. These experts unanimously supported synoptic reporting and the need for a classification system for imaging detected extranodal extension and most favoured 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 imaging detected extranodal extension using the new HNCIG classification system and it offers detailed and specific guidance using real-life examples. The atlas provides examples of orthogonal views in multiple planes for each imaging detected extranodal extension grade (appendix pp 2–52). The atlas shows extension into perinodal fat (grade 1) where spiculated foci of tissue extending clearly beyond the margin of the node can be distinguished. The key to diagnosing grade 2 imaging detected extranodal extension 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 imaging detected extranodal extension) are best evaluated by scrolling through images on a picture archiving communications system, ideally using multiple orthogonal planes. While nodes might still have partly visible planes, at least a portion of the periphery has been lost (ie, is not visible), indicating where the nodes have come together into a common mass. These characteristics are difficult to show with a solitary axial slice.

Randomised studies have shown that patients with histology detected extranodal extension who have had surgical treatment benefit from postoperative adjuvant chemoradiotherapy, which improves outcomes, but also adds considerable toxicity.[3] Imaging detected extranodal extension has the potential to direct treatment. If it were possible to reliably and consistently identify imaging detected extranodal extension before the start of treatment, patients could be offered non-surgical primary chemoradiotherapy, and would avoid the toxicity and cost of tri-modality therapy.[21,22] Alternatively, patients might actually benefit from treatment escalation; therefore, imaging detected extranodal extension might be used as an indication for induction chemotherapy or tri-modality treatment.

Furthermore, imaging detected extranodal extension might have prognostic power in the non-surgical setting. Using images from a randomised controlled trial, a recent study evaluated the prognostic value of imaging detected extranodal extension diagnosed on CT scans in patients with locally advanced head and neck squamous cell carcinoma treated with concurrent chemoradiotherapy and found pre-treatment imaging detected extranodal extension 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 imaging detected extranodal extension as a predictive marker by which to stratify patients into responders versus non-responders and to better tailor therapy.[23] Another study investigated the importance of imaging detected extranodal extension in HPV-mediated head and neck squamous cell carcinoma and showed that it is a strong prognostic factor (HR for overall survival 3·86, p<0·001) and might help better identify patients who are not suitable for deintensification trials. The study proposed a TNM staging system for HPV-mediated head and neck squamous cell carcinoma incorporating imaging detected extranodal extension, which outperformed the current TNM (eighth edition) system.[9] Several other studies have shown the prognostic power of imaging detected extranodal extension in nasopharyngeal cancer, where the presence of a "conglomerate/matted/coalescent" nodal mass was shown to be an independent prognostic factor for distant metastasis-free survival[24] and overall survival.[6] Other studies have also shown that using imaging detected extranodal extension to move patients with nasopharyngeal cancer and extranodal extension to stage N3 results in better and more accurate staging compared with the current eighth edition of the AJCC TNM staging system.[18,25,26]

For the **HNCIG consensus guidelines** see https://www.headneckcig.org/

However, despite the plethora of data, imaging detected extranodal extension is still not implemented in routine clinical practice. That is partly because, in contrast to histology detected extranodal extension, there is currently no level I trial evidence for the efficacy of imaging detected extranodal extension as a determinant of treatment. Furthermore, due to a lack of standardisation, existing studies have often used different criteria and definitions, making it difficult to generalise or compare findings. Additionally, there remains wide variability regarding the diagnostic accuracy of pre-treatment imaging in the detection of extranodal extension in head and neck squamous cell carcinoma[10–12,27,28] as assessed in several recent systematic reviews and meta-analyses. Taken together, the literature suggests that CT, MRI, and ultrasound are appropriate methods for identifying extranodal extension, but they differ in sensitivity and specificity, and that inter-observer concordance would likely benefit from more defined classification systems. Furthermore, a multicentre radiology study showed that a learning curve exists for imaging detected extranodal extension assessment, and that reliability can therefore be augmented by strategies including consolidated operating definitions and sharing experience among radiologists.[16]

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 most experts. We also provided a template for a synoptic report (panel 4). Experts favoured this new classification because it was more likely to have inter-observer agreement, more likely to be specific, and might 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 histologically detected extranodal extension, inter-rater agreement and reproducibility, and the prognostic power of the different grades. If validated, the system could be used in trials assessing its use for determining treatment selection, especially escalation or de-escalation of treatment according to imaging detected extranodal extension status.

This study has limitations. 15 of the 18 experts completed all five rounds of the process. These experts are academics who are more likely to be cognisant of diagnostic criteria and have higher levels of experience and expertise. Therefore, the generalisability of their views to routine clinical practice remains to be seen. 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.

Panel 4: **Template for a proposed synoptic report**

Synoptic reporting form questions

Was a core biopsy done (yes, no, or unknown)? If yes, provide date. Indicate if the features are present, absent, or 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 Head and Neck Cancer International Group imaging-detected extranodal extension grade (0–3)
- Textual description (including any equivocal or other features)

Search strategy and selection criteria

To identify areas of uncertainty in clinical practice regarding the diagnostic features of extranodal extension on imaging in head and neck cancer, and the available classification systems for imaging detected extranodal extension reporting, we did a literature search of PubMed, Embase, MEDLINE, and Google that included grey literature and relevant published guidelines. We used the 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". We searched for articles published between Jan 1, 1980 and April 15, 2023. We restricted 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 the 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 steering group. All questions were piloted by expert radiologists for readability and face and content validity.

Conclusion

An essential prerequisite for implementation of imaging detected extranodal extension into clinical practice is the availability of widely accepted, reliable, and consistent definitions and diagnostic criteria, which for the first time is now available from these international guidelines. The experts in our consensus process agreed strongly on the following as criteria for the diagnosis of imaging detected extranodal extension: indistinct or irregular nodal margin or border; extension into perinodal fat; extension into adjacent structures, such as muscle, skin, glands, and the neurovascular bundle; and conglomerate, matted, and 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 the extranodal extensions. 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 for imaging detected extranodal extension. The expert radiologists also support and are willing to use a standardised classification system and synoptic reporting in their routine clinical practice. Based on this Delphi consensus and existing data, these guidelines will serve to standardise definitions and classifications to aid reporting in both clinical practice and research. We also proposed a new classification system for the diagnosis of imaging detected extranodal extension that requires validation before wider clinical implementation.

Contributors

HM, CHe, and AKA-F conceived the study concept and initiated the study design. HM, CHe, AKA-F, CG, SHH, ADK, WML, LM, AAN,

PCN, BO'S, 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 authors 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; past President of the British Association of Head and Neck Oncologists; has received honoraria from AstraZeneca; served on speakers bureau for Merck Sharpe & Dohme (MSD) and Sanofi Pasteur; has received research funding from GSK Biologicals, MSD, Sanofi Pasteur, GSK, and AstraZeneca; and has received travel and accommodation expenses from Sanofi, Pasteur, and MSD. CG received royalties from Elsevier for authoring and editing books and chapters for Elsevier. WML is the Chair of the American Joint Committee on Cancer (ninth version) Head and Neck Task Force. All other authors declare no competing interests.

Data sharing

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

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