Head and Neck Cancer Consensus Recommendations 1

Standardised definitions and diagnostic criteria for extranodal extension detected on histopathological examination in head and neck cancer: Head and Neck Cancer International Group consensus recommendations

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Detection of extranodal extension on histopathology in surgically treated head and neck squamous cell carcinoma indicates poor prognosis. However, there is no consensus on the diagnostic criteria, interpretation, and reporting of histology detected extranodal extension, which has contributed to conflicting evidence in the literature, and likely clinical inconsistency. The Head and Neck Cancer International Group conducted a three-round modified Delphi process with a group of 19 international pathology experts representing 15 national clinical research groups to generate consensus recommendations for histology detected extranodal extension diagnostic criteria. The expert panel strongly agreed on terminology and diagnostic features for histology detected extranodal extension and soft tissue metastasis. Moreover, the panel reached consensus on reporting of histology detected extranodal extension and on nodal sampling. These consensus recommendations, endorsed by 19 organisations representing 34 countries, are a crucial development towards standardised diagnosis and reporting of histology detected extranodal extension, and more accurate data collection and analysis.

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This is the first in a **Series** of four papers on head and neck cancer consensus recommendations. All papers in the Series are available at www.thelancet.com/series/head-and-neck-cancer-consensus-recommendations

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Introduction

Extranodal extension on histopathological examination has for the last two decades been shown to be a substantial predictor for poor prognosis in surgically treated head and neck squamous cell carcinoma.[1,2] Histology detected extranodal extension is recognised as a sign of tumour aggressiveness and increases the risk of distant metastasis and locoregional failure.[3] Subsequently, histology detected extranodal extension has been incorporated into the staging system for non-viral head and neck cancer in the latest (eighth) edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging manual for head and neck squamous cell carcinoma.[4,5] Histology detected extranodal extension is also an indicator for treatment intensification and adjuvant therapy. Two large randomised trials—the EORTC 22931 and RTOG 9501 trials—showed that the addition of concomitant high-dose cisplatin to postoperative radiotherapy in patients with histology detected extranodal extension or positive margins can significantly decrease the risk of locoregional failure by 42% and death by 30% compared with adjuvant radiotherapy alone.[6]

Despite this, there are aspects of histology detected extranodal extension that remain unresolved or do not have consensus. There is wide variability in the definitions used[7] and consensus on the prognostic significance of minor (or microscopic) histology detected extranodal extension is missing.[8–11] This absence of consensus has resulted in considerable heterogeneity when making a diagnosis of histology detected extranodal extension, especially in challenging cases with matted nodes, nodal hilar involvement, or in instances of direct extension of primary tumour to the lymph nodes. As a result, there appears to be considerable variation in reported inter-rater correlation,[12] and the potential survival benefit of treatment escalation in human papillomavirus (HPV)-associated tumours with histology detected extranodal extension remains uncertain.[4,13–17]

The absence of universally accepted diagnostic criteria, interpretation and reporting of histology detected extranodal extension, and the heterogeneity in sample processing between different studies are some of the main reasons for the ongoing disagreements.[16] Without a standardised approach to defining and diagnosing histology detected extranodal extension, indications for treatment intensification might be applied inconsistently in both clinical and research settings. Furthermore, meaningful comparisons across studies to draw definitive conclusions about the prognostic importance of some types of histology detected extranodal extension might be difficult without standardisation. The approach of seeking expert group judgement is particularly useful in cases where empirical evidence on a particular topic is either controversial or not available and can shape clinical

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guidance by providing a valuable framework for decision making.[18] As such, we identified areas of uncertainty and solicited expert opinion from a group of international head and neck pathology experts using a modified Delphi method. Our objective was to generate consensus recommendations on the diagnosis of histology detected extranodal extension and to standardise protocols for sample processing and interpretation, to provide consistency in clinical decision making and research of histology detected extranodal extension moving forward.

Methods

Participant selection

A study steering group was established by the Head and Neck Cancer International Group (HNCIG), which is a consortium of 21 national head and neck oncology research groups. The multidisciplinary steering group led the overall study design and execution and formulated the questions (members are given in the appendix p 97). The group included head and neck pathologists, surgeons, and oncologists, with expertise in conducting Delphi consensus research.

To form a panel of experts for the consensus guidelines, all 21 member groups of the HNCIG were invited to nominate an expert head and neck pathologist to represent their group. Nominees had to be practising head and neck pathologists, national or international experts, and willing to complete all three rounds of the online Delphi process. 15 of the invited organisations provided nominees who participated in the process and were all included in the authorship of the manuscript. 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 (ECOG-ACRIN), the European Organisation for Research and Treatment of Cancer, the French Head and Neck Cancer Group, Fudan University Shanghai Cancer, 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

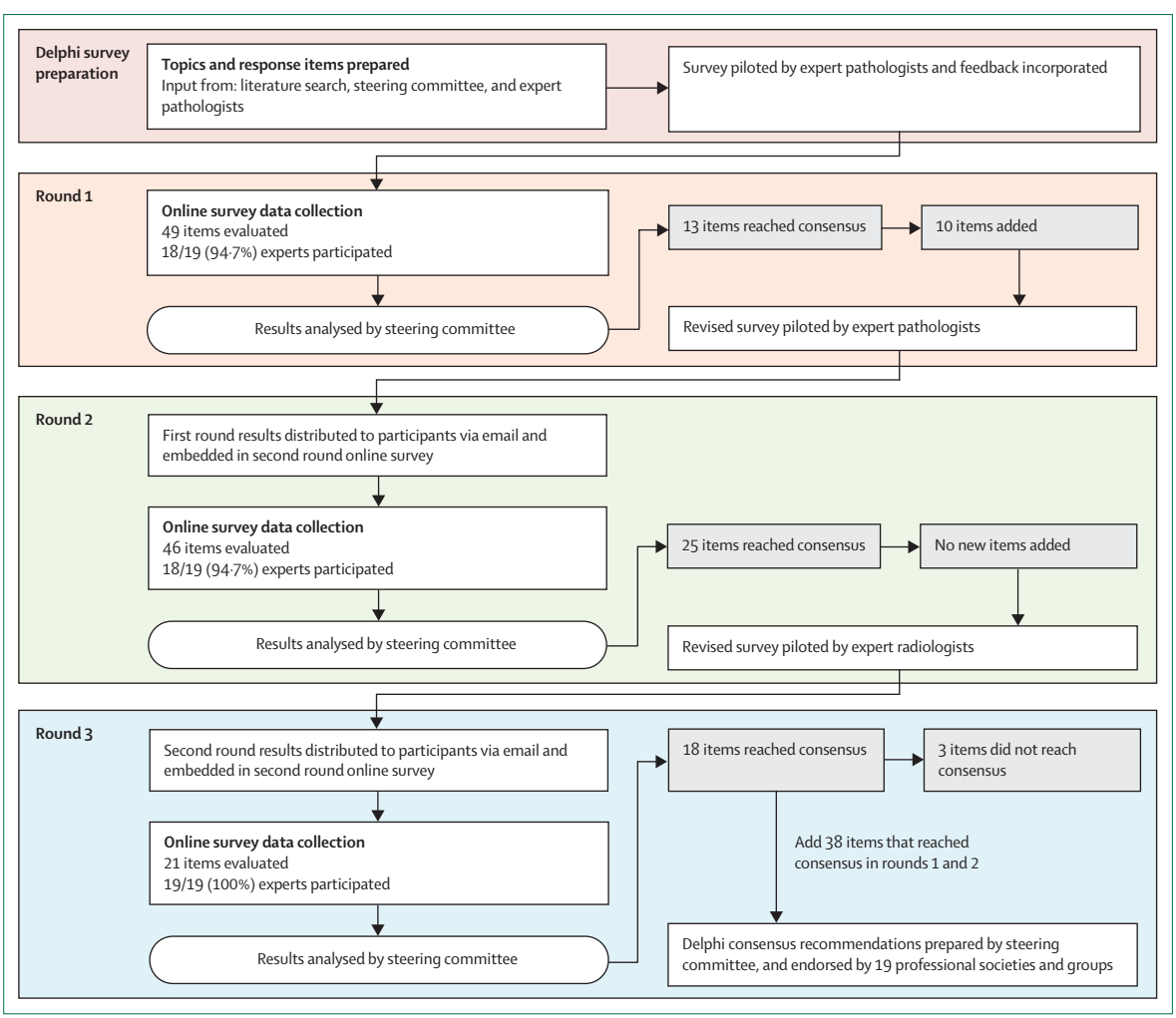

Figure 1: **Schematic of the modified Delphi process for pathological extranodal extension**

Oncology Group, Hong Kong Nasopharyngeal Cancer Study Group, the Latin American Cooperative Oncology Group, the National Cancer Centre Singapore, North West Italian Oncology Group, NRG Oncology (National Surgical Adjuvant and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group), and TATA medical centre (India).

Consensus process and data collection

To achieve consensus on the diagnosis and reporting of histology detected extranodal extension, an online modified Delphi process was conducted over three rounds using methods described previously.[19] The nominated expert head and neck pathologists were invited to complete an online questionnaire delivered by the Qualtrics online survey platform. The survey covered five main domains: definitions and reporting of histology detected extranodal extension, definitions and reporting of soft tissue metastasis, implications of primary tumour direct spread and of previous nodal core biopsy or fine needle aspiration for diagnosis, and criteria for nodal sampling and processing for evaluation. The steering group selected the survey domains and questions, which were revised or amended as necessary over subsequent rounds for clarity or on the basis of respondent feedback. Some new questions were also introduced to add granularity to particularly nuanced topics. Before each round, a small group of independent expert head and neck pathologists piloted the questions for readability, face validity, and content validity. An overview of the modified Delphi process is shown in figure 1.

Three rounds of the survey were undertaken. Each round was open for up to 14 days, and a reminder email was sent 3 days before the deadline. After each round, the multidisciplinary steering group collated and analysed the data using predetermined criteria for agreement extrapolated from the RAND (Research and Development Corporation) Delphi methodology.[20,21] Strong agreement was signified by consensus of 80% or higher for a statement, agreement was suggested by 67–79%, and no agreement was signified by 21–66%. Statements with 20% or less agreement were rejected (strong agreement against a statement). A statement was removed from the next round either when strong agreement or rejection was reached, or after completion of three rounds, whichever occurred first. After the third round, statements that did not reach strong agreement but reached at least 67% or higher were considered to have reached agreement.[19,21]

Results were iteratively shared with the panel participants after each round. 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, after reviewing the results and emerging consensus of the previous rounds. There was also a free text option for those who wished to elaborate on specific points or give explanations for their choices.

This study was granted a research ethics waiver from the Research Ethics Department at the University of Birmingham (Birmingham, UK), application number ERN_0910-2.

Results

Process

19 expert nominees representing 15 research groups participated in this study, as the Dutch, Danish, Japanese, and ECOG-ACRIN groups had more than one representative each. The full list of participants is provided in the appendix (p 97). 17 (89·5%) of 19 participants completed all three rounds. One participant was unable to complete the first round and another was unable to complete the second round (both left for personal reasons). In both cases, their responses to the questions they answered were included in the analysis. The final recommendations were endorsed by 19 national clinical research groups, representing 34 countries (panel 1).

In total, 49 questions were asked in the first round, 46 questions in the second round, and 21 questions in the third round. 13 (26·5%) of 49 questions were removed after the first round and 25 (54·3%) of 46 after the second round after reaching strong agreement for or against the

***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 (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

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See **Online** for appendix

For the **Qualtrics online survey platform** see https://www.qualtrics.com/uk/

statement. Only 3 (14·3%) of 21 questions asked in the third round failed to any agreement.

The reported rates of agreement reflect when an item first reached an agreement threshold, and might have been after one, two, or all three rounds of questioning. A summary of the consensus statements and recommendations in detail are available in panel 2. Full results and agreement levels of the questions asked in all three rounds are provided in the appendix (pp 98–105).

Definitions and reporting of extranodal extension on histopathology

Preferred terminology

There was strong agreement between 17 (94·4%) of 18 experts for "extranodal extension" as the preferred terminology to describe metastatic squamous cell carcinoma in the neck that has spread outside of a lymph node. The other terms "extracapsular extension", "extracapsular spread", or "extranodal spread" were rejected.

Diagnostic features for histology detected extranodal extension

All 19 experts unanimously agreed that a tumour in a lymph node that is directly extending into perinodal soft tissue is diagnostic for histology detected extranodal extension in both HPV-associated and HPV-negative cancers. 16 (88·9%) of 18 experts strongly agreed that other diagnostic features, irrespective of HPV status, are the presence of tumour cells in perinodal fat or soft tissue, and the penetration of tumour cells through the full thickness of the lymph node capsule. No consensus was reached regarding the presence of perinodal stromal desmoplasia as a feature for histology detected extranodal extension in either HPV-associated oropharyngeal cancers or in HPV-negative oropharyngeal, oral, laryngeal, or hypopharyngeal cancers.

The experts were in strong agreement that presence of thick pseudo-capsule, absence of lymphoid tissue, presence of matted nodes, tumour presence within lymphatics near an involved lymph node, and vascular invasion by cancer cells in perinodal soft tissue were not diagnostic features for histology detected extranodal extension for both HPV-associated and HPV-negative tumours.

Diagnostic features for soft tissue metastasis

There was strong agreement that an irregular deposit of tumour in the connective tissues of the neck, without a microscopically identifiable residual lymph node, is diagnostic for soft tissue metastasis for both HPV-associated tumours (17 [94·4%] of 18 experts agreed) and HPV-negative tumours (15 [83.3%] experts agreed). Moreover, 17 (89·5%) of 19 experts were in strong agreement that a circumscribed deposit of tumour without a microscopically identifiable residual lymph node is also diagnostic for soft tissue metastasis, regardless of the HPV status.

16 (88·9%) of the 18 experts strongly agreed that a diagnosis of soft tissue metastasis can be made if there is no residual lymph node on all slides of the metastasis, with 15 (83·3%) agreeing for HPV-associated and 16 (88·9%) for HPV-negative tumours. There was also strong agreement against making a diagnosis of soft tissue metastasis if no residual lymph node was observed on only one slide of the metastasis.

All 18 experts unanimously agreed that there is no minimum dimension or size of deposit required for the diagnosis of soft tissue metastasis, regardless of HPV status. There was also unanimous agreement in all 19 experts that in-transit metastasis (defined as presence of cancer cells in lymphatics outside nodal tissue) is not considered an indication for a diagnosis of soft tissue metastasis, irrespective of the HPV status.

Difficult cases of histology detected extranodal extension

Tumour in the fat at the hilum of a lymph node

15 (83·3%) of 18 experts strongly agreed that the definition of histology detected extranodal extension varies at the hilum of a lymph node where the capsule might be incomplete. However, the participants' opinion was divided in the first round as to whether the presence of tumour in the fat at the hilum of a lymph node is considered diagnostic for histology detected extranodal extension with nine (50·0%) agreeing for HPV-associated tumours and eight (44·4%) for HPV-negative tumours. The consensus panel reached an agreement in the third round with 14 (73·7%) agreeing that the presence of tumour in the fat at the hilum of a lymph node is only sometimes considered diagnostic for histology detected extranodal extension, regardless of the HPV status.

Primary tumour direct spread

There was agreement in 13 (68·4%) of 19 experts that when a lymph node is involved by direct extension from a primary tumour it should be reported as extranodal extension absent regardless of the HPV status. The remaining six (31·6%) experts signified they would report the profile as "extranodal extension cannot be evaluated". Panel members explained in their comments that extranodal extension should be a breach through the lymph node capsule that is discontinuous from the primary tumour.

Changes caused by nodal core biopsy or fine needle aspiration

Participants were asked about the effect of specific lymph node features that can be induced by nodal core biopsy or fine needle aspiration on the decision to render a diagnosis of histology detected extranodal extension. There was strong agreement that the following features, if present, should not be reported as histology detected extranodal extension: 18 (94·7%) of 19 agreed on tumour

Panel 2: Summary of consensus statements and recommendations

Terminology of histology detected extranodal extension

"Extranodal extension" is the preferred terminology to describe metastatic squamous cell carcinoma in the neck that has spread outside of a lymph node.

Features diagnostic of histology detected extranodal extension for both human papillomavirus (HPV)-mediated and HPV-negative head and neck cancer

- Tumour directly extending into perinodal soft tissue
- Tumour cells in perinodal fat or soft tissue
- Penetration of tumour cells through the full thickness of the lymph node capsule

Features not diagnostic for histology detected extranodal extension

- Absence of lymphoid tissue
- Thick pseudo-capsule
- Presence of matted nodes
- Vascular invasion by cancer cells in perinodal soft tissue
- Tumour within lymphatics near an involved lymph node
- Tumour infarction in the lymph node due to core biopsy or fine needle aspiration
- Lymph node infarction due to core biopsy or fine needle aspiration
- Linear needle tract with recent or old haemorrhage and neovascular proliferation due to core biopsy or fine needle aspiration
- Reactive fibroblastic proliferation with haemosiderin-laden macrophages due to core biopsy or fine needle aspiration

Features diagnostic of soft tissue metastasis for both HPV-mediated and HPV-negative head and neck cancer

- An irregular deposit of tumour in connective tissue without a microscopically identifiable residual lymph node
- A circumscribed deposit of tumour without a microscopically identifiable residual lymph node
- No residual lymph node on all slides of the metastasis
- There is no minimum dimension required for diagnosis of soft tissue metastasis

Features not diagnostic for soft tissue metastasis

- No residual lymph node on only one slide of the metastasis
- In-transit metastasis (defined as the presence of cancer cells in lymphatics outside nodal tissue)

Nodal sampling and processing for histology detected extranodal extension evaluation

- For macroscopic lymph node metastases, sample representative sections of larger lymph nodes and entirely submit small lymph nodes
- For lymph nodes that are not suspicious for metastases on gross examination, entirely submit every lymph node
- If a lymph node is suspicious for extranodal extension on gross or microscopic (slide) examination, the number of additional sections or blocks to collect varies by case

Reporting of histology detected extranodal extension and soft tissue metastasis

- Major and minor extranodal extensions should be explicitly reported
- Major histology detected extranodal extension is an extension of a tumour greater than 2 mm beyond the nodal capsule
- Minor histology detected extranodal extension is an extension of a tumour 2 mm or less beyond the nodal capsule
- Number of lymph nodes that have histology detected extranodal extension should be reported
- Size of the largest lymph node that has histology detected extranodal extension should be reported
- Precise measurement for the vertical and perpendicular extent of extranodal extension away from the lymph node capsule should not be reported
- Presence of soft tissue metastasis should be reported

Consensus results:

Strong agreement for consensus recommendations indicates a threshold of 80% and above. Agreement indicates a threshold of 67% and above after the third round for statements.

Definition of histology detected extranodal extension

Strong agreement: the preferred terminology to describe metastatic squamous cell carcinoma in the neck that has spread outside of a lymph node is "extranodal extension".

Diagnostic features for histology detected extranodal extension

The following are diagnostic features of histology detected extranodal extension in both HPV-mediated and HPV-negative head and neck cancer.

- Strong agreement: tumour directly extending into perinodal soft tissue
- Strong agreement: tumour cells in perinodal fat or soft tissue
- Strong agreement: penetration of tumour cells through the full thickness of the lymph node capsule
- Rejected: absence of lymphoid tissue
- Rejected: thick pseudo-capsule
- Rejected: presence of matted nodes
- Rejected: vascular invasion by cancer cells in perinodal soft tissue
- Rejected: tumour within lymphatics near an involved lymph node
- No agreement: presence of stromal desmoplasia
- Strong agreement: the definition of histology detected extranodal extension differs at the hilum of a lymph node (where the capsule might be incomplete)
- Agreement: if the tumour is identified in the fat at the hilum of a lymph node, it is sometimes but not always considered histology detected extranodal extension

(Panel continues on next page)

(Panel 2 continues from previous page)

Implications of nodal core biopsy or needle aspiration for histology detected extranodal extension diagnosis

The following lymph node changes induced by fine needle aspiration or core biopsy affect the decision to diagnose histology detected extranodal extension

- Strong agreement: tumour infarction in the lymph node should be reported as no histology detected extranodal extension
- Strong agreement: lymph node infarction should be reported as no histology detected extranodal extension
- Strong agreement: linear needle tract with recent or old haemorrhage and neovascular proliferation should be reported as no histology detected extranodal extension
- Strong agreement: reactive fibroblastic proliferation with haemosiderin-laden macrophages should be reported as no histology detected extranodal extension

Diagnostic features of soft tissue metastasis

The following are diagnostic features of soft tissue metastasis in both HPV-mediated and HPV-negative head and neck cancer

- Strong agreement: an irregular deposit of tumour in connective tissue without a microscopically identifiable residual lymph node
- Strong agreement: a circumscribed deposit of tumour without a microscopically identifiable residual lymph node
- Strong agreement: there is no minimum dimension for diagnosis of soft tissue metastasis
- Strong agreement: no residual lymph node on all slides of the metastasis
- Rejected: no residual lymph node on only one slide of the metastasis
- Rejected: in-transit metastasis (defined as presence of cancer cells in lymphatics outside nodal tissue) is considered an indication for a diagnosis of soft tissue metastasis
- Strong agreement: there is no minimum dimension for diagnosis of soft tissue metastasis

Nodal sampling and processing for histology detected extranodal extension evaluation

- Strong agreement: the recommended method for sampling macroscopic lymph node metastases to evaluate them for histology detected extranodal extension is to sample representative sections of larger lymph nodes and to entirely submit small lymph nodes
- Strong agreement: the recommended method for sampling lymph nodes that are not suspicious for metastases on gross examination to evaluate them for any metastases or histology detected extranodal extension is to entirely submit every lymph node for assessment
- Agreement: sampling differs if the lymph node exhibits extranodal extension on gross examination or if there are matted lymph nodes
- Strong agreement: if a lymph node is suspicious for histology detected extranodal extension on gross examination, the number of additional sections or blocks varies by case
- Strong agreement: if a lymph node is suspicious for histology detected extranodal extension on microscopic (slide) examination, the number of additional levels varies by case

Reporting of histology detected extranodal extension

- Rejected: in HPV-mediated oropharyngeal cancers, the pathologist should report a precise measurement for the vertical and perpendicular extent of histology detected extranodal extension away from the lymph node capsule
- No agreement: in HPV-negative head and neck cancer, the pathologist should report a precise measurement for the vertical and perpendicular extent of histology detected extranodal extension away from the lymph node capsule
- Strong agreement: when examined under the microscope, major and minor histology detected extranodal extension should be explicitly mentioned in the report
- Strong agreement: the definition of major histology detected extranodal extension is extension greater than 2 mm beyond capsule
- Agreement: in HPV-mediated oropharyngeal cancers, the number of lymph nodes that have histology detected extranodal extension should be reported
- Strong agreement: in HPV-negative head and neck cancer, the number of lymph nodes that have histology detected extranodal extension should be reported
- Strong agreement: the size of the largest lymph node that has histology detected extranodal extension should be reported
- Strong agreement: the presence of soft tissue metastasis should be reported
- Strong agreement: equivocal extranodal extension should be reported as "extranodal extension equivocal", not extranodal extension present or absent
- Strong agreement: when a lymph node is involved by direct extension from a primary tumour, it should be reported as "extranodal extension absent" since extranodal extension should be a breach through the lymph node capsule that is discontinuous from the primary tumour

infarction in the lymph node, 17 (89·5%) of 19 on lymph node infarction, 16 (88·9%) of 18 on linear needle tract with recent or old haemorrhage and neovascular proliferation, and 15 (83·3%) of 18 agreed on reactive fibroblastic proliferation with haemosiderin-laden macrophages.

Reporting of histology detected extranodal extension

Extent or grade of histology detected extranodal extension

There was strong agreement in 15 (83·3%) of 18 experts that major and minor (also called microscopic) histology detected extranodal extension should be explicitly mentioned in the report (figure 2). There was also strong

agreement that the preferred definition for major histology detected extranodal extension is extension greater than 2 mm beyond the capsule (measured as the perpendicular distance from the line connecting the remaining intact edges of the capsule surrounding the area of histology detected extranodal extension), with 12 (80·0%) of 15 agreeing for HPV-associated tumours and all agreeing for HPV-negative tumours. For HPV-associated tumours, 15 (83·3%) of 18 were in strong agreement that the pathologist should not report a precise measurement for the vertical or perpendicular extent or distance of extranodal extension from the lymph node capsule. However, the participants were unable to reach an agreement regarding that statement for HPV-negative tumours with 12 (63·2%) of 19 agreeing. We did not explicitly define the measurement of histology detected extranodal extension in the Delphi survey, so the authors recommend that this parameter is measured according to the International Collaboration on Cancer Reporting (ICCR) dataset for the histopathological reporting of nodal excisions and neck dissection specimens for head and neck tumours. Specifically, extranodal extension is measured as the greatest extent of tumour spread perpendicular to the external aspect of the node capsule. The exact site of the external region of the node capsule is subjective, but might be estimated by examination of the remaining intact capsule and contour of the node. If the greatest extent of extranodal extension is provided, the measurement can be rounded to the nearest millimetre or tenth of a millimetre, as per local convention.[22]

Number and size of lymph nodes with histology detected extranodal extension

15 (83·3%) of 18 experts strongly agreed that the number of lymph nodes that have extranodal extension should be reported for HPV-negative tumours. 15 (79·0%) of 19 agreed that this statement also applies for HPV-associated oropharyngeal cancers. There was also strong agreement that the size of the largest lymph node that has extranodal extension should be reported, with 15 (83·3%) agreeing for HPV-associated and 17 (94·4%) agreeing for HPV-negative tumours.

Equivocal cases

15 (83·3%) of 18 experts strongly agreed that equivocal extranodal extension should be reported as extranodal extension equivocal, and not extranodal extension present as agreed by two (11·1%) or absent as agreed by three (16·7%) experts.

Criteria for nodal sampling and processing for histology detected extranodal extension evaluation

Sampling of lymph nodes with metastasis

The experts came to a strong agreement with 17 (94·4%) of 18 deciding that the best approach for extranodal extension evaluation when sampling lymph node showing macroscopic or gross features of tumour metastases is to sample representative sections of larger lymph nodes and entirely submit small lymph nodes, regardless of the HPV status. For lymph nodes that look normal (with no evidence of metastases) on gross examination, there was strong agreement in 16 (84·2%) of 19 experts to recommend entirely submitting every node to evaluate them for any metastases or extranodal extension. The remaining three (15·8%) participants signified they would recommend sampling representative sections of larger lymph nodes and to entirely submit small lymph nodes if there was no suspicion for metastases on gross examination.

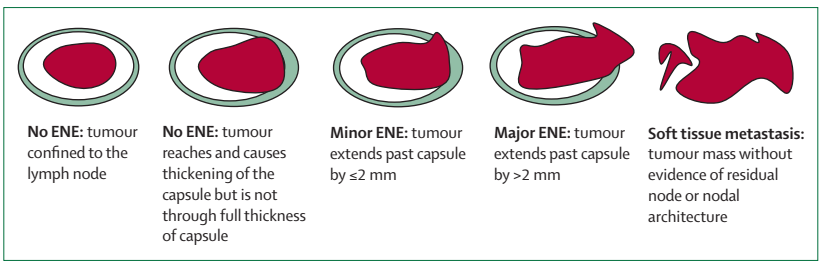

Figure 2: **Schematic diagram of the diagnostic criteria for pathological ENE and soft tissue metastasis**
ENE=extranodal extension.

Sampling of lymph nodes with gross extranodal extension

There was agreement from 15 (79·0%) of 19 experts that sampling strategies are different for lymph nodes that show signs of extranodal extension on gross examination or if there are matted lymph nodes. Moreover, there was strong agreement from all experts that the number of additional sections or blocks to sample would vary on a case-by-case basis, regardless of the HPV status.

The panel also strongly agreed that if a lymph node is suspicious for extranodal extension on microscope (slide) examination, the number of additional levels to be reviewed varies on a case-by-case basis for both HPV-associated tumours as agreed by 17 (94·4%) of 18 experts, and for HPV-negative tumours as agreed by all.

Educational resource

We have developed an educational resource to provide examples of histology detected extranodal extension, soft tissue metastasis, and examples of pitfalls—ie, cases that are not histology detected extranodal extension, but could be confused for it (appendix pp 2–96).

For the **Head and Neck Cancer International Group grading atlas** see https://www.headneckcig.org/

Discussion

The detection of extranodal extension on histopathological examination is considered a crucial finding in head and neck squamous cell carcinoma due to its substantial clinical implications, underscoring the necessity for well-defined and reproducible definitions. Patients who have had surgery and are confirmed to have extranodal extension will usually undergo treatment intensification with adjuvant chemoradiotherapy, which can cause

considerable toxicity and long-term effects on quality of life.[6] Despite the wide recognition of extranodal extension as an adverse feature, there remains ongoing disagreement regarding the prognostic utility of minor (microscopic) histology detected extranodal extension, especially in HPV-associated head and neck squamous cell carcinoma. The absence of standardised terminology and diagnostic criteria for histology detected extranodal extension and soft tissue metastasis is a contributing factor to this difference in opinion. Moreover, there is considerable variability in the histopathological sampling and processing of neck dissection specimens for histological evaluation, which adds another layer of inconsistency when generating reliable and widely applicable evidence. With the use of a robust modified Delphi process, a group of experts representing 15 prominent clinical research groups across 29 countries achieved consensus on the definitions and diagnostic criteria for histology detected extranodal extension and soft tissue metastasis in head and neck squamous cell carcinoma. Additionally, they achieved consensus on standardised criteria for some aspects of sampling neck dissection specimens for histology detected extranodal extension assessment.

To date, there have been no widely accepted diagnostic criteria for histology detected extranodal extension. Indeed, a systematic review[7] from 2021 identified 44 unique definitions for histology detected extranodal extension used in the literature, with 21 (47·7%) of 44 studies only describing a breach in the capsule. 19 (43·2%) also included additional information on perinodal tissue, and 4 (9·1%) specified reaction in the perinodal tissue in their definitions. Additionally, there is considerable variation in the rates of histology detected extranodal extension reported in the literature (ranging from 21% to 85%), poor inter-rater agreement among pathologists,[12,23,24] and considerable inconsistencies in diagnostic criteria being used for histology detected extranodal extension.

Our expert group reached consensus that the preferred terminology to describe metastatic squamous cell carcinoma in the neck that has spread outside of a lymph node is "extranodal extension", which concurs with the AJCC,[25] UICC,[26] and the ICCR[22] who all recently adopted the term extranodal extension. The experts in this study also achieved consensus on the diagnostic criteria and definitions for histology detected extranodal extension. Importantly, they also identified features that should not be considered diagnostic for histology detected extranodal extension, which should further improve diagnostic certainty and generalisability. Consensus was also reached on the irrelevance of HPV status when interpreting the different features for histology detected extranodal extension. Stromal desmoplasia was the only feature that did not reach agreement, which might reflect ongoing debate in the literature, as some authors consider this criterion to be important for histology detected extranodal extension diagnosis,[8,27–29] especially in equivocal cases.[7] Others indicate that stromal desmoplasia should not be used independently as it is not sensitive nor specific for extranodal extension diagnosis.[4,22,30,31]

Soft tissue metastasis is considered an advanced form of histology detected extranodal extension that should be appropriately identified and reported separately to major histology detected extranodal extension, as it has a profound prognostic effect on patients with head and neck squamous cell carcinoma irrespective of HPV status.[8,32–34] Soft tissue metastasis can either present as extra-lymphatic tumour deposits or a lymph node that is totally replaced by extensive extranodal extension, and can present with variable sizes and shapes.[8,22] The expert panel reached consensus that soft tissue metastasis can be diagnosed by the presence of either an irregular or circumscribed tumour deposit in the connective tissues of the neck, without any microscopically identifiable residual lymph node including the lymph node capsule. It is important for pathologists to confirm the absence of any residual lymph node structure on all histological slides of the metastasis to accurately diagnose soft tissue metastasis, but no minimum dimension is required for diagnosis.

To further enhance clarity, our guidelines also address circumstances where there might be difficulty or ambiguity in the diagnosis of histology detected extranodal extension. One such situation is the presence of tumour cells in the hilum of a lymph node, where the capsule might be incomplete. Determination of extranodal extension at the hilum of a lymph node is subjective and varies between pathologists. Currently, no studies exist regarding the clinical outcomes of metastasis in the hilum area. In the literature, some authors consider any tumour presence in the hilum as extranodal extension,[34,35] whereas others do not.[36] There was consensus among our experts that standard diagnostic features for histology detected extranodal extension should be interpreted differently at the hilum of a lymph node. There was also agreement that a tumour identified in the fat at the hilum can sometimes but not always be considered histology detected extranodal extension. In addition, some of our experts have suggested in their comments that the presence of accompanying stromal desmoplasia might be useful for diagnosis of histology detected extranodal extension in cases where there is an equivocal focal tumour deposit at the lymph node hilum, especially with an incomplete capsule. Our guidelines agree with the ICCR guidelines[22] in recommending a more selective and conservative approach to reporting metastasis at the hilum area. The authors recommend following the guidance from the ICCR dataset for the histopathological reporting of nodal excisions and neck dissection specimens for head and neck tumours. Specifically, these guidelines state that the node hilum can merge with adipose tissue, or there

might be a rim of lymphoid tissue external to the capsule. As such, a conservative approach is recommended. For instance, a tumour within fat near the hilum of a node should be considered intranodal if benign lymphoid tissue is identified nearby. Tumours within lymphatics near an involved lymph node should not be considered extranodal extension. However, tumour extending beyond a clearly identifiable node capsule is extranodal, even if there is a surrounding lymphoid response. A stromal desmoplastic reaction is not necessarily required.[22]

A second situation occurs when changes are induced by core biopsy or fine needle aspiration. Such changes indirectly complicate the evaluation of extranodal extension by causing tumour infarction, distortion of the lymph node capsule, induction of desmoplasia-like changes in perinodal soft tissue, or mimicking matted lymph nodes. There was consensus that these changes should not be reported as histology detected extranodal extension.

Third, according to the UICC[26] and the AJCC[25] principles for nodal classification on histopathology (pN), lymph nodes that are involved by direct extension from a primary tumour should be recorded as metastatic nodes. However, there is currently lack of consensus within the pathology community on how to determine and report histology detected extranodal extension status in such situations. Our expert panel reached strong agreement that nodes involved by direct extension from the primary tumour should be reported as no histology detected extranodal extension. However, it is important for pathologists to pay close attention to any component of the metastasis that extends through the lymph node capsule discontinuously from the primary tumour, as this may indicate the presence of extranodal extension in its own right.[22] Moreover, while there are currently no studies determining the outcomes of patients with nodes involved by direct extension of the primary tumour, this feature is still independently considered an indicator of aggressive disease, which can often lead to local relapse, and should be accurately reported as it may inform appropriate decisions on adjuvant treatment even in the absence of histology detected extranodal extension.

The experts reached consensus on important aspects of the reporting of histology detected extranodal extension, which will help harmonise reporting for patients with head and neck squamous cell carcinoma and allow for more informed decision making regarding patient care and treatment options. The expert panel strongly agreed that major and minor histology detected extranodal extension should be explicitly mentioned in the histopathology report, for both HPV-associated and HPV-negative tumours. There was also strong agreement that major histology detected extranodal extension should be defined as extension greater than 2 mm beyond the capsule, regardless of the HPV status of the tumour. Furthermore, in making this recommendation the panel was following current guidelines,[22] and the latest AJCC and UICC TNM staging system, which did not incorporate the exact extent of the extranodal extension in pathological node classification but did recommend that the degree of extension should be documented as major or minor. They defined major histology detected extranodal extension as any of the following: macroscopic extranodal extension, microscopic extranodal extension greater than 2 mm, or microscopic soft tissue metastasis. They defined minor histology detected extranodal extension as microscopic extranodal extension of 2 mm or less.[4] It is possible that as a result, the panel recommended against reporting the exact measurement of histology detected extranodal extension in HPV-negative cases and could not reach agreement for patients who are HPV-positive. This last recommendation might be divisive, as some would suggest that more research is required regarding the extent of extranodal extension and measurement of the exact extent on a continuous scale could perhaps be more useful in defining clinically relevant cutoff points.

Several efforts were made to standardise grading systems for histology detected extranodal extension,[34,36,37] with the aim of quantifying the degree of extension more specifically. However, these systems were often criticised for using vague definitions and applying arbitrary extension thresholds.[16] As a result, these grading systems have shown poor generalisability and failed to establish significance in HPV-associated or HPV-negative tumours.[32,38] Emerging evidence suggests that an extension threshold around 2 mm might have prognostic significance, although the available data are restricted and conflicting.[24,35,39,40] There is also contradictory evidence regarding the prognostic effect minor[13,41,42] or even any extranodal extension[17,43–45] has in HPV-associated tumours.

The expert panel strongly agreed that reporting a precise measurement for the perpendicular extent of extranodal extension away from the lymph node capsule is not required for HPV-associated tumours. There was no agreement on whether documenting a precise measurement of extranodal extension is required for HPV-negative tumours. These findings might be attributed to the perceived complexity, poor reproducibility, or unknown importance of reporting the precise measurement of extranodal extension, as opposed to only documenting minor and major extension. Currently, the ICCR guidelines require the reporting of the number of nodes that are involved. Our experts agreed and also recommended reporting the size of the largest node involved. There is little evidence to indicate that the size of the largest node has a prognostic effect; however, collection of such information might help with assessment.

Finally, the reporting guidelines published by the ICCR[22] and the College of American Pathologists[46] required that all reporting of lymph nodes with

metastasis from HPV-negative head and neck squamous cell carcinoma should include a comment on histology detected extranodal extension (reported as present, not identified, or cannot be determined). However, these reporting recommendations do not consider nodes with equivocal features for extranodal extension. It is possible that some pathologists could over-report cases with equivocal extranodal extension as "histology detected extranodal extension present", to avoid depriving those patients of potentially life-saving adjuvant therapy. This practice could lead to over-treatment and potential harm to patients. Our expert panel reached consensus that equivocal extranodal extension should be reported as "extranodal extension equivocal".

Despite using a rigorous modified Delphi approach to establish these consensus guidelines, this study has some limitations. Two of 19 participants were unable to complete all three rounds of the study. Moreover, although our panel of experts was highly experienced, it is possible that key perspectives in the field of head and neck pathology were not represented. It is also worth noting that the recommendations in this study were from highly specialised academic pathologists, which might not always align with the views of all pathologists in routine clinical practice. However, these limitations were mitigated by the wide endorsement of these consensus guidelines by 19 leading national research groups and organisations worldwide. Finally, future research is still needed to validate the effect of these consensus definitions and guidelines on histology detected extranodal extension reporting and clinical outcomes.

Search strategy and selection criteria

To identify areas of uncertainty in clinical practice regarding the diagnostic features of pathological extranodal extension, soft tissue metastasis in head and neck cancer, and pathological sampling and processing, 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 "pathological extranodal extension" OR "pathological extracapsular spread" OR "pathological extranodal spread" OR "pathological extracapsular extension", and searched for articles published between Jan 1, 1980, to 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 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 pathologists for readability, face validity, and content validity.

Contributors

HM, AKA-F, and CH conceived the study concept and initiated the study design. HM, AKA-F, CH, RDC, SHH, WML, LM, BO, BP-O, MR, and PCN were involved in study development, data analysis, and data interpretation of this Series paper. 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 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; reports receiving honoraria from AstraZeneca; is on the Speaker's Bureau for Merck Sharpe Dohme (MSD), Sanofi Pasteur, and Merck; received funding from GSK Biologicals, MSD, Sanofi Pasteur, GSK, and AstraZeneca; and received travel accommodation expenses from Sanofi Pasteur, MSD, and Merck. WML is the chair of American Joint Committee on Cancer 9th Version head and neck task force. RDC is a member of a steering committee for a phase 3 clinical trial of neoadjuvant pembrolizumab sponsored by Merck and also has a non-financial relationship with Caris Life Sciences as a member of their Precision Oncology Alliance. 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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