



International recommendations for plasma Epstein-Barr virus DNA measurement in nasopharyngeal carcinoma in resource-constrained settings: lessons from the COVID-19 pandemic

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The effects of the COVID-19 pandemic continue to constrain health-care staff and resources worldwide, despite the availability of effective vaccines. Aerosol-generating procedures such as endoscopy, a common investigation tool for nasopharyngeal carcinoma, are recognised as a likely cause of SARS-CoV-2 spread in hospitals. Plasma Epstein-Barr virus (EBV) DNA is considered the most accurate biomarker for the routine management of nasopharyngeal carcinoma. A consensus statement on whether plasma EBV DNA can minimise the need for or replace aerosol-generating procedures, imaging methods, and face-to-face consultations in managing nasopharyngeal carcinoma is urgently needed amid the current pandemic and potentially for future highly contagious airborne diseases or natural disasters. We completed a modified Delphi consensus process of three rounds with 33 international experts in otorhinolaryngology or head and neck surgery, radiation oncology, medical oncology, and clinical oncology with vast experience in managing nasopharyngeal carcinoma, representing 51 international professional societies and national clinical trial groups. These consensus recommendations aim to enhance consistency in clinical practice, reduce ambiguity in delivering care, and offer advice for clinicians worldwide who work in endemic and non-endemic regions of nasopharyngeal carcinoma, in the context of COVID-19 and other airborne pandemics, and in future unexpected settings of severe resource constraints and insufficiency of personal protective equipment.

Introduction

The COVID-19 pandemic is estimated by WHO to have claimed more than 6·4 million lives since December, 2019.¹ Various types of COVID-19 vaccines against the original strain of SARS-CoV-2 and the alpha (B.1.1.7) variant that emerged in January, 2021 have been shown to be safe and effective, as evidenced by clinical trials and real-world data.^{2–8} However, SARS-CoV-2, like other RNA viruses, is very prone to genetic evolution as it adapts to new human hosts.¹ So far, at least ten variants have been identified worldwide, of which the delta (B.1.617.2) variant and the more recent omicron (B.1.1.529) variant, in particular, have been jeopardising millions of people's lives since late November, 2021. The currently licensed and approved COVID-19 vaccines might not effectively prevent infection with these new and other imminent subvariants (eg, BA.2, BA.3, BA.4, and BA.5).^{9–13} Although the pandemic is seemingly contained in Europe and North America, at the time of writing, it continues to be widely active in southeast Asia, the Western Pacific region, and Africa. The more contagious omicron variants are still spreading relentlessly in these regions, which is leading to acute demand and subsequent scarcity of intensive care resources, quarantine and isolation facilities, and rapid antigen testing kits. Although international recommendation guidelines and consensus statements on risk stratification and treatment of head and neck cancers have been published,^{14–19} none exist for nasopharyngeal carcinoma, a malignancy that is endemic to the aforementioned geographical regions. Nasopharyngeal carcinoma is a unique, distinct disease entity distinguished

from head and neck squamous cell carcinoma by its strong association with Epstein-Barr virus (EBV).²⁰ Concerted efforts, over the past two decades, to improve and internationally harmonise detection limits have made plasma EBV DNA the most sensitive and specific biomarker for the screening, diagnosis, risk stratification, treatment response evaluation, relapse surveillance, and prognostication of this deadly malignancy.²¹ More detailed and sophisticated investigative tools with MRI with diverse sequences (compared with CT for head and neck squamous cell carcinoma), PET with integrated CT, and nasoendoscopy are very often indicated in the routine clinical management of nasopharyngeal carcinoma.^{22–25} However, nasoendoscopy has been classified, with a high degree of agreement, as an aerosol-generating procedure with a high risk for viral aerosolisation.^{15,26} Unfortunately, provision of these imaging and endoscopy services and typical face-to-face doctor–patient consultations had to be suspended or were severely delayed during the pandemic. Given the accuracy and reliability of plasma EBV DNA, and to address the urgent need for aerosol-free procedures to manage nasopharyngeal carcinoma in the face of the potential for future waves of the COVID-19 or other airborne pandemics, we used a modified online Delphi process, with representation from nasopharyngeal carcinoma experts worldwide, to develop consensus recommendations on the use of plasma EBV DNA for the management of nasopharyngeal carcinoma during the COVID-19 pandemic or other circumstances in which personnel and resources are severely constrained in an acute setting.

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Panel: Bodies and societies represented by the experts in this consensus development committee

- American Academy of Otolaryngology Head and Neck Surgery Foundation
- American Association for Cancer Research
- American Association for the Advancement of Science
- American Head and Neck Society
- American Joint Committee on Cancer
- American Radium Society
- American Society for Radiation Oncology
- American Society of Clinical Oncology
- Asian Society of Head and Neck Oncology
- BC Cancer Head and Neck Tumour Group
- Catalan-Balearic Society for Oncology
- China Anti-Cancer Association
- Chinese Society of Clinical Oncology
- European Head and Neck Society
- European Organisation for Research and Treatment of Cancer
- European Society for Medical Oncology
- European Society for Radiotherapy and Oncology
- Federations of Asian Organizations for Radiation Oncology
- Head and Neck Cancer International Group
- Hong Kong Cancer Therapy Society
- Hong Kong College of Otorhinolaryngologists
- Hong Kong College of Radiologists
- Hong Kong Head and Neck Society
- Hong Kong Nasopharyngeal Carcinoma Study Group
- Hong Kong Society of Clinical Oncology
- Hong Kong Society of Otorhinolaryngology, Head and Neck Surgery
- Indonesian Otorhinolaryngology Head and Neck Society
- International Academy of Oral Oncology
- International Commission on Radiation Units and Measurements
- International Federation of Head and Neck Oncologic Societies
- International Head and Neck Scientific Group
- Italian Association of Head and Neck Oncology
- Italian Association of Medical Oncology
- Malaysian Oncological Society
- National Cancer Staging Committee of China
- North-West Oncological Italian Group
- NRG Oncology
- Pan-Pearl River Delta Radiation Oncology Conference Committee
- Radiological Society of North America
- Royal College of Radiologists
- Singapore Radiological Society
- Singapore Society of Oncology
- Sociedad Española de Oncología Médica
- Société Française Radiation Oncology
- South East Asian Radiation Oncology Group
- Spanish Head and Neck Cancer Group
- Taiwan Head and Neck Society
- Taiwan Oncology Society
- Taiwan Society for Therapeutic Radiology and Oncology
- Thai Association of Radiation Oncology
- Union for International Cancer Control

Data collection, survey design, and participant recruitment

The steering committee (VH-FL, AW-ML, and W-TN) collated all published literature on plasma EBV DNA in nasopharyngeal carcinoma management, designed the online survey, and piloted the questions for the survey. During August, 2021, we invited 33 nasopharyngeal carcinoma experts from the fields of otorhinolaryngology or head and neck surgery, radiation oncology, medical oncology, and clinical oncology. Experts from four continents (Asia, North America, Europe, and Africa) were invited, specifically from China, Hong Kong, Taiwan, Thailand, Malaysia, Singapore, Indonesia, Italy, France, Belgium, Spain, the USA, Canada, and Tunisia. Experts were considered if they had practised as full-time clinicians in tertiary academic institutions and university teaching or affiliated hospitals for at least 10 years, managed and treated more than 200 patients with nasopharyngeal carcinoma in total, authored or coauthored at least 20 journal articles on nasopharyngeal carcinoma or plasma EBV DNA, and had clinical experience in using plasma EBV DNA in both clinical trials and routine clinical practice. The invited experts provided representation from 51 international professional societies and national clinical trial groups (panel).

Consensus establishment

The collected published literature and article of recommendations on the use of plasma EBV DNA in the management of nasopharyngeal carcinoma²¹ was shared with all participating experts. The article summarises all the published literature and provides a comprehensive overview and recommendation on the use of plasma EBV DNA in various routine clinical settings. The experts could comment on the literature and survey questions before the commencement of the online survey. Upon acceptance of invitation, they were given the link to complete the online questionnaire. Consensus statements were developed with an online, modified Delphi process done over three rounds (figure). The online survey consisted of two parts: the first on the use of plasma EBV DNA in diagnosis, pretreatment investigations, staging, response monitoring during radical treatment, surveillance, response monitoring for recurrent or metastatic nasopharyngeal carcinoma in a normal (non-pandemic) setting (questions 5–10); and the second on the use of plasma EBV DNA in the same clinical circumstances but in the context of severe personnel and resource constraints and risk of COVID-19 transmission as a result of a biopsy or the aerosol-generating nasoendoscopy procedure (questions 11–26; appendix pp 4–7).

Participants were invited by email to complete each round of the survey, which was open for a period of 3 weeks. A reminder email was sent 2 days and 1 day before the deadline to prompt participants who had not yet submitted their responses to complete the survey. When completing the survey, participants were expected

to consider an extremely constrained setting in terms of capacity and resources (including, but not limited to, a severe dearth in health-care professionals and other clinical clerical staff members, operating and endoscopy room capacity, inpatient and intensive care bed capacity, ventilation facilities, and rapid COVID-19 diagnostic tests) compared with baseline before and during the initial waves of the COVID-19 pandemic. Following each round of the survey, the steering committee analysed the results and applied the following predetermined criteria for agreement, which were based on the RAND method²⁷ and set in the protocol before the start of the project: 80% or higher agreement was classified as strong agreement for a statement, whereas 20% or lower indicated a strong disagreement. For each statement, the Delphi process was stopped either when strong agreement was reached or after completion of three rounds of the survey, whichever occurred first. Items that reached strong agreement were not included again in subsequent rounds of the survey. After the third round, statements that did not reach the strong agreement threshold but that reached a threshold of agreement of 67% or higher were considered to have reached agreement.¹⁸ Results from the first and second rounds were emailed to participants for review before the next round commenced. Participants were reminded that they could change their responses in the subsequent round for questions that had not yet reached strong agreement. When necessary, questions would be iteratively revised between rounds before being asked again, and new questions would be introduced to provide more granularity to the topic or to reduce ambiguity on the phrasing of a previous question. The consensus statement development process and the online survey were approved by the Institutional Review Board of the University of Hong Kong and of the Hong Kong West Cluster Hospital Authority.

Findings

The first four questions appeared only in the first round of the survey and asked participants for their name (question 1), specialty (otorhinolaryngology or head and neck surgery, radiation oncology, medical oncology, and clinical oncology; question 2), all affiliations with any local, regional, national, or international professional surgery or oncology organisations (question 3), and any membership in international surgery or oncology organisations (question 4; appendix pp 1–3).

A total of 22 questions pertaining to the objective of this consensus recommendation were asked in this survey. 22 questions were asked in the first round. A summary of the results of the three rounds of the survey is available in the appendix (pp 4–8) and in the table.

Consensus statement on measuring plasma EBV DNA in routine clinical management

All participants agreed that plasma EBV DNA should be routinely measured during pretreatment investigations.

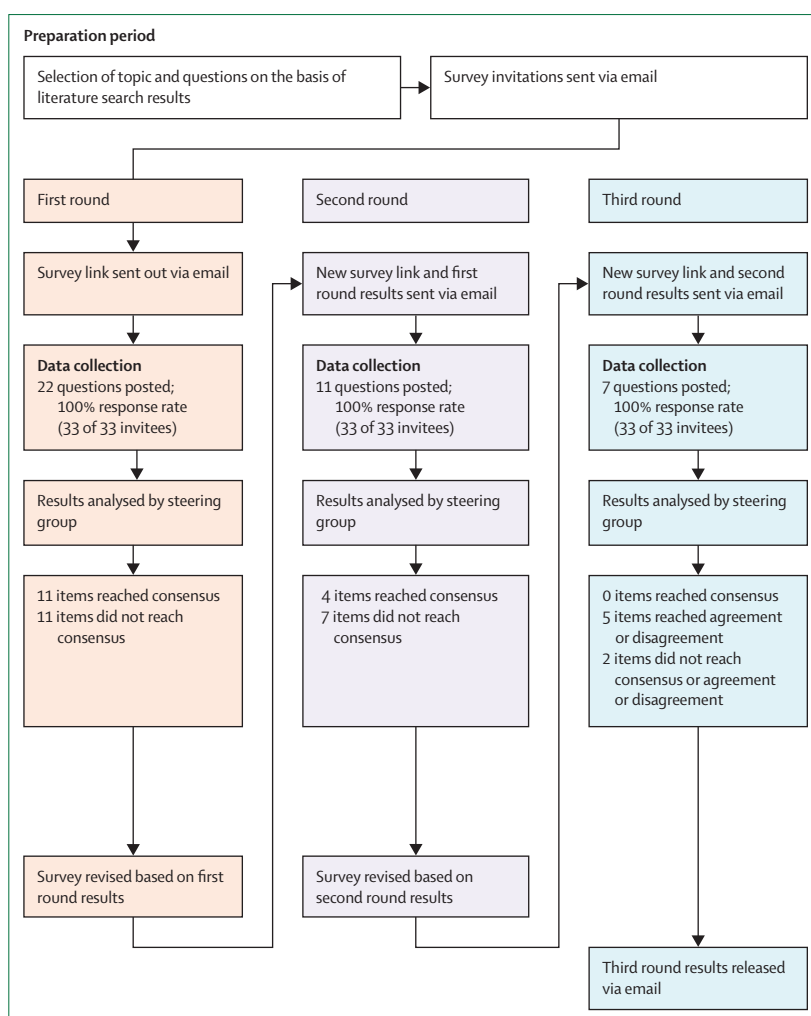


Figure: Modified Delphi process of the online survey

Although consensus was reached on the use of plasma EBV DNA for disease surveillance to rule out early relapse and to monitor treatment response during salvage treatment for recurrent or metastatic nasopharyngeal carcinoma, two (6%) participants queried its sensitivity to detect small, locally recurrent disease or early relapse. The question that did not reach any consensus or agreement (64%, question 5) was whether plasma EBV DNA could be considered for nasopharyngeal carcinoma screening in endemic regions, and whether its diagnostic sensitivity and cost-effectiveness could be further improved by combination with EBV IgA anti-viral capsid antigen testing. Slightly divided opinions on the use of plasma EBV DNA for screening appeared in question 5: although most of the experts commented that plasma EBV DNA and serology was cost-effective for nasopharyngeal carcinoma screening, others argued that neither plasma EBV DNA alone, or in combination with EBV IgA anti-viral capsid antigen or IgA early antigen, or both can further

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improve sensitivity and specificity, especially for small early-stage disease.

Measuring EBV DNA during resource constraints and to avoid aerosol generation

Screening and diagnosis

The participants were strongly against the use and repeated use (eg, 4 weeks after an initial undetectable titre) of plasma EBV DNA exclusively (88% disagreement, questions 11 and 13) or in combination with EBV IgA anti-viral capsid antigen (94% disagreement, question 12) to replace nasoendoscopy and other diagnostic or imaging tools in the clinic to screen for and diagnose nasopharyngeal carcinoma during the pandemic, when

resources were severely low and aerosol-generating procedures were to be avoided. Similarly, a consensus strong disagreement was also reached regarding the use of plasma EBV DNA without histological confirmation to diagnose nasopharyngeal carcinoma (97% disagreement, question 14), even for patients who present with salient clinical symptoms. Most of the participants commented that nasoendoscopic examination, biopsy (to rule out other EBV-associated malignancies, such as natural killer T-cell lymphoma, which is common in Asia and in Latin America), and imaging were still essential to nasopharyngeal carcinoma diagnosis, even in the setting of restricted resources. All experts who disagreed with plasma EBV DNA as the only investigation tool urged for

	Agreement or disagreement level
Part 1: use of plasma EBV DNA in typical (non-pandemic) circumstances	
For pretreatment investigation of newly diagnosed nasopharyngeal carcinoma	Strong agreement
To monitor response during radical treatment	Strong agreement
After completion of radical treatment	Strong agreement
For disease surveillance during subsequent follow-up for early detection of relapse	Strong agreement
To monitor response to salvage treatment for recurrent or metastatic nasopharyngeal carcinoma	Strong agreement
Part 2: use of plasma EBV DNA in a setting of acute and severe personnel and resource constraints (eg, during the COVID-19 pandemic)	
As the only screening and diagnostic tool for nasopharyngeal carcinoma, replacing nasoendoscopy, biopsy, and other diagnostic or imaging tools	Strong disagreement
In combination with IgA anti-VCA as the only screening and diagnostic tool for nasopharyngeal carcinoma, replacing nasoendoscopy, biopsy, and other diagnostic or imaging tools	Strong disagreement
For repeat testing (eg, 4 weeks later) as the only screening and diagnostic tool for a patient with clinical suspicion of nasopharyngeal carcinoma if the initial plasma EBV DNA titre is undetectable, replacing nasoendoscopy, biopsy, and other diagnostic or imaging tools in clinic	Strong disagreement
A high plasma EBV DNA concentration together with salient clinical symptoms but without histological confirmation is sufficient for the diagnosis of nasopharyngeal carcinoma	Strong disagreement
In combination with IgA anti-VCA with imaging tools (eg, ultrasonography, CT, MRI, bone scintigraphy, and PET-CT) as the only staging investigations for nasopharyngeal carcinoma, replacing nasoendoscopy and biopsy	Disagreement
In combination with IgA anti-VCA without imaging tools (except CT scan for radiotherapy planning purpose) as the only staging investigations for nasopharyngeal carcinoma, replacing nasoendoscopy and biopsy in clinic	Strong disagreement
As the only test to replace clinical consultations to monitor the progress of nasopharyngeal carcinoma in the course of radical treatment	Disagreement
As the only test without imaging tools (eg, ultrasonography, CT, MRI, and PET-CT), to replace nasoendoscopy and biopsy and other diagnostic tools in clinic to confirm complete local and regional remission after completion of radical treatment	Strong disagreement
In combination with imaging tools (eg, ultrasonography, CT, MRI, bone scintigraphy, and PET-CT) as the only surveillance tools for relapse of nasopharyngeal carcinoma after completion of radical treatment, replacing nasoendoscopy, biopsy, and other diagnostic tools	Agreement
As the only surveillance test without imaging tools (eg, ultrasonography, CT, MRI, bone scintigraphy, and PET-CT), replacing nasoendoscopy, biopsy, and other diagnostic tools for relapse of nasopharyngeal carcinoma after completion of radical treatment	Strong disagreement
As the only surveillance test, replacing clinical consultations, nasoendoscopy, biopsy, and other imaging or diagnostic tools for relapse of nasopharyngeal carcinoma after radical treatment	Strong disagreement
In combination with imaging tools (eg, ultrasonography, CT, MRI, and PET-CT), replacing nasoendoscopy, biopsy, and other diagnostic tools to diagnose clinically suspicious recurrent nasopharyngeal carcinoma	Disagreement
As the only test without imaging tools (eg, ultrasonography, CT, MRI, and PET-CT), replacing nasoendoscopy, biopsy, and other diagnostic tools to diagnose clinically suspicious recurrent nasopharyngeal carcinoma	Strong disagreement
An increased or progressively rising titre of plasma EBV DNA alone, without histological and imaging results, is sufficient for the diagnosis of recurrent nasopharyngeal carcinoma	Strong disagreement
As the only test without other diagnostic and imaging tools to monitor the tumour response during and after treatment for recurrent or metastatic nasopharyngeal carcinoma	Disagreement
Strong agreement corresponds to a threshold of 80% or higher agreement. Strong disagreement corresponds to a threshold of 20% or lower agreement. Agreement or disagreement corresponds to a threshold of 67% or higher after the third round for statements that did not reach a strong agreement or strong disagreement in previous rounds. EBV=Epstein-Barr virus. VCA=viral capsid antigen.	
Table: Consensus recommendations for the use of plasma EBV DNA in the management of nasopharyngeal carcinoma	

the use of full personal protective equipment to conduct risky endoscopic procedures. They further commented that a histological diagnosis of nasopharyngeal carcinoma was necessary before starting any treatment.

There was unanimous disagreement (100%) regarding the use of plasma EBV DNA and IgA anti-viral capsid antigen, without imaging tools, to replace nasoendoscopy and biopsy as the only staging investigations for nasopharyngeal carcinoma during the COVID-19 pandemic (question 16). Even with the availability of imaging tools, the participants expressed disagreement against the use of plasma EBV DNA to replace nasoendoscopy and biopsy as the only staging investigation during the pandemic (73% disagreement, question 15). Again, the participants suggested an endoscopic examination to evaluate the local extent of the disease, and histological confirmation to establish the diagnosis and exclude other EBV-associated malignancies, even in resource-constrained settings.

Treatment response monitoring

The participants did not support the use of plasma EBV DNA to replace clinical consultations to monitor the progress of nasopharyngeal carcinoma in the course of its radical treatment during the pandemic (73% disagreement, question 17). Clinical evaluations in the form of face-to-face consultations, as commented by the participants, were needed to monitor for acute toxicity during radical treatment.

Confirmation of disease remission after radical treatment

Although 55% of the participants agreed on the use of plasma EBV DNA and imaging tools to replace nasoendoscopy, biopsy, and other diagnostic tools to confirm local and regional remission of nasopharyngeal carcinoma after radical treatment during the pandemic (question 18), an agreement could not be reached because other participants believed that nasoendoscopy with or without biopsy were still necessary to evaluate local remission after radical treatment, and for patients whose pretreatment plasma EBV DNA was undetectable. By contrast, most participants strongly disagreed with the use of plasma EBV DNA only, without any imaging tools, nasoendoscopy, or biopsy (91% disagreement, question 19), as the only way to confirm local and regional remission following radical treatment.

Disease surveillance after completion of radical treatment

An agreement (70% agreement, question 20) was reached on the use of plasma EBV DNA and imaging, to replace nasoendoscopy and biopsy, as the only surveillance tools for nasopharyngeal carcinoma relapse after completion of radical treatment during the pandemic. However, strong disagreement (82% disagreement, question 21) was observed if only plasma EBV DNA was used as the

surveillance tool for nasopharyngeal carcinoma relapse, to replace nasoendoscopy, biopsy, and other imaging or diagnostic tools, and to replace clinical consultation, nasoendoscopy, biopsy, and other imaging or diagnostic tools in severely resource-constrained settings (85% disagreement, question 22).

Diagnosis of clinically suspicious recurrent disease

When asked whether plasma EBV DNA could replace nasoendoscopy and biopsy to diagnose clinically suspicious recurrent symptoms in patients who presented with symptoms highly suggestive of nasopharyngeal carcinoma recurrence, most participants disagreed, even when imaging scans were available (79% disagreement, question 23), and all strongly disagreed if imaging services were not provided at all due to resource constraints during the pandemic (100% disagreement, question 24). Similarly, most participants disagreed with increased or progressively rising titres of plasma EBV alone, without any histological and imaging correlation, as the only criterion to diagnose nasopharyngeal carcinoma recurrence during the pandemic (94% disagreement, question 25).

Monitoring treatment response in recurrent or metastatic disease

Most participants disagreed with measuring plasma EBV DNA only, without other imaging or diagnostic tools, to monitor the treatment response for recurrent or metastatic nasopharyngeal carcinoma during the pandemic (73% disagreement, question 26). The general opinion was that imaging assessment, even if done over a prolonged interval due to resource limitations, was still needed because it provided a clear presentation of the extent of the tumour response, which could not be accurately reflected by the change in titre of plasma EBV DNA.

Discussion

Endoscopic and imaging assessment are essential procedures for the clinical management of nasopharyngeal carcinoma. However, to our knowledge, the possibility of limited availability of these facilities and resources during a global pandemic had not before been considered, even in high-income countries and regions with well established health-care infrastructure and expertise. Plasma EBV DNA has been considered an accurate, reliable, and cost-effective tumour marker and biomarker of nasopharyngeal carcinoma, which has been widely used in screening, diagnosis, prognostication, surveillance for relapse, and treatment response evaluation during radical and salvage treatment.^{21,28} Histological confirmation from a tumour biopsy is still the gold standard for the diagnosis of cancer, including nasopharyngeal carcinoma. However, whether liquid biopsies, which can contain cell-free tumour DNA or circulating tumour DNA, could replace conventional diagnostic methods such as tumour biopsies and endoscopy and imaging assessment is a question worth

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See Online for appendix

exploring in light of the COVID-19 pandemic. Nasoendoscopy has been classified with a high level of consensus as a possibly aerosol-generating procedure.^{15,26} For this reason, and considering that the pandemic also occasioned a severe shortage of health-care personnel, personal protective equipment, and rapid diagnostic tests for SARS-CoV-2, we developed this global consensus recommendation on the use of plasma EBV DNA in routine clinical management of nasopharyngeal carcinoma, which aims to provide a guideline to health-care staff actively involved in the management of nasopharyngeal carcinoma and overwhelmed by the pandemic. These recommendations should not be considered as permanent, but as contingent on current conditions and in place for future pandemics or natural disasters. Furthermore, they should be interpreted in the context of global, national, regional, and local COVID-19 circumstances, which can drastically change in a short time.

Nasopharyngeal carcinoma is managed quite differently from head and neck squamous cell carcinoma. Nasoendoscopy and nasoendoscopic biopsy, imaging with MRI with numerous scanning sequences, and PET-CT scans are essential components for the diagnosis of nasopharyngeal carcinoma and its differentiation from post-treatment changes and treatment-related complications.^{22–25} Unlike head and neck squamous cell carcinoma, for which no accurate and reliable tumour

biomarker exists, nasopharyngeal carcinoma typically results in circulating cell-free EBV DNA, which can be easily and reliably extracted as plasma EBV DNA and evaluated in routine blood taking. Following the concerted efforts on international harmonisation of the performance level of the assay, plasma EBV DNA has come into worldwide usage in routine clinical care and as an important risk stratification factor in international, multicentre, randomised controlled trials.^{21,29,30}

During a pandemic, considering alternative emergency strategies for the management of nasopharyngeal carcinoma becomes imperative, as nasoendoscopy, imaging scans, and even in-person medical consultations pose substantial exposure risks to both health-care workers and patients, especially in situations of scarcity of front-line health-care workers and personal protective equipment.^{31,32} The results of our survey suggest that, although plasma EBV DNA (supplemented, when possible, by imaging scans) can be used in most clinical circumstances in the context of resource limitations, it cannot completely replace nasoendoscopy and tumour biopsy. All experts who disagreed with the use of plasma EBV DNA as the only tool in nasopharyngeal carcinoma management considered that these procedures are essential and that the patients' right to receive these standard investigations should not be suppressed, insofar as the health-care system allowed.

The invited experts represented a broad range of clinical disciplines relevant for the care of nasopharyngeal carcinoma, consisting of professionals experienced in managing this malignancy as front-line doctors from across four continents. They also hold leadership and membership positions in international and national surgical and oncological societies and come from both low-income and middle-income countries and high-income countries, being very familiar with their national, regional, and local clinical practice of nasopharyngeal carcinoma management. Our recommendations have taken into consideration various clinical scenarios from the joint perspectives of surgeons and non-surgeons, unlike previous recommendations published by surgeons and oncologists separately. In contrast to previous recommendations on flexible nasoendoscopy only for patients who are deemed to be at high risk of cancer recurrence and mortality from head and neck cancers and only when adequate personal protective equipment is available,¹⁷ our experts strongly disagreed with measuring plasma EBV DNA only to replace the conventional but essential nasoendoscopic examinations, even when imaging services were scarce. Plasma EBV DNA in combination with imaging scans can be considered an acceptable alternative in a very restricted clinical setting, but cannot replace face-to-face consultations and nasoendoscopy, and it cannot be used alone (without imaging) for the management of nasopharyngeal carcinoma. We believe that these recommendations, which are the concerted efforts and

Search strategy and selection criteria

To clarify uncertainty around the use of plasma Epstein-Barr virus (EBV) DNA in the clinical management of nasopharyngeal carcinoma in the setting of acute personnel and resource constraints during the COVID-19 pandemic, we did a literature search of PubMed, Embase, MEDLINE, and Google Scholar that included grey literature, individual association correspondence, and guidelines on COVID-19 (or COVID or pandemic) and nasopharyngeal carcinoma. We used the search terms "nasopharyngeal carcinoma" or "nasopharyngeal cancer", "COVID-19" or "COVID" or "SARS-CoV-2", and "EBV DNA" or "cell-free DNA" and searched for articles published in English between Nov 1, 2019, and April 30, 2022. We prioritised peer-reviewed journal articles, large case-series papers, and guidelines and recommendations published by local, regional, national, or international bodies. All participating experts held discussions to identify areas of uncertainty in the literature search and selection criteria. We did not identify any article or paper that fulfilled our selection criteria. Therefore, we designed and conducted three rounds of online survey with modified Delphi method and established consensus statements. All domains (part 1 and 2 in the survey) and questions within each domain were piloted by the steering committee (VH-FL, AW-ML, and W-TN) for readability and validity (appendix pp 4–8).

results of international collaboration and cooperation, can serve as references and be used in other acute settings or during natural disasters, where there is an unexpectedly high risk of health hazards to patients and health-care workers and a severe paucity of health personnel and resources. We also hope that our recommendations can further promote and invite international harmonisation and more affordable use of plasma EBV DNA for nasopharyngeal carcinoma and other accurate blood or liquid biomarkers for other cancers at institutions and hospitals in low-income and middle-income countries, so that patients treated in these locations are not underprivileged in the face of future pandemics or natural disasters.

Our recommendations have some limitations. They might not be fully applicable to countries or regions where nasopharyngeal carcinoma is sporadic, and where standardised and accurate plasma EBV DNA assays are not available. When asked to participate in this study, our experts were expected to be confronted with any eventuality and the most difficult situations when all the necessary resources and personnel were severely constrained and rationed, which might not actually occur in some countries or regions where the pandemic was better controlled. The time period over which this survey was conducted was the most critical and difficult for the Asian population affected by the omicron variant and subvariants, happening at a time when the most stringent infection control and physical distancing measures were gradually being lifted in North America and in Europe. A strong clinical network should be provided and duly modulated with continuous support to facilitate front-line clinicians when they are faced with extremely difficult and fluctuating situations in different regions of the world.

Conclusion

We are hoping that the pandemic is nearing its end, but global preparedness for a similar or different disruptor is highly advised. Although plasma EBV DNA has reached a crucial role in the clinical management of nasopharyngeal carcinoma, nasoendoscopic and imaging examinations and face-to-face consultations remain essential, even in the setting of acute resource and personnel limitations, such as during the COVID-19 pandemic. Our consensus recommendations illustrate an excellent example of international collaboration in times of current and imminent global challenges, which can be easily applied and adopted to suit different needs. Although these recommendations were specifically developed for the COVID-19 pandemic, they have the potential generalisability to be applied in other circumstances of severe shortage of health-care personnel and resources. Measures to ensure adequate protective equipment for the safety of patients and health-care workers and essential support for health facilities are urgently warranted before future pandemics or disasters arise.

Contributors

VH-FL, AW-ML, and W-TN conceived and designed the study and piloted the survey questions. All authors participated in study development, data collection and interpretation, manuscript preparation, and approved the final manuscript of this Policy Review. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

VH-FL reports personal fees and grants from AstraZeneca; and personal fees from AQUILAB, Amgen, Boston Scientific, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, and Takeda, all outside this Policy Review. GFH reports fees paid to the institution from Eli Lilly, Regeneron, Merck Sharp and Dohme, AB Science, Astellas, Tessa Therapeutics, Roche, Arcus Bioscience, AstraZeneca, and Pfizer; and personal fees from Merck Sharp and Dohme, Novartis, Roche, AstraZeneca, Boehringer Ingelheim, Pfizer, Ipsen, Bristol Myers Squibb, Janssen, and Taiho, all outside the scope of this Policy Review. WKJL is a shareholder of Illumina/GRAIL. Q-TL reports personal fees from the RTOG Foundation and NRG Oncology, outside the scope of this Policy Review, and is supported by the US National Institutes of Health (2U10CA180868-06, 1R01DE029672-01A1, P30CA124435, and R01DE030894-01A1). NYL is supported by the US National Institutes of Health (R01 CA238392-02A1 and 5UG1CA233290-02). DW-TL reports institutional fees from Bristol Myers Squibb, Merck Sharp and Dohme, Boehringer Ingelheim, Janssen, and Novartis, outside the scope of this Policy Review. RM reports personal fees from Merck Pharmaceuticals, Merck Sharp and Dohme, Bristol Myers Squibb, Roche, Amgen, AstraZeneca, Nanobiotix, Seattle Genetics, and Boehringer Ingelheim, all outside the scope of this Policy Review. RK-CN reports personal fees from Pfizer, Novartis, Sanofi, AstraZeneca, Eli Lilly, Merck Sharp and Dohme, Zai Lab, Roche, Eisai, Merck Pharmaceutical, Astellas, and Nuance (China), outside the scope of this Policy Review. RK-YT is the President of Hong Kong Society of Otolaryngology, Head and Neck Surgery, and past President of Hong Kong Head and Neck Society. All other authors declare no competing interests.

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