Philippine Head and Neck Cancer Clinical Practice Guidelines 2023

Commissioned by the Department of Health
to Jose R. Reyes Memorial Medical Center

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Disclaimer

This clinical practice guideline (CPG) is intended to be used by specialists and general practitioners who are primary care providers. Although adherence to this guideline is encouraged by the Department of Health (DOH), it is important to note that clinicians should not be restricted in their ability to exercise clinical judgment and take into account the values, needs, and preferences of their patients when handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and responses to tests and treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance with this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations outlined in this CPG should not be construed as directives to serve as the basis for legal proceedings.

The developers of this CPG are aware of its limitations. Evidence summaries under Key Findings are based on the best available international practice guidelines at the time of their formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of head and neck cancer. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

Contact Us

Send us an email at itlim@ust.edu.ph for any questions or clarifications on the outputs and process of this practice guideline.

Acknowledgments

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The credibility of this CPG is upheld by the Conflict of Interest (COI) Review Committee, which oversees the assessment of potential COIs among all members involved in this guideline development.

The Steering Committee was also indispensable in carrying out the legwork, coordinating among various society representatives and committees, and holding *en banc* meetings. The SC was also in charge of overall organization and management and is accountable for the quality of the CPG.

The Technical Working Group undertook extensive technical work in searching and synthesizing the evidence while ensuring objectivity in each stage of the process and presenting the evidence in the panel discussion.

The contribution of consensus panelists from various healthcare sectors renders this guideline invaluable. The panelists devoted their time and energy to sharing their knowledge, experience, and expertise to weigh the scientific evidence, patients' values and preferences, and other relevant issues such as best practices, accessibility, feasibility, and equity in the healthcare system of the country.

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Jose R. Reyes Memorial Medical Center Manila

UP Manila – National Institutes of Health

Philippine College of Surgeons

Philippine Society of Otolaryngology-Head and Neck Surgery

Philippine Society of General Surgeons

Philippine Academy for Head and Neck Surgery, Inc.

. Surgical Oncology Society of the Philippines

Academy for Head and Neck Oncology of the Philippines

Philippine College of Radiology

Philippine Radiation Oncology Society

Philippine Society of Medical Oncology

Philippine Association of Speech - Language Pathologists

Philippine Association of Plastic Reconstructive and Aesthetic Surgeons

Philippine Society for Parenteral and Enteral Nutrition

Philippine Society of Pathologists, Inc.

Pain Society of the Philippines

Philippine Academy of Family Physicians, Inc.

List of Abbreviations and Acronyms

AHNOP	Academy for Head and Neck Oncology of the Philippines
AJCC	American Joint Committee on Cancer
COI	Conflict of interest
CP	Consensus panel
CT	Computed tomography
CTRT	chemoradiosensitizing
DOH	Department of Health
DOI	Depth of invasion
END	Elective neck dissection
ENE	Extracapsular nodal extension
EBRT	External beam radiotherapy
FDG-PET	Fluorodeoxyglucose-positron emission tomography
HPV	Human papillomavirus
HR	Hazard ratio
IMRT	Intensity-modulated radiation therapy
JRRMMC	Jose R. Reyes Memorial Medical Center Manila
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
NBI	Narrow-band imaging
NCCN	National Comprehensive Cancer Network
NPC	Nasopharyngeal cancer
NPV	Negative predictive value
OR	Odds ratio
OS	Overall survival
PAFP	Philippine Academy of Family Physicians, Inc.
PAHNSI	Philippine Academy for Head and Neck Surgery, Inc.
PAPRAS	Philippine Association of Plastic Reconstructive and Aesthetic Surgeons
PASP	Philippine Association of Speech Pathologists
PCR	Philippine College of Radiology
PCS	Philippine College of Surgeons
PhilSPEN	Philippine Society for Parenteral and Enteral Nutrition
PROS	Philippine Radiation Oncology Society
PSGS	Philippine Society of General Surgeons
PSMO	Philippine Society of Medical Oncology
PSO-HNS	Philippine Society of Otolaryngology-Head and Neck Surgery
PSP	Philippine Society of Pathologists, Inc.
PICO	Population, intervention, comparator, outcome
PPV	Positive predictive value
RR	Risk ratio
RT	Radiation therapy
SC	Steering Committee
SOSP	Surgical Oncology Society of the Philippines
SLN	Sentinel lymph node
TSH	Thyroid stimulating hormone

TWG	Technical Working Group
NGC	National Guideline Clearinghouse
NICCA	National Integrated Cancer Control Act
UICC	Union for International Cancer Control
VMAT	Volumetric-modulated arc therapy

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Executive Summary

Head and neck cancers, which are usually of squamous cell origin and affect the upper aerodigestive area, remain one of the most significant causes of mortality and morbidity. Although oral cavity, laryngeal, and nasopharyngeal cancers seem rare globally, head and neck cancer still rank among the top 20 most common cancers in the country. These cancer sites are covered in this clinical practice guideline.

This CPG on head and neck cancer aims to provide recommendations on diagnostic and therapeutic aspects of oral cavity, laryngeal, and nasopharyngeal cancer from the early stage to the advanced and metastatic stage, where variability in clinical practice may be observed. It does not aim to address every aspect of head and neck cancer care, but this guideline is intended to be used by general practitioners and specialists, other healthcare professionals, administrators, or policymakers to improve the management of head and neck cancer. Its target beneficiaries are patients with oral cavity cancer, laryngeal cancer, or nasopharyngeal cancer.

This guideline is based on the adapted international guidelines (literature search up until August 2022), best practices, and resources in the country. Distinct working groups were established to oversee the guideline methodology, review the evidence, and formulate the recommendations. A multisectoral panel of representatives and experts collaborated to develop a set of recommendations that were agreed upon by consensus.

The following tables show the summary of recommendations for three sites of head and neck cancer.

Summary of Recommendations: General Question

Table 1. Summary of recommendation statements, strength of recommendation, and certainty of evidence on general question on head and neck cancer

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
1	1.1 We recommend an MDT approach to improve the quality of care of the head and neck cancer patients.	Moderate	Strong
	1.2. We recommend a pre- and posttreatment multidisciplinary tumor board for all head and neck cancer patients.	Moderate	Strong

Summary of Recommendations: Oral Cavity Cancer

Table 2. Summary of recommendation statements, strength of recommendation, and certainty of evidence on diagnosis and management of oral cavity cancer

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
1	1.1. We recommend that patients with the following signs and symptoms be referred to a specialist for further evaluation and treatment. Clinical features of suspicious lesions in the oral cavity include mucosal changes lasting more than two weeks with any of these findings: ● non-healing ulcers ● red/white patches ● hardening of the mucosa ● bleeding Other symptoms that may be associated with suspicious oral cavity lesions: ● chronic pain in the throat ● painful or difficulty swallowing ● difficulties in mouth opening and chewing ● trismus ● loosening of the teeth, numbness or loss of adjacent teeth not associated with periodontal disease and /or malocclusion ● unilateral foreign body sensation ● decreased tongue mobility	Low	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
	● numbness of the tongue, teeth or lip ● fetor or halitosis ● presence of neck masses		
	1.2. We recommend identifying risk factors such as a history of betel nut chewing, tobacco use, and alcohol consumption in a patient with suspicious oral cavity lesions.	Low	Strong
2	2. We recommend performing tissue biopsy (incisional or punch biopsy) prior to initiating treatment in patients suspected of having oral cavity cancer.	Moderate	Strong
3.1	3.1.1. We recommend the use of contrast-enhanced CT or MRI for evaluating the extent of the primary tumor. Moderate certainty of evidence, Strong recommendation	Moderate	Strong
	3.1.2. We recommend a panoramic dental x-ray for assessing mandibular involvement in tumors located at the tongue, floor of the mouth and gingiva, if CT is not accessible.	Moderate	Strong
3.2	3.2.1. We recommend evaluating the cervical lymph node basin with contrast-enhanced CT scan or MRI.	Moderate	Strong
	3.2.2. We recommend the use of an ultrasound to evaluate the neck in low-resource settings.	Moderate	Strong
3.3	3.3.1. We recommend at least a chest CT with contrast for asymptomatic patients with locally advanced disease.	Moderate	Strong
	3.3.2. We recommend a symptom-directed approach to evaluate distant metastases in patients with oral cavity cancer. In low-resource settings, a chest x-ray is recommended to assess for lung metastases.	Moderate	Strong
3.4	3.4.1. We recommend assessment of oral functions such as mastication, speech, and swallowing prior to treatment.	Moderate	Strong
	3.4.2. We recommend a pre-treatment assessment of the nutritional status of patients with oral cavity cancer.	Moderate	Strong
	3.4.3. We recommend a preoperative dental evaluation, especially for patients with locally advanced lesions.	Moderate	Strong
	3.4.4. We recommend evaluating for second primary malignancies with the use of panendoscopy (except bronchoscopy) or a PET/CT.	Moderate	Strong
3.5	3.5. We suggest using the latest edition of the AJCC staging system for staging oral cavity cancers.	Very Low	Weak

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
4.1	4.1 We recommend surgery (preferred) possibly followed by radiation therapy or chemoradiation therapy if indicated for patients with early-stage oral cavity cancer.	High	Strong
4.2	4.2. We recommend a gross surgical margin of at least 1 cm of surrounding normal tissue with the ultimate goal of having a pathologic margin of at least 5 mm.	High	Strong
4.3	4.3. We recommend intraoperative margin assessment using frozen section whenever available.	Low	Strong
4.4	4.4. We recommend elective ipsilateral supraomohyoid neck dissection (levels I, II, and III) in patients with the following: ● cT2 oral cavity cancer ● cT1 disease which is moderate to poorly differentiated or with depth of invasion of > 3 mm.	High	Strong
4.5	4.5. We recommend elective contralateral supraomohyoid neck dissection in patients with cT2 oral cavity cancer, cT1 tumors that are moderate to poorly differentiated, or those with DOI > 3mm which: ● crossed the midline of the hard palate and tongue ● located at the floor of the mouth.	High	Strong
4.6	4.6. We recommend radiation therapy as an option for patients unfit for surgery or those who refuse surgery	High	Strong
4.7	4.7.1. We recommend the use of adjuvant therapy in early stage oral cavity cancer in those with adverse features.	High	Strong
	4.7.2. We recommend adjuvant chemoradiation therapy for primary tumors with a positive margin on a final histopathologic report that is not feasible for re-excision.	High	Strong
5.1	5.1. We recommend surgical resection of the primary tumor and the involved and at-risk cervical lymphatics.	High	Strong
5.1.1	5.1.1. We recommend a gross surgical margin of at least 1 cm of surrounding normal tissue with the ultimate goal of having a pathologic margin of at least 5 mm.	Low	Strong
5.1.2	5.1.2. We recommend performing intraoperative margin assessment using frozen section, with samples taken from the resected specimen, whenever possible.	Low	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
5.1.3	5.1.3.1. We recommend the following resections for tumor adjacent to the mandible: a. periosteal stripping for tumors abutting the fixed gingiva b. marginal mandibulectomy for tumors involving the periosteum but not eroding the cortex c. segmental mandible resection if there is extension through the mandibular cortex or in a tooth root	Low	Strong
	5.1.3.2. If uncertainty exists about bony involvement, we recommend exposing and inspecting the bone before deciding about marginal mandibulectomy vs. segmental mandibulectomy.	High	Strong
5.2.1	5.2.1.1. We recommend doing ipsilateral selective neck dissection in patients with locally advanced (T3 or T4) oral cavity cancer.	High	Strong
	5.2.1.2. We recommend selective neck dissection I-III for oral cavity sites, except the lateral tongue, for which we recommend selective neck dissection I-IV.	Low	Strong
	5.2.1.3. We do not recommend level IIb dissection if there are no suspicious lymph nodes at level IIa.	Low	Strong
	5.2.1.4. We recommend contralateral neck dissection if the primary tumor touches/abuts or has crossed the midline.	High	Strong
5.2.2	5.2.2. We recommend that in patients with clinically N+ disease, a comprehensive neck dissection be performed on the ipsilateral side (removal of levels I-IV, and non-lymphatic structures if indicated).	High	Strong
	5.2.2.2. We do not recommend level V dissection unless the neck has lymph node involvement in more than one level.	Low	Strong
	5.2.2.3. We recommend an elective contralateral neck dissection if the primary tumor site touches/abuts or has crossed the midline.	Low	Strong
5.2.3	5.2.3. We recommend at least 18 lymph nodes for an adequate comprehensive dissection.	Low	Strong
	5.2.4. We recommend that at the very least, the number of total nodes, the number and size of positive nodes, and the presence or absence of extranodal extension should be stated in the histopathology report.	High	Strong
5.3	5.3. We recommend combined modality treatment of surgery followed by radiation therapy with/without chemotherapy as indicated.	Moderate	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
6	6.1. We recommend individualized treatment decision-making with consideration of performance status for patients with metastatic oral cavity cancer.	High	Strong
	6.2. We recommend palliative care in the following situations: ● significant or multifocal recurrence ● advanced primary disease where complete resection and/or use of adjuvant therapy are not possible	High	Strong
	6.3. We recommend the use of palliative systemic therapy in metastatic oral cavity cancer with a performance status of 0-2.	Moderate	Strong
7	7.1. We recommend individualized treatment decision-making with consideration of performance status for patients with very advanced head and neck cancer.	Moderate	Strong
	7.2. We recommend the use of concurrent chemoradiotherapy in resectable oral cavity cancer patients who refuse surgery or who are poor candidates for surgery.	Moderate	Strong
8	8.1.1. We recommend including reconstruction as part of the surgical plan always.	Low	Strong
	8.1.2. We recommend reconstruction of defects after surgery of oral cavity cancer to preserve function	Low	Strong
	8.2. We recommend the following for soft tissue reconstruction depending on the size and soft tissue involvement: healing by secondary intention, primary closure, skin grafting, local, regional or free flap reconstruction.	Low	Strong
	8.3.1. We recommend the use of the following procedures for bone reconstruction depending on the extent of bony defect: bone graft or osteocutaneous free flap.	Low	Strong
	8.3.2. We recommend that if bony reconstruction is not available, primary soft tissue closure or reconstruction with a regional flap be used as an alternative.	Low	Strong
9	9.1.1. We recommend that patients must have a follow-up consultation every 1-3 months on Year 1, every 2-6 months on Year 2, every 4-8 months on Years 3-5, and every 12 months after Year 5.	Moderate	Strong
	9.1.2. We recommend that all patients should be assessed for signs and symptoms of possible tumor recurrence, health behaviors, nutrition, dental health, and speech and swallowing function.	Moderate	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
	9.1.3. We recommend that tumor evaluations must be performed by specialists skilled in head and neck clinical examination.	Moderate	Strong
	9.1.4. We recommend a complete head and neck exam, mirror and fiberoptic examination during follow-up.	Moderate	Strong
	9.1.5. We recommend thyroid-stimulating hormone (TSH) evaluation every 6-12 months, if the neck was exposed to radiation treatment.	Moderate	Strong
	9.1.6. We recommend regular dental care, oral hygiene and early interventions for oral and dental complications once every six months.	Moderate	Strong
	9.1.7. We recommend evaluation and close monitoring of the nutritional status of patients with oral cavity cancer.	Moderate	Strong

Summary of Recommendations: Laryngeal Cancer

Table 3. Summary of recommendation statements, strength of recommendation, and certainty of evidence on diagnosis and management of laryngeal cancer

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
1	1. We recommend the following clinical data to suspect a diagnosis of laryngeal cancer: a. Clinical • With hoarseness lasting longer than 3 weeks • Odynophagia or dysphagia longer than 6 weeks • Associated otalgia, globus, stridor, and weight loss b. Physical Examination • Dysphonia • Signs of airway compromise • Cervical lymphadenopathy Any of the clinical findings, along with one of the physical examination findings, especially among those aged >50 years with extensive smoking and drinking history, should warrant a referral to a specialist.	Low	Strong
2	2. We recommend the use of rigid or flexible laryngoscopy in detecting the disease among patients suspected of having laryngeal cancer.	Low	Strong
3	3. We recommend direct laryngoscopy with microlaryngeal surgery under general anesthesia to obtain tissue samples for biopsy.	Moderate	Strong
4	4.1. We recommend the use of contrast-enhanced (CE) computed tomography (CT) scan and/or magnetic resonance imaging (MRI) to detect local invasion and nodal involvement.	Moderate	Strong
	4.2 We recommend the use of PET/CT, if available in a high-resource setting, in the following situations: 3. in the evaluation of laryngeal cancer with equivocal CT or MRI findings 4. to accurately detect regional or distant metastases and second cancers or synchronous primary tumors 5. in advanced laryngeal cancer when definitive treatment is needed.	Moderate	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
5	5.1. We recommend endoscopic resection or radiotherapy for cases of carcinoma-in-situ.	Moderate	Strong
	5.2.1. We recommend transoral laser microsurgery or open partial laryngectomy for early-stage laryngeal cancer (T1-T2 N0).	Moderate	Strong
	5.2.2.We recommend external beam radiotherapy (EBRT) in the treatment of early-stage laryngeal cancer (T1-T2 N0).	High	Strong
6	6.1. We recommend concurrent chemoradiation or RT alone for the following: a. Patients with no to minimal aspiration and without cartilage invasion b. Patient with unresectable laryngeal cancer and who are medically unfit or refuses surgery	High	Strong
	6.2. We recommend surgery and adjuvant radiation +/- chemotherapy in patients with aspiration and with cartilage invasion.	High	Strong
	6.3. We recommend induction chemotherapy with response assessment in selected locally advanced and potentially resectable laryngeal cancer after a multidisciplinary team consensus.	Moderate	Strong
7.1	7.1. We recommend total laryngectomy as the primary surgical modality for T3/T4 glottic cancers.	Low	Strong
7.2	7.2.1. We recommend primary soft tissue flap reconstruction with or without gastric pull-up following tumor resection not amenable for primary closure.	Moderate	Strong
	7.2.2. We recommend tracheo-esophageal fistula with or without voice prosthesis (as an option for voice rehabilitation) be performed at the time of total laryngectomy (primary) or later stage (secondary).	Low	Strong
7.3	7.3.1. We do not recommend elective neck dissection in T1N0 and T2N0 glottic cancers.	Moderate	Strong
	7.3.2. We recommend the following neck dissection to all surgically managed laryngeal cancer: 1. If clinically N0, do selective neck dissection (levels II-IV) for the following: a. T1-T2, supraglottic and/or subglottic cancer b. T1-T2, laryngeal cancer primarily managed with partial laryngectomy c. T3-T4, glottic cancer 2. If clinically N+, do modified radical neck dissection a. Any T, N1-N2b glottic cancer	Moderate	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
	b. T3-T4 supraglottic and/or subglottic cancer c. extra-laryngeal extension and/or extracapsular nodal extension (ENE)		
	7.3.3. We recommend bilateral neck dissection in glottic cancers that cross the midline, all supraglottic, subglottic, and transglottic cancer, and N2c-N3 laryngeal cancer.	Moderate	Strong
8	8. We recommend the use of adjuvant or postoperative therapy depending on the adverse feature seen on a surgical histopathological report. • In cases with extranodal extension, combined chemotherapy and radiation therapy is the preferred adjuvant therapy. • Among those with close or positive margins, surgical re-resection is preferred. However, when surgical treatment is not an option, adjuvant chemoradiation should be provided for those with close or positive margins. • Radiation therapy is recommended for those with other adverse features, specifically pT4, pN2, or pN3, perineural, vascular, or lymphatic invasion.	High	Strong
9	9. We recommend the following consultation intervals for patients with laryngeal cancer who have received primary or definitive treatment. • First year of monitoring: every 1-3 months • Second year of monitoring: every 2-6 months • Third to fourth year of monitoring: every 4-8 months • Beyond 5 years of monitoring: annually	Moderate	Strong
10	10.1 We recommend rigid or flexible laryngoscopic examination to check for local recurrence.	Low	Strong
	10.2.1.1. We recommend FDG PET/CT scan 3 months after completion of definitive therapy to assess treatment response.	Moderate	Strong
	10.2.1.2. We recommend CT scan or MRI within 6 months after treatment to serve as baseline imaging.	Moderate	Strong
	10.2.2.1. We recommend FDG PET/CT scan 3 months after completion of definitive therapy to accurately detect regional or distant metastasis.	Moderate	Strong

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
	10.2.2.1. We recommend ultrasound among patients suspected of having neck lymph node recurrence	Moderate	Strong
	10.3 We recommend that TSH be evaluated among patients who had a total thyroidectomy and/or after neck irradiation to screen for hypothyroidism. TSH should be monitored every 6-12 months.	Moderate	Strong

Summary of Recommendations: Nasopharyngeal Cancer

Table 4. Summary of recommendation statements, strength of recommendation, and certainty of evidence on diagnosis and management of nasopharyngeal cancer

Question No.	Recommendation	Certainty of evidence	Strength of Recommendation
1	1. We suggest against screening for NPC among asymptomatic individuals in the Philippines.	Low	Weak
2	2. We recommend to look for the following signs and symptoms of NPC: a. Cervical lymphadenopathy b. Nasal obstruction c. Epistaxis d. Conductive hearing loss or ear fullness e. Ptosis f. Diplopia	Moderate	Strong
3	3. We recommend the following baseline examinations: • Nasopharyngoscopy (flexible or rigid) (High CoE) • Tissue biopsy of nasopharyngeal mass or cervical lymphadenopathy (High CoE) • EBER staining if clinically indicated (High CoE) • Panendoscopy or examination under anesthesia if clinically indicated (Low CoE)	Low to High	Strong

4	4. We recommend the following examinations: • MRI with contrast of the NP and neck is preferred for locoregional staging. • CT with contrast of the nasopharynx and neck is complementary. • FDG PET-CT is the preferred method to evaluate distant metastases. • CT of the chest (with contrast as clinically indicated) and upper abdomen, and bone scan are alternatives.	High	Strong
5	5. We recommend the following pretreatment evaluation procedures: • Baseline audiogram • Dental clearance • Nutrition consult and assessment for enteral feeding • Thyroid function test	High	Strong
6.1	6.1. We recommend definitive radiotherapy using intensity-modulated radiotherapy (IMRT) technique for T1-T2N0 NPC.	High	Strong
6.2.	6.2.1. We do not recommend concurrent chemotherapy for T1N0 disease.	High	Strong
	6.2.2. We do not recommend concurrent chemotherapy for T2N0 unless with bulky disease.	Moderate	Strong
6.3	6.3 We recommend 69.96 to 70.0 Gy in 33-35 fractions (2.0 to 2.12 Gy per fraction) delivered over 6 $^1/_2$ to 7 weeks, once daily, five times per week to the primary tumor and involved lymph nodes.	High	Strong
6.4	6.4. We recommend 59.4-63.0 Gy in 1.8-2.0 Gy per fraction be given to sites of intermediate risk target volume, and 50-56 Gy in 1.6-2.0 Gy per fraction may be given to sites of low-risk target volume.	High	Strong
7.1	7.1. We recommend definitive concurrent chemoradiation in patients with T1-T2N1 and T3N0 NPC.	High	Strong
	7.1.1. We recommend 69.96 to 70Gy in 33-35 fractions (2.0 to 2.12Gy per fraction) delivered over 6.5-7 weeks, once daily, 5x per week to the primary tumor and involved lymph nodes.	High	Strong
	7.1.2. We recommend that simultaneous integrated boost (SIB) or sequential boost be offered.	High	Strong
	7.1.3. We recommend that elective nodal coverage for NPC should cover the bilateral retropharyngeal lymph nodes and levels II to V.	High	Strong
7.2	7.2. We recommend that concurrent chemotherapy be offered for T1-2N1 patients.	High	Strong

7.3	7.3. We recommend concurrent chemotherapy for T3N0 disease.	High	Strong
7.4	7.4. We recommend adjuvant or induction chemotherapy for T1-2N1 and T3N0 with bulky disease.	Moderate	Strong
7.5	7.5. We recommend giving cisplatin either triweekly or weekly.	High	Strong
7.6	7.6. We recommend radiotherapy alone for patients ineligible to receive any systemic agent provided that patient understands that inferior outcome of this monotherapy.	High	Strong
8	8. We recommend concurrent chemoradiation with induction or adjuvant chemotherapy for T1-2N2, T3N1-2, any T4, and any N3 NPC.	High	Strong
9	9.1. We recommend systemic treatment for symptom palliation and best supportive care.	High	Strong
	9.2. We recommend consideration of local consolidation therapy (both to primary and metastatic sites) with radiotherapy if with good response after systemic treatment.	High	Strong
10	10.1. We recommend the following follow up schedule: • Every 1 to 3 months for year 1 • Every 2 to 6 months for year 2 • Every 4-12 months for years 3 to 5 • Annually thereafter	High	Strong

	10.2. We recommend the following tests during follow-up:
	• History and physical examination
	• Nasopharyngoscopy
	• MRI with contrast of the NP and neck and/or CT scan with contrast of the NP and neck should be done 10-12 weeks after completion of radiotherapy. MRI with DWI (if available) may be done at 4 weeks post radiotherapy.
	• FDG PET/CT scan may be done at least 12 weeks after completion of treatment if there is need to restage.
	• Baseline post treatment audiogram
	• TSH should be requested every 6-12 months.
	• Pituitary function must be evaluated periodically for those with signs of symptom.
	• Refer to supportive care and rehabilitation services
	  • Speech and swallowing evaluation and rehabilitation
	  • Nutritional evaluation and rehabilitation
	  • Ongoing surveillance for depression
		High	Strong

	• Smoking cessation and alcohol counselling • Lymphedema evaluation and rehabilitation		
11	11.1. We recommend repeat biopsy for patients suspected to have recurrent disease (for either local or regional) for confirmation.	High	Strong
	11.2 We recommend complete recurrent TNM staging workup be done (see N4).	High	Strong
12.1	12.1. For patients with resectable disease, we recommend: 12.1.1. Nasopharyngectomy be considered for highly selected patients, including but not limited to: (a) rT1, early rT2 (with minimal parapharyngeal extension); (b) select rT3 (i.e. involvement of the floor of the sphenoid); and (c) minimal skull base extension	Moderate	Strong
	12.1.2. We recommend salvage neck dissection for patients with resectable regional recurrence	High	Strong
	12.1.3 We recommend adjuvant reirradiation for patients with positive or close margins (≤ 2mm) to either local or regional site of recurrence.	Moderate	Strong
	12.1.4. We recommend concurrent chemotherapy with reirradiation for eligible patients.	Moderate	Strong
	12.1.5. We recommend salvage reirradiation for patients not amenable for surgical option.	Moderate	Strong
12.2	For patients with unresectable and/or inoperable tumor recurrence: 12.2.1. We recommend salvage reirradiation, preferably with concurrent chemotherapy	Moderate	Strong
	12.2.2. We recommend systemic therapy for patients not amenable to any local therapy.	Moderate	Strong
13	13.1. We recommend systemic therapy for patients with distant metastatic disease.	High	Strong
	13.2. We recommend consideration of local therapy to the metastatic site for patients with oligometastatic disease.	Moderate	Strong

CHAPTER 1.

INTRODUCTION

1.1. Background

The National Integrated Cancer Control Act (NICCA), which was signed into law in February 2019, introduced positive reforms in cancer management in the country. It seeks to "prevent cancer, improve cancer survivorship, and make cancer care and treatment equitable and available to all Filipinos."[1] It also mandates the creation of the National Integrated Cancer Control Council, which functions as the policy-making, planning, and coordinating body on cancer control. Among the many roles of the Council is the development, update, and promotion of evidence-based treatment standards and guidelines for cancer of all ages and stages.

In spite of technological advancement and updated policies, there has been minimal improvement in the prognosis and survival of patients with head and neck cancers due to unaddressed gaps between clinical practice, evolving science, and patient preferences. The key to increasing recurrence-free survival and quality of life outcomes among the patients would be to detect the cancer at an early stage and provide appropriate and cost-effective management at the soonest possible time. One of the strategies of the DOH is to strengthen the generation and implementation of clinical practice guidelines to help clinicians decide on the best available management options. Practice guidelines aim to reduce variations in practice, manage healthcare costs, and help in appropriate resource allocation.[2]

Head and neck cancers, which are usually of squamous cell origin and affect the upper aerodigestive area, remain one of the most significant causes of mortality and morbidity.[3] Annually, it accounts for an estimated 900,000 cases and over 400,000 fatalities worldwide.[4] While oral cavity, laryngeal, and nasopharyngeal cancers may exhibit a relatively low prevalence on a worldwide scale, it is noteworthy that head and neck cancer continues to remain in the top 20 most often occurring malignancies in the country.[5]

These cancer sites are covered in this clinical practice guideline. Diagnostic and therapeutic aspects of these cancers, from the early stage to the advanced and metastatic stage, were also tackled.

This guideline, if approved by the DOH National Guideline Clearinghouse (NGC), may be used to help align the implementation of NICCA with the Universal Health Care Act. The guideline could also be used as the basis for benefit packages offered by the Philippine Health Insurance Corporation, which will include primary care screening, detection, diagnosis, treatment assistance, supportive care, survivorship, follow-up care, rehabilitation, and palliative care for all types and stages of cancer across all age groups.

1.2. Scope and Purpose

Overall objective

The overall objective of this CPG is to present evidence-based recommendations on head and neck cancers, including screening of high-risk individuals, diagnosis and preoperative evaluation, treatment according to stage, adjuvant treatment, and palliative care. These recommendations serve as a guide for clinicians including, but not limited to, general practitioners, specialists (e.g., surgeons, medical oncologists, radiation oncologists, palliative care specialists, nutritionists), and allied medical professionals (e.g., nurses, speech and language pathologists) in providing care for these patients with head and neck cancer.

Health questions

The guideline questions on screening, diagnosis, treatment (preoperative and post-treatment, treatment of recurrent complications), rehabilitation, palliative, and supportive care for head and neck cancer are divided according to the general question common to head and neck cancer (n = 1) and specific queries about the three common sites such as the larynx (n = 10), nasopharynx (n = 13), and oral cavity (n = 9). This guideline also addresses the composition and roles of a multidisciplinary team in the preoperative setting and management. The guideline questions are listed in Tables 4 and 5.

Table 5. Guideline questions for general head and cancer

Site	Area	Question
Head and Neck (General)	Pretreatment Evaluation and Management	Can a multidisciplinary team (MDT) approach improve the quality of care for the head and neck cancer patient?

Table 6. Guideline questions for specific subsites

Site	Area of Management	Guideline Question
Oral Cavity	Diagnosis and Preoperative Management	1. What clinical findings would make you suspect oral cavity cancer in a patient? 2. Among patients suspected of having oral cavity cancer, what diagnostic tests are recommended in establishing the diagnosis? 3. Among patients diagnosed with oral cavity cancer, what diagnostic tests are necessary to determine the stage of the disease? 3.1 What diagnostic tests are recommended for assessing the primary tumor? 3.2 What diagnostic tests are recommended for assessing regional metastasis in patients with oral cavity cancer? 3.3 What diagnostic tests are recommended for assessing distant metastatic spread in patients with oral cavity cancer? 3.4 What other parameters need to be evaluated in patients with oral cavity cancer? 3.5. What staging system should be used in assessing oral cavity cancer?

Management	4. Among patients with early-stage oral cavity cancer, what is the recommended treatment for managing the disease? 4.1. What are the recommended surgical and pathologic margins in the treatment of early-stage oral cavity cancers? 4.2.What is the role of the frozen section in the wide excision of the primary lesion of early-stage oral cavity cancer? 4.3. What is the recommended management of the ipsilateral N0 neck nodes in patients with early-stage oral cavity cancer? 4.4. What is the recommended management of the contralateral N0 neck in patients with early-stage oral cavity cancer? 4.5. What is the role of definitive radiation therapy in the management of patients with early-stage oral cavity cancer? 4.6. What is the recommended adjuvant therapy in the management of patients with early-stage oral cavity cancer? 5. Among patients with locally advanced resectable oral cavity cancer, what is the recommended treatment for managing the disease? 5.1. What is the recommended initial treatment for the primary site? 5.1.1. How much surgical margin should be removed? 5.1.2. What is the role of the frozen section in assessing surgical margins? 5.1.3. How should the mandible be managed? 5.2. What is the recommended treatment for the neck? 5.2.1. What is the recommended treatment for the N0 neck? Elective neck dissection (ND) versus RT? 5.2.2. What is the recommended treatment for the N+ neck? 5.2.3. What is considered a good-quality neck dissection? 5.2.4. What findings do we want clearly stated in the histopathology report for the neck dissection? 5.3. What adjuvant treatment should be given for locally advanced resectable oral cavity cancer (T3-T4a, N0-3)? 6. Among patients with metastatic oral cavity cancer, what is the recommended treatment for managing the disease? 7. Among patients with technically unresectable disease (T4b), resectable oral cavity cancer who are poor surgical candidates, or those who refuse surgery, what is the recommended treatment for managing the disease? 8. Among patients who underwent surgery for oral cavity cancer, what is the recommended reconstructive procedure for soft tissue and bony defects?
Surveillance	9. Among patients with oral cavity cancer who received primary or definitive treatment, how should surveillance be done?

Larynx	Diagnosis and Preoperative Management	1. What clinical data support a diagnosis of laryngeal cancer? 2. Among patients suspected of having laryngeal cancer, what laryngoscopic method/s can be used to detect the disease accurately? 3. Among patients suspected of having laryngeal cancer, what is the cost-effective method of obtaining tissue samples for biopsy? 4. Among patients with suspected or proven laryngeal cancer, what imaging tests are necessary for pre-treatment assessment and staging? a. What are the roles of computed tomography (CT) and magnetic resonance imaging (MRI)? b. What is the role of positron emission tomography-computed tomography (PET-CT)?
	Primary and Adjuvant Treatment	5. What are the treatment options for in-situ and early-stage laryngeal cancer? 6. What are the treatment options for locally advanced laryngeal cancer? 7. What is the appropriate surgical management for advanced laryngeal cancer? a. What is the extent of surgery for the primary? b. Which reconstructive procedures can be performed following total laryngopharyngectomy +/- esophagectomy among patients with advanced-stage laryngeal cancer? c. What is the extent of the neck dissection? 8. What adjuvant treatments can be offered after surgical management?
	Surveillance	9. Among patients with laryngeal cancer who received primary or definitive treatment, what is the interval for history and physical examination during surveillance or follow-up? 10. Among patients with laryngeal cancer, what are the evaluation methods during surveillance? a. What is the role of endoscopy during surveillance? b. What is the role of imaging studies during surveillance? c. What is the role of thyroid-stimulating hormone (TSH) monitoring during surveillance among laryngeal cancer patients after definitive treatment?
Nasopharynx	Screening, Diagnosis, and Initial Assessment/ Pretreatment Evaluation	1. Is screening for nasopharyngeal cancer (NPC) recommended among asymptomatic individuals in the Philippines? 2. What clinical findings would make you suspect NPC in a patient? 3. Among individuals suspected of having NPC after a complete history and physical examination, what initial diagnostic tests are necessary? 4. Among individuals diagnosed with NPC, what further tests are necessary for staging? 5. Among individuals diagnosed with NPC who have completed staging work-up, what additional procedures are necessary to request prior to the start of definitive treatment?
	Treatment	6. What is the appropriate management for patients with T1-2N0 NPC? 7. What is the appropriate management for patients with T1-2N1 and T3N0 NPC?

		8. What is the appropriate management for patients with T1-2N2, T3N1-2, any T4, or any N3? 9. What is the appropriate management for patients with M1 NPC?
	Follow-up Care	10. What is/are the recommended follow-up strategy for patients who have completed treatment for NPC?
	Treatment of Recurrent Disease	11. What diagnostic test/s are necessary to evaluate patients in the residual, persistent or recurrent setting? 12. What is/are the management option/s for patients with locoregional recurrence? 13. What is/are the management option/s for patients with distant failure of NPC?

Population

The guideline questions and recommendations were formulated to provide better care for adult patients suspected of or diagnosed with head and neck carcinoma, regardless of comorbidities. The three common sites of head and neck cancer (i.e., larynx, nasopharynx, and oral cavity) and different stages of the disease were covered. These guideline recommendations do not apply to non-carcinoma malignancies.

1.3. Stakeholder Involvement

The Steering Committee was composed of physicians or specialists in head and neck cancer and administrators from JRRMMC. The Technical Working Group was convened by the lead CPG developer and was composed of specialists in head and neck cancer and a clinical epidemiologist. The Consensus Panel was a multisectoral group that included patient advocate, health care practitioners, or medical professionals whose practice is directly affected by the guidelines or can influence the uptake of CPG recommendations.

The patient advocate, who was also a patient, played an active role in finalizing the recommendations during all panel meetings. Apart from other panel members' clarifications, the patient's inquiries and recommendations were duly acknowledged and taken into consideration during the panel discourse.

Appendix B shows the names, institutions, and geographical location of specific individuals who were involved and the group to which they belonged in the development process. The roles of the group are further described in Guideline Preparation.

Target Guideline Users

The recommendations contained herein are intended to aid in the decision-making of the following stakeholders: general practitioners, internists, surgeons, both general surgeons and otorhinolaryngologists, radiation oncologists, medical oncologists, radiologists, pain medicine and palliative care specialists, family physicians, rehabilitation specialists and pathologists, allied

health professionals, patients and families, hospital administrators, policymakers, and other stakeholders including government institutions and third-party payors.

CHAPTER 2.

GUIDELINE DEVELOPMENT METHODS

2.1. Guideline Preparation

The development of this CPG on head and neck cancer followed the methodology delineated in the *Manual for Clinical Practice Guideline Development*. The DOH selected JRRMMC, a public tertiary hospital, to spearhead the guideline development and to create the Steering Committee. The UPM-ICE guided the SC in CPG development.

The SC created a roster of physicians, institutions, and organizations that are involved in providing care for patients with head and neck cancer and invited them as stakeholders in the CPG development. The SC also finalized clinical issues and set up the working groups (i.e., Technical Working Group and Consensus Panel). The TWG and CP assisted the steering committee in creating PICO clinical questions based on identified clinical issues.

The TWG members were tasked with performing a systematic literature search, reviewing the existing CPGs, drafting evidence-based recommendations based on those CPGs, and presenting their findings to the Steering Committee.

The TWG presented the draft recommendations during the nine *en banc* meetings, which were held online via Zoom with the CP. The CP members were given a copy of the drafted recommendations before the meeting to review. The TWG prepared the evidence summaries for each guideline question.

With the help of a moderator from the Steering Committee, the CP finalized the statements and the strength of the recommendation. They were also tasked with rating of health outcomes through an online survey. The whole process of formulating the final recommendations is discussed in Section 2.3.

Editorial Independence

An external (conflict of interest) COI committee was also created to evaluate each Task Force member's potential conflict of interest and provide management of identified COI throughout the process.

Before the start of guideline preparation or the formulation of consensus statements, all task force members (including the task force chair, steering committee members, technical coordinator, evidence reviewers, technical writer, and potential consensus panelists) were required to submit a complete disclosure. These included financial, intellectual, or other personal interests that other might perceive as influencing their judgment on issues this CPG addresses. The members were also tasked with disclosing potential COIs of immediate family members. The disclosures and contributions to the field of the panelists were assessed both individually and collectively to create a balanced panel.

Members who declared and were assessed to have COI were restricted from voting on certain recommendations.

2.2. Evidence Synthesis

Search Methods and Strategies

The TWG members, which were divided into three groups according to head and neck CA subsite, searched various databases, such as MEDLINE via PubMed, Google Scholar, HERDIN PLUS, and other institutional databases deemed relevant by the TWG, to identify relevant existing CPGs on their assigned clinical questions from June to August 2022. They utilized search terms in free text and medical subject headings (MeSH) for each keyword. Table 6 summarizes the keywords used in the search strategy. Other terms included in the search were specific to sites, such as the tongue, floor of the mouth, buccal mucosa, gingiva, and glottis. The TWG also searched for research that could provide an answer if the guideline question was not addressed by existing recommendations, such as meta-analyses, randomized controlled trials, or observational studies. Appendix D shows the full search strategy.

Table 7. Keywords used to search and retrieve practice guidelines from MEDLINE, Google Scholar, and HERDIN PLUS

Database	Keywords
MEDLINE, Google Scholar, other institutional databases deemed relevant	"head and neck carcinoma," "head and neck cancer," "oral cavity cancer," "laryngeal," "nasopharyngeal," "chemotherapy," "radiation therapy," "surgery," "practice guidelines," "clinical practice guideline," "evidence-based guidelines," "recommendation"
HERDIN PLUS	"head and neck cancer," "oral cavity cancer," "laryngeal cancer," "nasopharyngeal cancer," "guideline"

Inclusion and Exclusion Criteria

Each guideline was initially assessed based on the following criteria:

Table 8. Inclusion and exclusion criteria for selecting a head and neck cancer clinical practice guideline

Inclusion criteria	Exclusion criteria
• About adults with head and neck cancer (nasopharyngeal, oral cavity, laryngeal cancer) • Published in text or online • Written in English or with English translations • Published in the last 5 to 10 years (2012 onwards)† • Must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence	• Older versions of the guideline • Guidelines involving pediatric patients • Guidelines involving pregnant patients

† If the guideline had an update, the update was retrieved and reviewed

Study Quality Assessment and Data Synthesis

At least three members evaluated the CPG identified for adaptation using AGREE II. The AGREE-II is a 23-item checklist used to evaluate the guideline development process and the standard of reporting. A cutoff score of 75% was needed for a guideline to be considered in this CPG. The TWG was allowed to use any appraisal tool to examine the validity of the methods and results of each clinical study used as evidence in cases where questions were not addressed by the included CPG.

Appendix C presents the rating of each guideline adapted for this CPG.

The certainty of evidence for each drafted recommendation was based on Table 8, which was in line with the recommendations of DOH for utilizing the GRADE approach.

Table 9. Certainty of evidence for each final recommendation

Certainty	Definition	Implications
High	The group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Note: Adapted from DOH (modified from GRADE)

2.3. Formulation of Recommendations

An online meeting was held on September 24, 2022, to orient the consensus panel members regarding the guideline development process. The guideline questions, composition of the CPG groups, and whole consensus process were discussed by the CPG SC head.

The TWG prepared a draft recommendation answering the clinical questions based on the evidence collected from the CPGs. These drafts were sent to the consensus panel at least a week prior to the online *en banc* meeting. During the meetings (n = 9 meetings), 75% of the representatives from the 15 participating societies, or at least 12 panelists, were present along with the patient advocate to finalize the recommendations. Eventually, when it was agreed that recommendations on pain management will not be included and the national clinical practice guideline on pain and palliative car, will be used as a reference the representative from Pain Society of the Philippines was no longer required to attend the CP meetings.

If there were no recommendations due to a lack of evidence, the panel members were allowed to generate a statement based on best practices. Other considerations are the availability of resources, feasibility, patients' values and preferences, clinical experiences, and the costs of diagnostic tests and treatment procedures.

Certainty of Evidence and Strength of Recommendations

The TWG drafted the recommendation statement/s based on the included studies that served as evidence. The certainty of evidence can be high, moderate, low, or very low. Table 8 presents the interpretation for each certainty.

The strength of recommendation was contingent upon the decision of the panel subsequent to the deliberation of evidence of benefit and harm, along with other pivotal factors in the decision-making process, such as patients' views and preferences, resource accessibility, feasibility, and costs.

Rating of Outcomes

The CP members were asked to rate the outcomes for each question numerically on a scale of 1 to 9 per question (7 to 9 = critical; 4 to 6 = important; 1 to 3 = of limited importance). Critical outcomes were treatment efficacy in terms of improvement of function, quality of life, survival outcomes for questions on management, and diagnostic accuracy for diagnostic tests.

Patients' Views and Preferences

This guideline guaranteed that patients' views and preferences were considered in all the recommendations through the involvement of a patient representative who participated in all *en banc* meetings for the deliberation of the recommendations. The TWG also looked for studies on patients' preferences and cost-effectiveness that could support evaluations of the tests and treatments considered in these guidelines.

Consensus Process

The CP members were given an orientation on September 24, 2022, to discuss the consensus process prior to the nine *en banc* meetings (October 2022 to January 2023). A quorum could only be achieved if there were at least 10 CP members (50% of the 15 societies plus 1) including the patient representative.

The facilitator from the Steering Committee led the discussion with the panel to address any queries or concerns regarding the evidence presentation before the voting process.

Three rounds of voting were allowed until consensus (75% of total votes) was reached on the direction of the recommendation statement (i.e., for or against). Once consensus was reached, the group discussed and voted on the strength of the recommendation. Similarly, voting was allowed for up to three rounds. The CP arrived at consensus on all recommendations.

2.4. External Review

A group of independent reviewers who are not part of the TWG or the CP evaluated the manuscript. Experts in the content and research methodology from professional medical societies

and other non-specialty organizations engaged in head and neck cancer management were part of the External Review Panel.

The Steering Committee for this guideline invited six (6) external reviewers to comprise the Task Force Guideline Panel, which focused on the methodological aspects of CPG development, including its reporting. The prescribed tool for use is the Appraisal of Guidelines Research & Evaluation AGREE-II checklist and/or the AGREE-REX (Recommendations Excellence) checklist. The AGREE-REX aids in ensuring the clinical credibility and applicability of the guideline recommendations. The information of the external reviewers is listed on Table 9.

Table 10. Invited external reviewers of the Head and Neck Cancer CPG

Reviewer	Background
Dr. Jose Modesto Abellera III	Member of the PCS Research Committee
Dr. Kathryn Braganza	Clinical Epidemiologist (a candidate for a Master's Degree)
Dr. Manuel Tesoro, Jr.	Head and Neck Surgeon from Davao
Dr. Paulyn Gaddi	Otorhinolaryngologist from Pampanga
Dr. Warren Bacorro	Radiation Oncologist; (PhD in Research)
Dr. Marc Vincent Barcelona	Head and Neck Radiation Oncologist

The AGREE-REX, which consists of three theoretical areas and nine items, is a valid and reliable method for assessing the quality of guideline recommendations. Similar to AGREE II, the overall score was calculated by computing the obtained score (i.e., adding the scores of individual reviewers for each item on a scale, ranging from 1=strongly disagree to 7=strongly agree). The following formula was used to convert the total obtained score into a percentage of the maximum possible scale.

$$Overall\ score = \frac{Obtained\ score - Minimum\ possible\ score}{Maximum\ possible\ score - Minimum\ possible\ score}$$

wherein,
Maximum possible score = 7 (highest quality) x 9 items x no. of appraisers
Minimum possible score = 1 (lowest quality) x 9 items x no. of appraisers

The AGREE scores from each of the members of the External Review Panel were pooled and analyzed. The acceptable cutoff for the AGREE score will be set at an overall mean of 75%, with no domain scoring less than 75%. After at least two favorable recommendations from the six External Review Panel members, the CPG will be submitted to the Secretary of Health for final approval as a DOH-endorsed CPG, or "National CPG".

In no particular order of the external reviewers mentioned above, the results of the individual review can be seen in Tables 10 and 11.

AGREE-II Scores

Three reviewers evaluated the CPG manuscript using AGREE-II checklist. Overall, the maximum possible score is 483 while the minimum possible score is 69 for this 23-item checklist. The sum of the domain scores is 472. Using the aforementioned formula, the overall score of this CPG is 97.3% (403/414).

Table 11. Individual reviewer's scores on the domains and items of the AGREE-II for this Head and Neck Cancer CPG

Domains	R1	R2	R3	Domain Score (%)
1. Scope and Purpose (3 items)	21	21	21	63 **(100)**
2. Stakeholder Involvement (3 items)	21	21	20	62 **(98.4)**
3. Rigour of Development (8 items)	56	54	56	166 **(98.8)**
4. Clarity of Presentation (3 items)	17	21	21	59 **(93.7)**
5. Applicability (4 items)	28	28	24	80 **(95.2)**
6. Editorial Independence (2 items)	14	14	14	42 **(100)**

R: Reviewer

AGREE-REX Scores

Five reviewers evaluated this CPG using the AGREE-REX tool. Overall, the maximum possible score is 315, while the minimum possible score is 45 for this 9-item checklist. The sum of the domain scores is 281. Using the formula above, the overall score of this CPG is 87.4% (236/270). All reviewers recommend the guideline recommendations for use in the appropriate and local context, except for one reviewer with suggested modifications.

Table 12. Individual reviewer's scores on the domains and items of the AGREE-REX for this Head and Neck Cancer CPG

Domains	Items	R1	R2	R3	R4	R5	Domain Score (%)
1.Scope and Purpose (105; 15)	1. Evidence	4	7	6	5	7	93 **(88.6)**
	2. Applicability to Target Users	5	7	6	6	7	
	3. Applicability to Patients/Populations	7	7	6	6	7	
2.Stakeholder Involvement (140;20)	4. Values and Preferences of Target User	5	7	6	7	7	123 **(87.8)**
	5. Values and Preferences of Patients/Populations	5	5	6	5	7	
	6. Values and Preferences of Policy/Decision-Makers	5	6	6	7	7	

Domains	Items	R1	R2	R3	R4	R5	Domain Score (%)
	7. Values and Preferences of Guideline Developers	7	6	6	6	7	
3.Implementability (70;10)	8. Purpose	7	7	7	7	7	65 **(92.8)**
	9. Local Application and Adoption	5	6	5	7	7	

R: Reviewer

Table 12 shows the specific remarks of the reviewers in the AGREE-REX.

Table 13. External reviewers' remarks with regard to the Head and Neck Cancer CPG

Item	Remarks
1. Evidence	• The updated Head and Neck CPG is of high quality. All the necessary steps to evidence generation have been met, and it is comprehensive in its consideration of all parameters necessary to recommend a certain treatment, including the treatment effect and possible adverse effects as well as societal costs. • The guideline did not specify how the evidence was collected and assessed. Some key questions did not present the search strategy and Grade Profile in the Appendix. • It was not clear to me how the assessment of the quality of evidence was done. It would be best to include the process in the text. • The following are not explicitly stated in the majority (~60% of the discussions of evidence): (1) the level of strongest evidence available (e.g., previous meta-analyses, meta-analyses done for the CPG if none previously done, RCTs, non-RCTs, prospective studies, or retrospective studies), (2) the nature and/or number of risk of biases (or strengths) that justified downgrading (or upgrading) the evaluation of the certainty of evidence (whether adopted as stated from previous guidelines, modified, or derived from a de novo review for the current CPG), and (3) the precision of results (confidence intervals).
2. Applicability to Target Users	• The guidelines do address the need to guide clinical practice in the diagnosis, treatment, and management of head and neck cancers. The intended target users were clearly specified, as well as the patient population for whom the guidelines are intended. There was good alignment between the scope of practice and the guideline recommendations. Each guideline also presented clearly the possible benefits and harms of each treatment, and the grading of the strength of recommendations based on the level of evidence was sound

Item		Remarks
		• The recommendations were mostly justified within the context of the local applicability and availability of the intervention or practice. However, in sections where the certainty of evidence was low or moderate and the recommendation was strong, there was no explicit statement of (a highly) favorable benefit-harm/cost ratio. • Some key findings were included in the text, as well as the direction of the recommendations. However, not all key questions discussed the harms and benefits of each diagnostic criteria or therapeutic management.
3.	**Applicability to Patients/Populations**	• The guideline is very relevant to the target population and end users. • Published outcomes (overall survival, disease-free survival, locoregional control, toxicity, and functionality) that are relevant to patients were reviewed and formed the basis of recommendations. A patient advocate was part of the consensus panel and was given an active role. • The guidelines are relevant to the target population (head and neck cancer patients). Relevant outcomes were considered and used to guide evidence generation. • However, in recommendations where functionality outcomes were the main considerations, there did not seem to be routine reference to any (or no further) input (affirmation or otherwise) from the patient advocate.
4.	**Values and Preferences of Target User**	• The values and preferences of all those involved in head and neck cancer patient care were sought, and consideration of the local Philippine setting as well as resource constraints were considered. Treatment recommendations that had unequivocal evidence of benefit were recommended, and those whose evidence seemed weaker included a statement on tailoring treatment decisions. • Whenever appropriate, the recommendations provide for flexibility by adding the phrase “whenever possible”. There was adequate discussion of relevant applicability issues and resource implications. • This was not discussed in the text. It is best to also look for studies that look into the values and preferences of target users. Should there be no available study, this should also be written in the text.
5.	**Values and Preferences of Patients/Populations**	• The input of representatives of the head and neck cancer population was sought and included. Considerations such as socioeconomic circumstances and accessibility to certain services were also included. • In recommendations where functionality outcomes were the main considerations, there did not seem to be routine discussion on the practical integration of patient preferences in shared or patient-centered decision-making. The lack of local research on patient compliance and other

Item	Remarks
	patient-centered outcomes (QOL, costs) was adequately discussed • This was also not discussed in the text. It is also best to look for studies that look into the values and preferences of target users. Should there be no available study, this should also be written in the text. • This is an aspect of the guideline that appears lacking and can be improved upon in subsequent updates. There should also be more representation of the target population throughout the guideline development process.
6. Values and Preferences of Policy/Decision-Makers	• The input of representatives of healthcare policymaking was sought and included. Considerations such as the economic capacity of the country and the possible costs to the healthcare system were considered in the making of the CPGs. • There was adequate discussion of relevant applicability issues and resource implications as they relate to policymaking. • This was discussed in the guidelines. • It would be better if the cost-effectiveness of the diagnostic procedures and therapeutic management were also discussed as well to ascertain their impact on health equity. • More policymakers and decision-makers could have been involved during the guideline development process.
7. Values and Preferences of Guideline Developers	• This was clearly discussed in this guideline. • The rationale, objectives, and methodology were adequately described to reflect the intended level of rigor, representativeness, and transparency. How guideline developer and stakeholder values and preferences were integrated into the interpretation of benefit-harm balance was mostly discussed whenever relevant. • Members of the guideline-developing committee were selected by their various societies for their expertise in the field. They have clearly stated their values and preferences and have done their best to align the guidelines with the values and preferences of all stakeholders. • In recommendations where functionality outcomes were main considerations, there did not seem to be routine reference to any (or no further) input (affirmation or otherwise) from the patient advocate.
8. Purpose	• The scope and objectives were clearly stated, and the recommendations were aligned to these objectives. The impact of the recommendations on organizations and/or systems was described. • The guidelines have clearly stated the purpose and anticipated impacts of the publication of the CPGs.
9. Local Application and Adoption	• The clinical practice guidelines have been tailored to the local, Philippine setting and have taken into account the geographic challenges and socioeconomic circumstances of implementing said recommendations in the said setting.

Item	Remarks
	• Local considerations for generalizability of evidence, implementation of recommendations (e.g., expertise or technology availability), and acceptability (e.g., costs) were mostly discussed where relevant. Monitoring and evaluation plans were described. • More detailed strategies for dissemination, application, monitoring, and evaluation could have been written to guide users and those who will subsequently update the guidelines. • The current practices in the local setting were not discussed in the guidelines; hence, the impact of the current review and recommendations cannot be assessed.

CHAPTER 3.

EVIDENCE AND RECOMMENDATIONS

3.1. GENERAL QUESTION

1. Can a multidisciplinary team (MDT) approach improve the quality of care for the head and neck cancer patient?

1.1 We recommend an MDT approach to improve the quality of care of the head and neck cancer patients.
Moderate certainty of evidence, Strong recommendation

1.2. We recommend a pre- and posttreatment multidisciplinary tumor board for all head and neck cancer patients.
Moderate certainty of evidence, Strong recommendation

Key Findings

Numerous studies have demonstrated that MDTs positively affect treatment decisions. The University of Pennsylvania Medical Center documented a change in diagnostic image interpretation in 41% of patients, with staging revision in 34% of patients. A pre- and post-MDT conference comparison also showed a 39% change in diagnosis, a 59% change in treatment, and a 9% change in both.[4,5] A prospective study at the Sydney Head and Neck Cancer Institute also compared pre- and post-MDT conference plans. It showed a 67% change in treatment modality and 30% minor alterations (change in RT field, change in treatment dose, addition of diagnostic test).[4,6] A retrospective study by the Istituto Nazionale Tumori in Milan showed further diagnostic recommendations in 50% of cases, diagnosis changes in 3% of cases, and treatment changes in 10% of cases.[4,7] After MDT implementation in Ipswich Hospital, local guideline adherence improved.[4,8]

Different studies have also concluded that MDTs result in a reduction in time to treatment. A retrospective chart review in the University of Cincinnati Veteran's Administration Hospital revealed that time from being seen at the general clinic to being seen in the otolaryngology clinic and time from biopsy report to intimidation of definitive treatment decreased significantly from 27.5 to 16.5 days ($P < 0.001$) and 35 to 27 days ($P = 0.04$), respectively.[4,9] A retrospective study at Charing Cross Hospital in London showed a significant association between initial review by a non-MDT member and treatment delay ($P < 0.001$).[4,10] A comparative study found that the MDC cohort had fewer instances of delays greater than 30 days for referral to treatment initiation (28 [41%] vs. 43 [59%]) and the first appointment to treatment initiation (7 [10%] vs. 17 [23%]) compared to the traditional clinic cohort.[11]

Research studies have also shown that MDTs can improve patient outcomes. Another comparative study performed in the Sir Charles Gairdner Hospital Head and Neck Cancer Clinic discovered that stage IV MDT patients had significantly improved 5-year survival compared to non-MDT patients (hazard ratio = 0.69, 95% CI 0.51 to 0.88, $P = 0.004$). [12] The SWAHN I study

showed an increased survival trend for MDT patients, while the SWAHN II study confirmed survival improvement in the MDT cohort (HR = 0.7, *P* = 0.02).[4,13] The University of Cincinnati Veteran's Administration Hospital also reported a decrease in the 5-year mortality rate on a retrospective review of the data.[1,6] A large study (n = 9297) in Taiwan matched patients who were treated with and without the MDT approach and found that the former had a reduced relative risk of death (HR = 0.84, 95% CI 0.78 to 0.90).[4,14]

Remarks

Both statements achieved consensus. During the discourse, the panel made it clear that a tumor board will include, but not be limited to, treatment decisions (pre- and post-management), surveillance of late effects, and survivorship.

3.2. ORAL CAVITY CANCER

3.2.1. Diagnosis and Preoperative Management

1. What clinical findings would make you suspect oral cavity cancer in a patient?

1.1. We recommend that patients with the following signs and symptoms be referred to a specialist for further evaluation and treatment.

Clinical features of suspicious lesions in the oral cavity include mucosal changes lasting more than two weeks with any of these findings:

- non-healing ulcers
- red/white patches
- hardening of the mucosa
- bleeding

Other symptoms that may be associated with suspicious oral cavity lesions:

- chronic pain in the throat
- painful or difficulty swallowing
- difficulties in mouth opening and chewing
- trismus
- loosening of the teeth, numbness or loss of adjacent teeth not associated with periodontal disease and /or malocclusion
- unilateral foreign body sensation
- decreased tongue mobility
- numbness of the tongue, teeth or lip
- fetor or halitosis
- presence of neck masses

Low certainty of evidence, Strong recommendation

Key Findings

Assessment of suspicious lesions in the oral cavity should start with a complete history and a comprehensive physical examination. This should be supported by appropriate ancillary tests that would help in confirming the diagnosis and assessing the extent of the disease.

The guidelines[6-8] utilized as references enumerated several clinical findings pointing to a possible malignancy in the oral cavity. As most are based on epidemiological studies, the quality of the evidence is low.

The symptoms enumerated were separated into early and late changes in discussing some of these guidelines. Mucosal changes present for at least two weeks have been identified as the earliest sign of possible oral cavity cancer. These may include any of the following: a non-healing ulcer, irregularly shaped red or white patches, a thickening or hardening of the mucosa, or unexplained bleeding in certain areas of the oral cavity.[6-8] Early lesions can be asymptomatic as compared to those discovered in a more advanced state. Larger lesions, because of invasion of adjacent tissues, may present with functional impairments such as difficulty or painful swallowing, limited mouth opening or trismus, difficulty speaking and chewing, and pain.

The presence of symptoms can also depend on the site of the primary tumor. Tumors located on the tongue and floor of the mouth can impair tongue movement and thus contribute to speaking difficulties. It is also important to assess the mobility of the lesions, especially those that are adjacent to bony areas, as this may indicate bony involvement. These lesions may be associated with the teeth, such as loosening, numbness, or loss of adjacent teeth, or malocclusion. Numbness in the area of the tongue, teeth, lip, or mentum may indicate the involvement of specific cranial nerves, which is the basis for performing a complete cranial nerve examination in patients with large tumors. In patients with more advanced lesions, regional involvement manifested as enlargement of cervical lymph nodes may be apparent.[6-8]

As part of the comprehensive physical examination, the neck should always be palpated for any lymphadenopathy. Lymph node metastases may be present in up to 40% of patients.[7] The first level of nodal involvement for oral cavity cancer would be level 1, or the submental and ipsilateral submandibular triangles and the upper jugulodigastric nodes.[9] For locally advanced diseases that are near the midline, the contralateral nodes should also be evaluated. Any masses present in the area should be described as to their location, size, number, and mobility.[6] Distant metastases may be asymptomatic but should also be investigated, especially in locally advanced tumors with nodal metastases.[7]

Remarks

The panel highlighted that ‘bleeding’ in the recommendation statement refers to unexplained bleeding in the oral cavity accompanied by other persistent suspicious lesions. The recommendation statement warranted a strong recommendation since there would be no harm. However, the panel acknowledged that this recommendation may incur additional expense due to the patient being referred to a specialist.

1.2. We recommend identifying risk factors such as a history of betel nut chewing, tobacco use, and alcohol consumption in a patient with suspicious oral cavity lesions.

Low certainty of evidence, Strong recommendation

Key Findings

Supportive information, such as the presence of risk factors, can strengthen the suspicion of a possible oral cavity cancer. The guidelines recommend that patients be asked for risk factors that are strongly associated with the development of this type of malignancy, such as tobacco use, alcohol intake, and betel nut chewing. Studies have shown that chronic tobacco use and alcohol intake can increase the risk of developing oral cavity cancer six-fold individually and up to 30-fold if both are present.[7] HIV infection is considered a minor risk factor, whereas HPV infection is not considered a prognostic factor due to its low incidence, which ranges from 4–7% with a prevalence of 5%.[8]

Remarks

The panel raised clarification regarding HPV as a risk factor. The TWG clarified that HPV is a risk factor for oropharyngeal cancer rather than oral cavity cancer. The inquiry regarding the use of vape was also made; however, it was clarified that there was no reference to vape usage in the literature. The recommendation statement warranted a strong recommendation since there will be no harm and it is low-cost.

2. Among patients suspected of having oral cavity cancer, what diagnostic tests are recommended for establishing the diagnosis?

2. We recommend performing tissue biopsy (incisional or punch biopsy) prior to initiating treatment in patients suspected of having oral cavity cancer.

Moderate certainty of evidence, Strong recommendation

Key Findings

All the guidelines[6-8,10,11] agreed that it is essential to obtain histological confirmation of the diagnosis before proceeding with treatment. These guidelines were appraised as high-quality evidence. However, due to the risk of bias found in the studies used, the evidence was downgraded to moderate.

One guideline used systematic reviews to examine other non-invasive technologies, such as vital staining, cytological techniques, light-based detection systems, optical biopsy, saliva-based oral cancer diagnosis, and other molecular analyses for confirming the diagnosis.[10] However, due to the risk of bias, the latter tests were not considered acceptable alternatives to a definitive biopsy.

In another guideline, Cervenka and his group suggested the careful use of slide photography for the evaluation of external consultants in low-resource settings based on low-level evidence.[6]

Specific recommendations with regard to the performance of the sampling were also given in some of the guidelines. It is more advantageous to perform photo documentation prior to performing a biopsy. The preferred sampling should be an incisional biopsy with the specimen taken at the margins to avoid necrotic tissue. The German guideline suggested repeating the sampling if there were no conclusive results from the initial biopsy.[7] Finally, to avoid any image distortion due to tissue reactions, biopsies should be performed after the completion of all imaging tests.

Remarks
No consensus issues were raised.

3. Among patients diagnosed with oral cavity cancer, what diagnostic tests are necessary to determine the stage of the disease?

3.1 Among patients diagnosed with oral cavity cancer, what diagnostic tests are recommended for assessing the primary tumor?

3.1.1. We recommend the use of contrast-enhanced CT or MRI for evaluating the extent of the primary tumor.
Moderate certainty of evidence, Strong recommendation

3.1.2. We recommend a panoramic dental x-ray for assessing mandibular involvement in tumors located at the tongue, floor of the mouth and gingiva, if CT is not accessible.
Moderate certainty of evidence, Strong recommendation

Key Findings
Imaging is essential in determining the extent of the primary tumor and in planning surgical treatment. The reference guidelines deemed it necessary to assess the extent of the primary tumor using a contrast-enhanced CT scan or MRI.[6-8,10-13] Contrast-enhanced CT is one of the most commonly used imaging modalities for oral cavity cancer. It shows a sensitivity of 61%, a specificity of 100%, and an accuracy of 66% in detecting a primary tumor in the oral cavity.[10] Moreover, it also provides high accuracy in detecting cortical bone involvement.[7,10] However, images from a CT scan are prone to distortion in the presence of metal artifacts. Compared to an MRI, CT showed lower soft tissue resolution. It is for this reason that some studies consider MRI more suitable for assessing primary tumors of the oral cavity. However, evidence from the guidelines used here showed inconsistent results with regard to the superiority of one test over the other.[7,10] An MRI can give better detail on the relationship of the primary tumor to adjacent tissues. It is recommended for patients with suspected perineural, intramuscular, or perivascular extension and tongue involvement.[7,11,14] The choice between the two should be influenced by the information needed.

Certain limitations in resource-constrained settings entail a careful selection of imaging studies. In the guidelines by Cervenka, they recommended its use only if it would alter the management.[6] In the same paper, they recommended that a panorex can be utilized if a CT scan is unavailable. A panorex can also be used as an adjunct to CT or MRI in patients with locally advanced disease, as it can give information on the status of the dentition and mandibular height. It is considered part of the complete evaluation of the dental system, especially for patients who will need postoperative RT.[7,14]

Another imaging modality that can be used to assess the primary tumor is a PET/CT. This study enables us to correlate functional information with the anatomical details of the tumor. Although it has been shown to be very sensitive in the detection of the primary tumor, several of the guidelines stated that it does not provide sufficient information that can help in planning the surgical treatment.[7,10]

Remarks

No consensus issues were raised on the use of contrast-enhanced CT or MRI for evaluating the extent of the tumor. On the other hand, the panel highlighted the importance of the qualifier "if CT is not accessible" in recommending panoramic dental x-rays for assessing mandibular involvement.

3.2 What diagnostic tests are recommended for assessing regional metastasis in patients with oral cavity cancer?

3.2.1. We recommend evaluating the cervical lymph node basin with contrast-enhanced CT scan or MRI.
Moderate certainty of evidence, Strong recommendation

3.2.2. We recommend the use of an ultrasound to evaluate the neck in low-resource settings.
Moderate certainty of evidence, Strong recommendation

Key Findings

A CT and MRI can evaluate the primary tumor and the status of the cervical nodes concurrently. In terms of efficacy, studies from two guidelines have shown that CT is comparable to MRI. [6,10] Both imaging tests showed sensitivity of 24% to 79% and specificity of 31% to 89% in detecting metastatic lymph nodes and were seen to be superior to clinical examination alone. However, the guideline of moderate certainty favor MRI for its advantage in visualizing nodes along the vascular nerve sheath.[6]

Guidelines for PET/CT are inconsistent. Included in one guideline[10], moderate certainty evidence from a meta-analysis found that PET, US, CT, and MRI show similarities in

sensitivities and specificities in assessing metastatic lymph nodes.[15] Another guideline also presented a meta-analysis showing lower accuracy for CT and MRI compared to PET/CT.[14]

An ultrasound evaluation of the neck can also be performed. It was shown that it was comparable to CT and MRI in assessing the status of the cervical lymph nodes. Aside from that, this imaging modality can be used to guide sampling of the nodes. This was deemed ideal enough to be recommended in a low-resource setting.[6]

Remarks

There were no consensus issues raised on using either contrast-enhanced CT or MRI for evaluating the cervical lymph node basin. The panel emphasized the importance of patient education regarding health facilities with ultrasound to evaluate oral cavity-cancer-related concerns.

No recommendation for a biopsy was made because it is presumed that enlarged nodes on the affected side observed during physical examination or imaging are regional metastases; therefore, a biopsy is unnecessary.

3.3 What diagnostic tests are recommended for assessing distant metastatic spread in patients with oral cavity cancer?

3.3.1. We recommend at least a chest CT with contrast for asymptomatic patients with locally advanced disease.
Moderate certainty of evidence, Strong recommendation

3.3.2. We recommend a symptom-directed approach to evaluate distant metastases in patients with oral cavity cancer. In low-resource settings, a chest x-ray is recommended to assess for lung metastases.
Moderate certainty of evidence, Strong recommendation

Key Findings

The guidelines utilized for these recommendations all agree that investigations to detect distant metastases are warranted in locally advanced tumors.[6,12,16] In large primary tumors or in patients with multiple enlarged cervical nodes, chest imaging should at least be performed to rule out lung metastases. In one guideline, it was recommended that this be performed even in the early stages.[16] The NCCN guidelines mentioned that chest CT without contrast is sufficient enough to screen for lung metastasis but is not adequate to evaluate mediastinal adenopathy.[12] In areas where a CT scan is unavailable, a chest X-ray is recommended for disease stages III and IV.[6]

Several guidelines recommend a PET-CT to detect distant metastases in patients with locally advanced diseases.[7,12,16] They all acknowledge that a chest CT is a viable alternative. The NCCN

guideline also recommends that directed imaging (specifically CT or MRI) be done if metastatic disease is confined to a specific anatomical area. [12]

Remarks
No disagreements were raised regarding these statements.

3.4 What other parameters need to be evaluated in patients with oral cavity cancer?

3.4.1. We recommend assessment of oral functions such as mastication, speech, and swallowing prior to treatment.
Moderate certainty of evidence, Strong recommendation

3.4.2. We recommend a pre-treatment assessment of the nutritional status of patients with oral cavity cancer.
Moderate certainty of evidence, Strong recommendation

3.4.3. We recommend a preoperative dental evaluation, especially for patients with locally advanced lesions.
Moderate certainty of evidence, Strong recommendation

3.4.4. We recommend evaluating for second primary malignancies with the use of panendoscopy (except bronchoscopy) or a PET/CT.
Moderate certainty of evidence, Strong recommendation

Key Findings

Assessment of Oral Functions
It is recommended to perform mastication, speech, and swallowing assessments, nutritional status assessments, dental evaluations, and secondary primary malignancies evaluations.

The preoperative assessment of oral cavity function, including mastication, swallowing, and phonation, should be performed[10] for selected at-risk patients, such as those with speech and/or swallowing dysfunction or patients whose treatment is likely to affect speech and swallowing.[12] The resection of a substantial amount of soft tissue and bone may further affect these functions and also affect the patient's quality of life.[10] Physicians can gauge the decline and create a restoration strategy by evaluating these functions.[10] Evidence were rated as moderate quality, except for one guideline[12].

Pretreatment Assessment of Nutritional Status
The patient's overall status should also be completely evaluated, including nutritional status. The performance status with the identification of all co-morbidities present should be assessed, as this may determine patient operability. Those with significant weight loss should start nutritional

supplementation through whatever route possible, as severely malnourished patients can have significantly worse outcomes, such as quality of life and survival.[6]

Preoperative Dental Evaluation
A dental examination with the identification and extraction of teeth with dental caries or loose teeth should also be performed prior to treatment. Alternatively, one guideline recommends that the extraction of compromised teeth be performed by the surgeon at the time of surgical resection of the primary tumor.[6]

Evaluation of Second Primary Malignancies
Patients with head and neck malignancies are known to have a risk of developing second primary malignancies. The incidence ranges from 3-33% and is associated with the site and size of the primary tumor and lymph node involvement.[10,16] These second primaries can be identified in the head and neck, lung, or esophagus.

In one of the guidelines, 6.4% of these patients with synchronous second primaries were asymptomatic.[16] Due to this, the guidelines recommended the performance of a panendoscopy, which includes a laryngoscopy, bronchoscopy, and esophagoscopy. In some guidelines, the use of these diagnostic modalities should be guided by the presence of symptoms or other diagnostic findings.[7,11] The Korean guidelines do not recommend the routine use of bronchoscopy, as chest CT was found to be superior in detecting lung malignancies.[10] Detecting second primary malignancies using a PET-CT can also be useful, but one of the guidelines claims that it is ineffective for smaller lesions.[10]

Remarks
No issues were raised regarding these recommendations.

3.5. What staging system should be used in assessing oral cavity cancer?

3.5. We suggest using the latest edition of the AJCC staging system for staging oral cavity cancers.
Very low certainty of evidence, Weak recommendation

Key Findings
Three guidelines[11-13] recommended the use of the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Staging System for accurate staging and treatment of patients with oral cavity cancer.

Remarks
No further comments on the statement were raised apart from the suggestion to modify it and include the word "latest."

3.2.2. Management

4. Among patients with early-stage oral cavity cancer, what is the recommended treatment for managing the disease?

4.1. What are the recommended surgical and pathologic margins in the treatment of early-stage oral cavity cancers?

4.1. We recommend surgery (preferred) possibly followed by radiation therapy or chemoradiation therapy if indicated for patients with early-stage oral cavity cancer. *High certainty of evidence, Strong recommendation*

Key Findings

The NCCN guidelines recommend surgical therapy for resectable early-stage oral cavity tumors.[12] The goal of treatment is to achieve permanent or sustained locoregional tumor control with as minimal functional or aesthetic impairment as possible.[12] The functional outcome after primary surgical management of early-stage oral cavity cancer is often good, provided with advances in reconstruction techniques. Some very small or superficial cancers are managed more expeditiously with a surgical resection without resultant functional deformity or an undesirable cosmetic result. The guidelines also recommend definitive RT as an option for patients who are unfit for surgery or for those who refuse surgery.[12]

Multicenter studies examining the superiority of surgical therapy or radiotherapy for early oral cavity cancer were found. In a cohort study among 8274 patients with early-stage oral cavity squamous cell cancer, the five-year overall survival (OS) was 30.3% for those who did not receive treatment, 34.3% for those who received RT alone, and 71% for those who underwent surgery alone. Similarly, a cohort study of 20,779 patients with Stage I and II oral cavity squamous cell cancer from the National Cancer Database reported a five-year OS of 71% and 36% for the primary surgery and RT cohorts, respectively.[17] Factors such as age and comorbidities play a significant role in treatment decisions.[17] This also supports the idea that patients treated with definitive radiation are more likely to be poor surgical candidates because of their medical comorbidities or refusal of surgery.

Remarks

This recommendation statement achieved a unanimous decision among the voting panel. No concern was raised.

4.2. What are the recommended surgical and pathologic margins in the treatment of early-stage oral cavity cancers?

4.2. We recommend a gross surgical margin of at least 1 cm of surrounding normal tissue with the ultimate goal of having a pathologic margin of at least 5 mm.
High certainty of evidence, Strong recommendation

Key Findings

Four international guidelines[8,10,12,13] recommend gross surgical resection margins of at least 1 cm to achieve a negative pathologic margin of 5 mm or more after post-excisional contraction of the specimen.

A pathologic distance from the invasive tumor to the resection margin of 2-5 mm is labeled as a close margin. Similarly, a pathologic distance from the invasive tumor to the resection margin of less than 2 mm is labeled as a positive margin.

Several studies[18-20] describe the survival advantage of 5 mm margins. A recent study[21], however, challenged the adequacy of the 5 mm margin. Singh and colleagues reported that each millimeter increase in margin provided a 3.67-month survival advantage from 2.1 mm to 7.5 mm while a substantial advantage of 15 months was seen from 7.5 to 7.6 mm.[21] No significant advantage was gained when the margin was increased by a millimeter from the cut-off value (P = 0.602). Thus, while most guidelines recommend the 5 mm pathologic margin, a wider margin of 7.5 to 7.6 mm may offer an additional advantage.

Remarks

This recommendation statement achieved a consensus. No concern was raised.

4.3. What is the role of the frozen section in the wide excision of the primary lesion of early-stage oral cavity cancer?

4.3. We recommend intraoperative margin assessment using frozen section whenever available.
Low certainty of evidence, Strong recommendation

Key Findings

Two guidelines[6,12] recommend the use of frozen section assessment whenever possible. The ultimate goal is negative final margins which is defined as > 5 mm on permanent pathology.

One randomized controlled trial[22] and one cohort study[23] reported that 21% to 43% of patients had pathologically inadequate margins and benefited from further excision. On the other hand, two different investigations[24,25] concluded that the benefit of a frozen section for margin assessment is negligible.

Due to the potential advantage of a frozen section over the cost of the procedure and the possible risk of inadequate margins, a frozen section is recommended by the guidelines[6,14] whenever available.

Remarks
One research gap identified during the discussion was local data on frozen sections that may be addressed by future studies.

Despite the low certainty of evidence, the statement garnered a strong recommendation due to its potential benefit. The pathologist on the voting panel, however, raised the need to specify the margin that will be subjected to the frozen section assessment (biopsies taken from the operative bed or a margin section from the resected specimen). It was mentioned that most literature reported that the latter correlates with local control and recurrence. Using the margin section from the resected specimen also has the advantage of being measured in terms of distance from the tumor.

4.4. What is the recommended management of the ipsilateral N0 neck nodes in patients with early-stage oral cavity cancer?

4.4. We recommend elective ipsilateral supraomohyoid neck dissection (levels I, II, and III) in patients with the following:
- cT2 oral cavity cancer
- cT1 disease which is moderate to poorly differentiated or with depth of invasion of > 3 mm.

High certainty of evidence, Strong recommendation

Key Findings
High certainty evidence from various guidelines[14,26] recommend elective neck dissection for early-stage (N0) oral cavity cancers. Elective neck dissection of oral cavity cancer includes dissection of levels I, II, and III cervical node basins.

An RCT (n = 500 patients) with cT1N0M0 and cT2N0M0 oral cavity cancer reported that the 3-year overall survival for patients who underwent elective node dissection is 80.0% (95% CI 74.1 to 85.8) compared to 67.5% (95% CI 61.0 to 73.9) for patients who underwent watchful waiting followed by therapeutic neck dissection once with relapse.[27] The patients in the elective-surgery group also had a higher rate of disease-free survival (69.5% vs. 45.9%, $P < 0.001$). However, in a subgroup analysis, patients with 3 mm or less depth of invasion showed no benefit from elective neck dissection. Critics of this approach have pointed out that 70% of patients received unnecessary surgery as there was no evidence of disease; however, the overall findings for the

whole population suggest that routine elective neck dissection for cT1-cT2N0M0 oral cavity cancer improved overall survival.

Several systematic reviews have addressed the issue of sentinel lymph node (SLN) biopsy in oral cavity carcinoma.[28-31] Sentinel lymph node biopsy is an alternative to elective neck dissection for identifying occult cervical metastasis in patients with early-stage (T1 or T2) oral cavity carcinoma in centers where expertise for this procedure is available. Technical experience and judgment are required for the successful execution of lymphatic mapping and SLN. Its advantages include reduced morbidity and an improved cosmetic outcome. Detection rates exceeding 95% in sentinel lymph node biopsy have been widely reported.[28-31].

Remarks
This recommendation statement achieved consensus after modifying it to further clarify the subset of patients eligible for an elective neck dissection.

4.5. What is the recommended management of the contralateral N0 neck in patients with early-stage oral cavity cancer?

4.5. We recommend elective contralateral supraomohyoid neck dissection in patients with cT2 oral cavity cancer, cT1 tumors that are moderate to poorly differentiated, or those with DOI > 3 mm which:
- crossed the midline of the hard palate and tongue
- located at the floor of the mouth.

High certainty of evidence, Strong recommendation

Key Findings
Evidence of high certainty from clinical practice guidelines[6,11,14] recommend elective supraomohyoid neck dissection (levels I, II, and III) of the contralateral neck for clinically node-negative early-stage oral cavity cancers in the cases wherein: (1) T2 lesions cross the midline; (2) T1 lesions are moderate to poorly differentiated or DOI > 3 mm that crosses the midline; or (3) floor of the mouth cancer with DOI > 3 mm that crosses the midline.

Management of the contralateral clinically N0 neck presents a therapeutic challenge as it requires a cost-benefit analysis of the morbidity of neck dissection rather than a chance of occult locoregional metastasis given the location, size, and depth of invasion of the primary tumor. The likelihood of contra- or bilateral metastasis is increased in carcinomas of the floor of the mouth and in midline-near carcinomas in general.[32] Studies have shown a risk of metastasis of 49–54%, even in patients with early oral cavity cancers.[32,33] Thus, supraomohyoid neck dissection (levels I, II, and III) is recommended based on the above criteria.

Remarks

The issue raised in this recommendation was the scope of management, particularly for the mass that is on the midline but does not cross the midline. One panel member pointed out that because the mass is three-dimensional, it will still cross the midline, and the laterality will depend on where the bulk of the mass falls.

4.6. What is the role of definitive radiation therapy in the management of patients with early-stage oral cavity cancer?

4.6. We recommend radiation therapy as an option for patients unfit for surgery or those who refuse surgery.
High certainty of evidence, Strong recommendation

Key Findings

Disease in its early stages should be treated as much as possible with a single-modality treatment.[8] Surgery is the preferred modality of treatment for operable early-stage oral cavity cancers. For similarly staged patients who are medically unfit or refuse surgery, definitive radiation therapy can be offered. [7,8,11,12,16,34] This can be delivered via external beam radiation therapy or brachytherapy (for well-selected tumors, done in centers with expertise). External beam RT is recommended to be delivered via highly conformal techniques such as intensity-modulated RT (IMRT) or its variant volumetric-modulated arc therapy (VMAT) in order to decrease toxicity.

Remarks

These recommendations achieved consensus. No issues were raised.

4.7. What is the recommended adjuvant therapy in the management of patients with early-stage oral cavity cancer?

4.7.1. We recommend the use of adjuvant therapy in early stage oral cavity cancer in those with adverse features.
High certainty of evidence, Strong recommendation

4.7.2. We recommend adjuvant chemoradiation therapy for primary tumors with a positive margin on a final histopathologic report that is not feasible for re-excision.
High certainty of evidence, Strong recommendation

Key Findings

Post-operative radiation therapy for early-stage oral cavity cancers[35] [36-38] demonstrated improved disease-free survival at five years among those patients who underwent post-operative radiation

therapy for early-stage oral cavity cancers with adverse features (75.63% vs. 62.74%, *P* =.047) but not overall survival (*P* = .73).

Postoperative adjuvant treatment depends on the presence of adverse features. Adjuvant RT is recommended for the following adverse features: pT3-T4 primary, pN2-N3 nodal disease, nodal disease in level IV or V, perineural invasion, vascular invasion, lymphatic invasion, and close margins (if re-resection is not feasible). Adjuvant radiation is also suggested for pN1 who did not undergo high-quality neck dissection (< 18 lymph nodes included during ipsilateral neck dissection).[26] Adjuvant radiation therapy with systemic therapy, on the other hand, is recommended for extranodal extension or positive margins (if re-resection is not feasible). It is recommended to start adjuvant RT within 6 weeks from the date of surgery.

For early-stage oral cavity cancers that underwent resection with positive margins on the final histopathologic report, re-excision with adequate margins is preferred. However, when re-excision is not feasible, cisplatin-based chemo-radiation offers dismal progression-free benefit.[36,37]

Remarks
These recommendations achieved consensus. No consensus issues were raised.

5. Among patients with locally advanced resectable oral cavity cancer, what is the recommended treatment for managing the disease?

5.1. What is the recommended initial treatment for the primary site?

5.1. We recommend surgical resection of the primary tumor and the involved and at-risk cervical lymphatics.
High certainty of evidence, Strong recommendation

Key Findings
In one randomized controlled trial among newly diagnosed patients with resectable, nonmetastatic stage III/IV locally advanced head and neck squamous cell carcinoma (n = 119), the overall 5-year OS rates were higher in those who underwent radical surgery followed by adjuvant RT when compared with those who received a combination chemotherapy with cisplatin and 5-fluoracil and concurrent RT alone (45% vs. 35%, *P* = .262). For the oral cavity, 5-year disease-specific survival was significantly better in patients who underwent surgery and RT than those in combination chemotherapy and concurrent RT alone (68% vs. 12%, *P* = .038)[39]

Remarks
These recommendations achieved consensus. No issues were raised.

5.1.1. How much surgical margin should be removed?

5.1.1. We recommend a gross surgical margin of at least 1 cm of surrounding normal tissue with the ultimate goal of having a pathologic margin of at least 5 mm.
Low certainty of evidence, Strong recommendation

Key Findings

Four international guidelines[8,10,12,13] recommend gross surgical resection margins of at least 1 cm to achieve a negative pathologic margin of 5 mm or more after post-excisional contraction of the specimen.

A pathologic distance from the invasive tumor to the resection margin of 2-5 mm is labeled as a close margin. Similarly, a pathologic distance from the invasive tumor to the resection margin of less than 2 mm is labeled as a positive margin.

Several studies[18-20] describe the survival advantage of 5 mm margins. A recent study[21], however, challenged the adequacy of the 5 mm margin. Singh and colleagues reported that each millimeter increase in margin provided a 3.67-month survival advantage from 2.1 mm to 7.5 mm, while a substantial advantage of 15 months was seen from 7.5 to 7.6 mm.[21] No significant advantage was gained when the margin was increased by a millimeter from the cut-off value (P = 0.602). Thus, while the 5 mm pathologic margin is recommended by most guidelines, a wider margin of 7.5 to 7.6 mm may offer an additional advantage.

Remarks

Despite the low certainty of evidence, this statement garnered a strong recommendation aligned with the international guideline recommendation.

5.1.2. What is the role of the frozen section in assessing surgical margins?

5.1.2. We recommend performing intraoperative margin assessment using frozen section, with samples taken from the resected specimen, whenever possible.
Low certainty of evidence, Strong recommendation

Key Findings

Due to the potential advantage of a frozen section over the cost of the procedure and the possible risk of inadequate margins, a frozen section is recommended by the guidelines[6,14] whenever available.

Assessing the frozen section margin is always at the discretion of the surgeon and should be taken into account when it will facilitate complete tumor excision.[14]

Remarks

The panel unanimously decided on this recommendation after careful consideration of using the terms that are more appropriate (i.e., resected vs. removed) and sound more imperative (i.e., whenever vs. if possible). It was clarified prior to voting that, in this statement, the frozen section will be taken from the resected specimen.

5.1.3. How should the mandible be surgically managed?

5.1.3.1. We recommend the following resections for tumor adjacent to the mandible:

a. periosteal stripping for tumors abutting the fixed gingiva
b. marginal manibulectomy for tumors involving the periosteum but not eroding the cortex
c. segmental mandible resection if there is extension through the mandibular cortex or in a tooth root

Low certainty of evidence, Strong recommendation

5.1.3.2. If uncertainty exists about bony involvement, we recommend exposing and inspecting the bone before deciding about marginal mandibulectomy vs. segmental mandibulectomy.
High certainty of evidence, Strong recommendation

Key Findings

Locally advanced disease presents with a tumor that usually invades the mandible or beyond. [14] A positive bone margin associated with malignancy increases the risk of morbidity in theory; this could affect postoperative further treatment options and result in a poor prognosis.[10] The options for management of the bony mandible balance sparing structural integrity with achieving adequate bony margins for safe resection.[10] In one experimental study, the amount of residual bone necessary to withstand a fracture was compared. Barttelbort and Ariyan showed that at least 1 cm of bone at the inferior border of the mandible should be kept to reduce the risk of fracture.[40]

Remarks

There were no comments on recommendation statement 5.1.3.1 aside from the clarification that the said resections of the mandible depend on the extent of mandibular involvement. Each of the three recommendations (a, b, and c) stands alone. No consensus issues were raised on the statement 5.1.3.2.

5.2. What is the recommended treatment for the neck?

5.2.1. What is the recommended treatment for the N0 neck? Elective neck dissection versus RT?

5.2.1.1. We recommend doing ipsilateral selective neck dissection in patients with locally advanced (T3 or T4) oral cavity cancer.
High certainty of evidence, Strong recommendation

5.2.1.2. We recommend selective neck dissection I-III for oral cavity sites, except the lateral tongue, for which we recommend selective neck dissection I-IV.
Low certainty of evidence, Strong recommendation

5.2.1.3. We do not recommend level IIb dissection if there are no suspicious lymph nodes at level IIa.
Low certainty of evidence, Strong recommendation

5.2.1.4. We recommend contralateral neck dissection if the primary tumor touches/abuts or has crossed the midline.
High certainty of evidence, Strong recommendation

Key Findings

The extent of neck dissection (i.e., comprehensive or selective) is defined by preoperative clinical staging, is identified depending on the surgeon's discretion, and is based on that initial preoperative staging.[12] The common paths for the spread of head and neck malignancies to regional nodes are the basis for selective neck dissection.[12] For the purpose of removing the nodules that are frequently associated with metastasis in the oral cavity, a selective neck dissection is recommended, encompassing the nodules situated superior to the omohyoid muscle (levels 1-III) and occasionally the upper regions of level IV).[12] In an evidence with low certainty[6], it was specified that in cases where the tumor is located in the lateral tongue, level 4 removal should also be performed.

Remarks

There were no remarks on both recommendation statements. Despite the low certainty of evidence in 5.2.1.2., the statement garnered a strong recommendation as it was discussed by a surgeon who specializes in head and neck cancer.

The discussion clarified that suspicious lymph nodes are those with enlarged lymph nodes. Statement 5.2.1.3 was unanimously approved following a discussion on rephrasing with the goal of recommending against performing level IIb dissection if there are no enlarged lymph nodes.

The initial recommendation statement 5.2.1.4. used the word "approaches" before it was changed to "touches" or "abuts," as the pathologist among the voting group stated that "approaches" can

also imply "touches." Although this statement reached consensus, the surgeon on the panel disagreed with the use of "touches/abuts" because international standards, such as the NCCN, provide a different recommendation (bilateral neck dissection) if the tumor is already close to the midline.

5.2.2. What is the recommended treatment for the N+ neck?

5.2.2.1. We recommend that in patients with clinically N+ disease, a comprehensive neck dissection be performed on the ipsilateral side (removal of levels I-IV, and non-lymphatic structures if indicated).
High certainty of evidence, Strong recommendation

5.2.2.2. We do not recommend level V dissection unless the neck has lymph node involvement in more than one level.
Low certainty of evidence, Strong recommendation

5.2.2.3. We recommend an elective contralateral neck dissection if the primary tumor site touches/abuts or has crossed the midline.
Low certainty of evidence, Strong recommendation

Key Findings
Ipsilateral levels I, II, and III are the most frequently affected sites in advanced oral cancers, particularly in cervical metastasis.[41] In the Korean guideline, they acknowledged that levels IV and V are rarely involved in oral cavity cancers.[10] However, level IV or V are considered in dissection based on individual patient factors, such as advanced T stage, multiple clinically positive nodes, and extracapsular spread. These factors were found to be associated with neck failure due to metastasis to levels IV and V or high recurrence rates. [10]

A therapeutic neck dissection for oral cavity cancer does not commonly include level V dissection because it poses a significant risk to the spinal accessory nerve. It may be offered to patients with multi-level disease.[26]

In the same guideline, contralateral neck dissection was not routinely considered due to the low incidence of contralateral metastasis in oral cavity cancers. Contralateral lymph node metastasis was associated with multiple clinically positive nodes and level IV or V involvement. In a report cited, the occult rate dropped from 11% to 2.9% when tumors close to the midline were excluded.[42]

Remarks
These recommendation statements earned a unanimous vote among the consensus panel members. Recommendation statement 5.2.2.1 was only revised from “radical or modified radical neck dissection” to “comprehensive neck dissection” to align the terminologies with those of updated international practice guidelines on head and neck cancer as suggested by a surgeon.

5.2.3. What is considered a good-quality neck dissection?

5.2.3. We recommend at least 18 lymph nodes for an adequate comprehensive dissection.
Low certainty of evidence, Strong recommendation

Key Findings

In a retrospective cohort (n = 4,771) of patients diagnosed with oral cavity squamous cell carcinoma, it was found that among those patients with a depth of invasion < 4 mm, neck dissection with 18 or more nodes harvested was one of the factors associated with improved survival (HR 0.67, 95% CI 0.54 to 0.85). For patients with DOI ≥ 4 mm, neck dissection with 18 or greater nodes harvested was also associated with improved survival (HR 0.47, 95% CI 0.34 to 0.64).

Remarks

The panel arrived at a consensus in making a strong recommendation for using at least 18 lymph nodes for a comprehensive dissection since this is based on best practice. A panel member emphasized that pathologists follow this recommended number of lymph nodes. No other remarks were made on this recommendation.

5.2.4. What findings do we want clearly stated in the histopathology report for the neck dissection?

5.2.4. We recommend that at the very least, the number of total nodes, the number and size of positive nodes, and the presence or absence of extranodal extension should be stated in the histopathology report.
High certainty of evidence, Strong recommendation

Key Findings

One guideline[6] appraised to have high certainty recommends that for all neck dissection specimens, the number and size of positive nodes and the presence or absence of extranodal extension should be specified in a histopathology report.

Remarks

After a voting member suggested changing the "extracapsular" extension to "extranodal," there were no comments or objections from the panel. This statement earned a unanimous vote.

5.3. What adjuvant treatment should be given for locally advanced resectable oral cavity cancer (T3-T4a, N0-3)?

5.3. We recommend combined modality treatment of surgery followed by radiation therapy with/without chemotherapy as indicated.
Moderate certainty of evidence, Strong recommendation

Key Findings

Surgery followed by postoperative adjuvant radiation therapy is recommended, and systemic therapy is considered for locally advanced oral cavity cancers with the following adverse features: pT3-T4 primary, pN2-N3 nodal disease, nodal disease in level IV or V, perineural invasion, vascular invasion, lymphatic invasion, and close margins (if re-resection is not feasible).[8]

Adjuvant radiation is also suggested for pN1 who did not undergo high-quality neck dissection (<18 lymph nodes included during ipsilateral neck dissection).[26] Adjuvant radiation therapy with systemic therapy is recommended for extranodal extension with positive margins (if re-resection is not feasible). It is recommended to start within 6 weeks from the date of surgery.

External beam radiation therapy is recommended to be delivered via highly conformal techniques such as IMRT or VMAT in order to decrease toxicity.

Remarks

No consensus issues arose during the discussion of this recommendation statement.

6. Among patients with metastatic oral cavity cancer, what is the recommended treatment for managing the disease?

6.1. We recommend individualized treatment decision-making with consideration of performance status for patients with metastatic oral cavity cancer.
High certainty of evidence, Strong recommendation

6.2. We recommend palliative care in the following situations:
- significant or multifocal recurrence
- advanced primary disease where complete resection and/or use of adjuvant therapy are not possible

High certainty of evidence, Strong recommendation

6.3. We recommend the use of palliative systemic therapy in metastatic oral cavity cancer with a performance status of 0-2.
Moderate certainty of evidence, Strong recommendation

Key Findings

The goal for patients with metastatic disease at presentation now shifts to palliation or prolongation of life. Derived from high certainty evidence from three guidelines, individualized clinical decision-making taking into consideration the patient's performance status is recommended for patients with metastatic oral cavity cancer. Only NCCN guidelines reported a method to classify performance status. Eastern Cooperative Oncology Group[43] categorized performance status on a five-point scale with the following interpretation: 0 means fully active or no performance, 1 – strenuous physical activity restricted or fully ambulatory and able to carry out light work; 2 – able to perform all self-care activities but unable to perform any work activities and up and about > 50% of waking hours; 3 – able to perform limited self-care and confined to bed or chair > 50% of waking hours; 4 – completely disabled or cannot carry out any self-care and totally confined to bed or chair.

In the same guideline, patients with significant or multifocal recurrence (i.e., unresectable recurrence with the presence of distant metastasis and locoregional failure), palliative care may be considered to alleviate tumor burden-related symptoms.

Options for treatment at the metastatic stage may include surgery or definitive radiation therapy (with or without systemic therapy) for selected patients with limited metastasis, palliative surgery, palliative radiation therapy, or best supportive care.[7,8,14] Enrollment in clinical trials is preferred, if feasible.

Either a combination or single-agent systemic therapy can be offered to patients with a performance status of 0-1. Cisplatin and 5-fluorouracil (5-FU) or methotrexate are options for single-agent systemic therapies, while a cisplatin-based combination regimen includes cisplatin-5-FU. Other options include RT, or systemic therapy or RT and surgery, which can be done for selected patients with limited metastases. The best supportive care can also be offered.

Patients with a performance status of 2 can be offered with single-agent systemic therapy or best supportive care with or without palliative RT. Palliative surgery is also an option, especially for relief of some symptoms.

Patients with a performance status of 3 are no longer candidates for systemic therapy and can be given best supportive care with or without palliative RT or palliative surgery to relieve symptoms.

Immunotherapy, such as pembrolizumab, together with platinum-based chemotherapy (cisplatin or carboplatin) and 5-FU, is the preferred first-line systemic treatment for metastatic or recurrent oral cavity cancer. For tumors expressing PD-L1 with CPS ≥1, Pembrolizumab may be given as monotherapy. Nivolumab is another immunotherapy that can be offered for subsequent therapies after disease progression or after platinum therapy.

For targeted therapy, patients with metastatic or recurrent disease who do not express PD-L1 can be offered Cetuximab with platinum based chemotherapy and 5-FU.

Remarks

Statement 6.1 was approved by a unanimous vote. There were no other comments raised regarding the statement aside from the query of the patient representative about the meaning of performance status. It was clarified that performance status is measured by a certain tool or scale that will indicate whether the patient can handle a certain treatment, such as surgery. The tool used in the guideline cited was further defined in the Key Findings.

No consensus issues were raised regarding statements 6.2. and 6.3.

7. Among patients with technically unresectable disease (T4b), resectable oral cavity cancer who are poor surgical candidates, or those who refuse surgery, what is the recommended treatment for managing the disease?

7.1. We recommend individualized treatment decision-making with consideration of performance status for patients with very advanced head and neck cancer.
Moderate certainty of evidence, Strong recommendation

7.2. We recommend the use of concurrent chemoradiotherapy in resectable oral cavity cancer patients who refuse surgery or who are poor candidates for surgery.
Moderate to High certainty of evidence, Strong recommendation

Key Findings

For patients with very advanced head and neck cancer (locally advanced non-metastatic, unresectable, or unfit for surgery), individualized decision-making taking into consideration the patient's performance status is recommended.

Options for treatment may include (a) concurrent radiation therapy with systemic therapy, (b) induction systemic therapy followed by radiation therapy (+/-systemic therapy), (c) surgery followed by CTRT for NACT responders, (d) radiation therapy alone (with definitive or palliative intent), or (e) systemic therapy alone (combination or single agent) and best supportive care.[8,14]

Patients with T3, N1, or T4a disease who refuse surgery or are poor candidates for surgery can be given concurrent systemic therapy or RT. Clinical response is assessed after 4-8 weeks. Patients with residual primary, persistent, or noted to have progression are advised to undergo CT or MRI with contrast or FDG PET/CT. Those with unresectable disease and noted to have locoregional recurrence or persistent disease without prior RT are encouraged to enroll in clinical trials if available. Those with a performance status of 0-1 can be offered concurrent systemic therapy/RT or induction systemic therapy followed by RT or systemic therapy/RT. Patients with a performance status of 2 can either receive RT or concurrent systemic therapy/RT while palliative

RT, single-agent systemic therapy, or best supportive care are options for those with a performance status of 3.

The Indian CPG on management of oral cavity cancer recommends neoadjuvant chemotherapy for technically unresectable diseases such as edema up to zygoma, involvement of the vallecula, disease close to the hyoid or invading the high infratemporal fossa superior to the sigmoid notch.[16] Responders may opt to have surgery followed by chemoradiotherapy. For those with no response, chemoradiotherapy or palliative treatment can be offered. In the NCCN guidelines, it was acknowledged that although it can be feasible, further investigation is still warranted.[14,44]

Remarks

The consensus panel had no other remarks on these statements apart from the need to provide details of treatment in the evidence summary for patients with T4b lesions, those with resectable disease but who are poor surgical candidates, or those who refuse surgery. These populations are further discussed in the Key Findings above.

8. Among patients who underwent surgery for oral cavity cancer, what is the recommended reconstructive procedure for soft tissue and bony defects?

8.1.1. We recommend including reconstruction as part of the surgical plan always.
Low certainty of evidence, Strong recommendation

8.1.2. We recommend reconstruction of defects after surgery of oral cavity cancer to preserve function.
Low certainty of evidence, Strong recommendation

8.2. We recommend the following for soft tissue reconstruction depending on the size and soft tissue involvement: healing by secondary intention, primary closure, skin grafting, local, regional or free flap reconstruction.
Low certainty of evidence, Strong recommendation

8.3.1. We recommend the use of the following procedures for bone reconstruction depending on the extent of bony defect: bone graft or osteocutaneous free flap.
Low certainty of evidence, Strong recommendation

8.3.2. We recommend that if bony reconstruction is not available, primary soft tissue closure or reconstruction with a regional flap be used as an alternative.
Low certainty of evidence, Strong recommendation

Key Findings

Reconstruction, specifically flap, is recommended to preserve adequate speech and swallowing in patients with considerable defects after oral cancer surgery, as stated in the two guidelines.[7,10] Partial glossectomy defect approaching half of the tongue or more, to improve swallowing function

is also recommended in the guidelines. Similarly, flap reconstruction and post-operative rehabilitation are strongly recommended for patients who underwent subtotal or total glossectomy to preserve the mobility of the tongue for functional speech and swallowing. It is recommended for floor of mouth defects to prevent communication between the neck and oral cavity and considerable buccal defects to preserve mouth-opening ability and for structural cosmesis.[7,10]

Low-quality evidence on the radial forearm and anterolateral thigh-free flaps is considered for the reconstructive methods for oral soft tissue defects while other types of reconstructive surgery were considered depending on the extent of primary resection, patient's morbidity, and surgeon's preference.[10,13]

Evidence with low certainty showed benefits such as preservation, or in the case of secondary reconstruction, restoration of chewing, speaking, and swallowing function as well as facial aesthetics. Reconstructive procedures include local flap plasty, free skin, mucosa, or bone grafting, muscle-targeted grafts, and microvascular tissue transfer.[7]

Deciding on the optimal reconstructive option is a complex decision and needs to take into account the location, size, structures involved in the defect, the patient's pre-surgical functional status, pulmonary reserve, surgical expertise, and local health care infrastructure for peri- and postoperative management.[6]

An example is reconstruction of the tongue. Secondary intention and primary closure are the simplest types of repairs, but they require tongue defects of less than or equal to 3 cm and with intact floor of mouth and mandibular mucosa. Split thickness skin grafting can be used for larger tongue defects with extension to the floor of mouth or mandible. It is important to place the graft with maximal redundancy to avoid contraction when healed.[6]

When the defects are larger and skin grafting alone will lead to such a loss of tongue volume that deglutition and speech will not effectively be achieved, local flaps can be used such as buccinator or tongue myomucosal flaps, nasolabial flap, facial artery musculomucosal (FAMM) flaps, platysmal, or infrahyoid myocutaneous flaps.[6]

In larger defects such as hemiglossectomy or involvement of the adjacent floor of mouth, where a larger volume of tissue is needed, regional flaps can be considered like submental island, pectoralis major, and supraclavicular island flaps. Free flap reconstruction such as radial forearm free flaps or anterolateral thigh flaps can yield excellent results, but these require specialty training and instrumentation.[6]

Floor-of-mouth reconstruction can be achieved using a very similar algorithm to oral tongue reconstruction. Buccal defects can often be closed primarily. The largest morbidity from a buccal resection is the risk of contracture and trismus. Larger defects are often amenable to skin grafts or local flaps described above.[6]

The guidelines[6,10] used to support the recommendations on bone reconstruction depending on the extent of the bony defect suggested osteocutaneous free flaps, especially the fibular free flap, as the primary method of mandibular reconstruction.

When bony reconstruction is not available, primary soft tissue closure or reconstruction with a regional flap such as a pectoralis or supraclavicular island can be used, and the mandible left to swing.[6]

Remarks

No consensus issues were raised regarding statements 8.1.1 and 8.3.2. In formulating recommendation statement 8.1.2., the panel agreed to omit the specific outcomes (e.g., preserve mouth-opening ability, speech, mastication, and swallowing and prevent communication between the neck and oral cavity) included in the recommendation statement and include a general outcome such as preserving function.

Recommendation statement 8.2, which was revised mainly by the plastic surgeon in the voting panel, is based on the reconstructive ladder. However, it does not necessarily mean that the sequence is strictly followed. A reconstructive ladder indicates that you can ascend to the level of the patient's immediate need and consider the soft tissue involvement. Despite the low certainty of evidence, it earned approval, making it a strong recommendation based on benefits and best practices. A research gap in plastic surgery was identified; most of the evidence supporting the recommendations in reconstruction is based on low certainty of evidence. Statement 8.3.1. achieved consensus to recommend the said procedures depending on the size or extent of the bony defect.

3.2.3. Follow-up/ Surveillance

9. Among patients with oral cavity cancer who received primary or definitive treatment, how should surveillance be done?

9.1.1. We recommend that patients must have a follow-up consultation every 1-3 months on Year 1, every 2-6 months on Year 2, every 4-8 months on Years 3-5, and every 12 months after Year 5.
Moderate certainty of evidence, Strong recommendation

9.1.2. We recommend that all patients should be assessed for signs and symptoms of possible tumor recurrence, health behaviors, nutrition, dental health, and speech and swallowing function.
Moderate certainty of evidence, Strong recommendation

9.1.3. We recommend that tumor evaluations must be performed by specialists skilled in head and neck clinical examination.
Moderate certainty of evidence, Strong recommendation

9.1.4. We recommend a complete head and neck exam, mirror and fiberoptic examination during follow-up.
Moderate certainty of evidence, Strong recommendation

9.1.5. We recommend thyroid-stimulating hormone (TSH) evaluation every 6-12 months, if the neck was exposed to radiation treatment.
Moderate certainty of evidence, Strong recommendation

9.1.6. We recommend regular dental care, oral hygiene and early interventions for oral and dental complications once every six months.
Moderate certainty of evidence, Strong recommendation

9.1.7. We recommend evaluation and close monitoring of the nutritional status of patients with oral cavity cancer.
Moderate certainty of evidence, Strong recommendation

Key Findings

The recommendation was based on one guideline with high certainty.[14] The schedule slightly varied from another guideline,[7] which has moderate certainty and recommends a maximum of 3 months for the follow-up during the 1st and 2nd years and 6 months for the 3rd to 5th year, even if the patient is symptom-free. The German guideline has no particular recommendation about the frequency of follow-up after the 5th year.[7] The primary goal of follow-up consultations is to carefully examine the oral cavity and neck to exclude any tumors that might have recurred. Another benefit of tumor follow-up is the detection of second malignant tumors or distant metastases.[7]

In the NCCN guidelines, it is recommended that all patients have regular follow-up visits to examine symptoms and possible tumor recurrences, health behaviors, nutrition status, dental health, and speech and swallowing function.[14] Tumor evaluations must be performed by specialists trained in head and neck clinical examination.

Patients who received radiotherapy, in particular, should be checked to manage possible dental carries and gingival status periodontal abnormalities. Postoperative oral care examinations may also reduce the risk of postoperative wound infection. Patients who are unable to feed themselves sufficiently with solid or liquid food or maintain an adequate amount of water due to feeding and swallowing problems should be evaluated since they are at risk of malnutrition. In NCCN guidelines, all patients, particularly those who undergo radiotherapy, are recommended to receive dietary counseling simultaneously with treatment initiation.[14] Dysphagia (swallowing disorder) as well as speech morbidity may also arise after surgical management of oral cavity cancer. These dysfunctions reduce quality of life, may interfere with targeted tumor treatment, and can lead to serious adverse events, such as aspiration pneumonia.[7]

Thyroid stimulating hormone levels should be assessed every 6-12 months, especially among those whose cancer has been treated with RT.[14] If the skull was exposed to radiation, changes in TSH levels may indicate hypopituitarism or thyroid gland dysfunction.[14]

Remarks

There were no objections to statements 9.1.1 and 9.1.2 after defining a “regular” follow-up consultation by outlining the intervals of the consultation schedule annually. The bases for frequency of schedule are risk of relapse, second primaries, treatment sequelae, and toxicities.

Despite the concerns about the availability of clinical experts in the country, statement 9.1.3 garnered consensus due to patients' perceived benefits from seeing trained specialists in head and neck clinical assessment.

On statement 9.1.4, the rehabilitation specialist in the panel suggested including, as part of the head and neck exam, an assessment of swallowing function post-surgery using a modified barium swallow or a fiberoptic endoscopic evaluation of swallowing. However, another panelist expressed concern with the availability of barium; therefore, contrast swallow studies may be advised instead.

No consensus issues arose during the discussion of recommendation statements 9.1.5 to 9.1.7.

9.2.1. We recommend short-term post-operative imaging for patients with locoregionally advanced cancer prior to starting postoperative adjuvant therapy for the following:
- those at high risk of early recurrence
- those who show signs of early recurrence

Moderate certainty of evidence, Strong recommendation

9.2.2. We recommend CT and/or MRI within 3-4 months after surgical treatment for patients with locoregionally advanced disease or with altered anatomy causing challenging physical exam assessment to establish a new baseline for future comparison.
Moderate certainty of evidence, Strong recommendation

9.2.3. We recommend a CT or MRI within 4-8 weeks post-treatment for those with incomplete response.
Moderate certainty of evidence, Strong recommendation

9.2.4. We recommend US guided biopsy of the neck for targeted sampling of any suspicious lesions.
Moderate certainty of evidence, Strong recommendation

9.2.5. We recommend FDG PET/CT to be performed within 3-6 months of definitive radiation or chemoRT for assessment of treatment.
Moderate certainty of evidence, Strong recommendation

9.2.6. We recommend using FDG-PET/CT 3 months after chemoRT for patients with the node-positive disease to assess the necessity of neck dissection.
High certainty of evidence, Strong recommendation

9.2.7. We recommend chest CT for comprehensive evaluation of the pulmonary system.
Moderate certainty of evidence, Strong recommendation

Key Findings

As per the NCCN guidelines, patients diagnosed with locoregionally advanced disease who have undergone surgery should be referred for postoperative imaging in cases of early recurrence indications or if they are deemed to be at a high risk of early recurrence.[14] Patients who are at particular risk for rapid recurrence after surgery are those with positive margins, advanced T or N stage, or oral cavity cancers in general.[14]

Imaging is frequently a component of the evaluation that follows definitive therapy. New symptoms or physical examination findings in the long-term evaluation of those recurrent diseases also prompt requests for imaging. The type of imaging performed should be carefully considered.

After surgical treatment among patients with locoregionally advanced disease or with altered anatomy causing challenging physical exam assessment, the NCCN guidelines recommend CT or MRI within 3-4 months to establish a new baseline for future comparison.[14]

If there is a concern about an incomplete response to treatment, the aforementioned guidelines recommend imaging using CT or MRI as early as 4-8 weeks. According to the guideline, the proximity to recent treatment can complicate the interpretation of imaging studies; therefore, it is essential to communicate with the interpreting radiologist in order to differentiate between recurrent disease and post-treatment effects.[14]

Image-guided needle biopsy of cystic neck nodes may offer a better diagnostic yield than fine-needle aspiration by palpation alone for assessing suspicious lesions.[14]

After radiotherapy, FDG PET/CT is recommended by the same guideline. In the meta-analysis[45] of 27 studies conducted among patients with head and neck squamous cell carcinomas following radiotherapy with or without chemotherapy, the PPV and NPV for FDG PET/CT were 52.7% and 96.3%, respectively, in detecting local residual or recurrent disease.[14] The values of PPV (72.3%) and NPV (88.3%) were higher in terms of detecting nodal residual or recurrent disease. To reduce the false-positive rate, the first scan should be done at minimum of 3 months after treatment during surveillance.[14]

Contrast-enhanced chest CT is also recommended to be utilized if there is a concern about metastasis in the pulmonary system and/or mediastinal lymph node involvement. For patients with a heavy smoking history, an annual low-resolution chest CT should be considered.

Remarks

Statements 9.2.1, 9.2.6, and 9.2.7 achieved consensus without issues. Prior to voting and arriving at a consensus on recommendation 9.2.2, it was made clear that the statement is different from 9.2.1 because the second recommendation has a distinct indication (i.e., altered anatomy causing a challenging physical assessment to establish a new baseline for future comparison). Statement 9.2.3. achieved consensus without reservations after the clarification of the period for post-treatment imaging for those with incomplete responses.

Statement 9.2.4. achieved a unanimous decision to strongly recommend using an US-guided biopsy of the neck for targeted sampling of suspicious lesions.

Regarding recommendation 9.2.5, a panel member recognized the issue of accessibility and cost of PET/CT in this recommendation. The use of PET/CT was strongly supported, with the expectation that the government would extend its availability beyond the confines of Metro Manila. The use of ultrasound in surveillance, which was brought up in the deliberation, is mentioned as being situation-specific.

3.3. LARYNGEAL CANCER

3.3.1. Diagnosis and Pre-operative Management

1. What clinical data support a diagnosis of laryngeal cancer?

1. We recommend the following clinical data to suspect a diagnosis of laryngeal cancer:
   a. Clinical
   - With hoarseness lasting longer than 3 weeks
   - Odynophagia or dysphagia longer than 6 weeks
   - Associated otalgia, globus, stridor, and weight loss

   b. Physical Examination
   - Dysphonia
   - Signs of airway compromise
   - Cervical lymphadenopathy

   Any of the clinical findings, along with one of the physical examination findings, especially among those aged >50 years with extensive smoking and drinking history, should warrant a referral to a specialist.
   Low certainty of evidence, Strong recommendation

Key Findings

The clinical data supporting a diagnosis of laryngeal cancer include a detailed medical history and systematic physical examination with focused inspection of mucosal surfaces, indirect mirror examination, and neck palpation.[11,46]

The larynx is divided into three clinically important anatomic levels: supraglottis, glottis, and subglottis. Symptoms associated with malignancy would depend on the location of the tumor or the affected subsite and the stage at presentation.[47]

Glottic cancers present at an earlier stage because voice changes may manifest early. Supraglottic tumors, on the other hand, often present with nonspecific symptoms such as persistent otalgia, odynophagia, dysphagia, and, in a more advanced stage, weight loss and cervical neck masses.[47] The American Head and Neck Society states that clinical findings of hoarseness lasting longer than 3 weeks, odynophagia, or dysphagia lasting more than 6 weeks and complaints that include hoarseness, voice changes, sore throat, stridor, dyspnea, dysphagia, odynophagia, otalgia, neck mass, and weight loss should warrant a referral to a specialist. Subglottic tumors, which are rare, manifest with airway obstruction or vocal cord paralysis[47,48].

In a guideline review conducted by Tamaki et al., the typical patient is a male in his 50s with a history of smoking and alcohol use. Tobacco and alcohol are well-established risk factors and have a synergistic effect on increasing the risk.[47,48] A meta-analysis showed that individuals who smoked for 40 or more pack-years had nine times the risk of laryngeal cancer (RR 9.14, 95% CI

6.24 to 13.39), and subjects who smoked 40 or more years had more than five times the risk compared to never smokers (RR 5.76, 95% CI 3.69 to 8.99).[49] A case-control study showed that the consumption of hard liquor for more than 5 years was associated with 2.59 times higher odds of having laryngeal cancer (OR 2.59, 95% CI 1.14 to 5.87), while exposure to cigarette smoking for more than 10 years has 7.29 times higher odds of developing laryngeal cancer compared to those without such exposure (OR 7.29, 95% CI 2.41 to 22.09).[50]

Remarks

The panel recognized a barrier to implementing this recommendation: the scarcity of experts in geographically isolated and disadvantaged areas who can provide further evaluation if the patient is suspected of having laryngeal cancer. Nonetheless, it was strongly recommended to refer these patients, as this would lead to management if these cases turned out to be malignant.

2. Among patients suspected of having laryngeal cancer, what laryngoscopic method/s can be used to detect the disease accurately?

2. We recommend the use of rigid or flexible laryngoscopy in detecting the disease among patients suspected of having laryngeal cancer**.**
Low certainty of evidence, Strong recommendation

Key Findings

An instrument-based laryngeal examination could lead to the early detection of laryngeal cancer. Paul and colleagues compared the diagnostic accuracy of history, laryngoscopy, and stroboscopy.[51] They found that diagnoses were more consistently identified using laryngoscopy (100%) and stroboscopy (100%) compared to history and physical examination alone.[51]

Rigid or flexible laryngoscopy is used to detect the disease among patients suspected of having laryngeal cancer.[52] Stroboscopy and narrow-band imaging (NBI) may also be used to evaluate lesions suspected of laryngeal cancer.[52]

Flexible laryngoscopy has augmented the abilities of clinicians to conduct laryngeal assessments in individuals who may not tolerate rigid laryngoscopy and mirror examination. It allows examination that is less operator-dependent and patient-dependent than mirror laryngoscopy.[53]

Although not readily available locally, stroboscopy facilitates vocal fold vibratory capabilities and can evaluate suspicious lesions in the vocal folds.[54,55] On the other hand, the ability of NBI to detect changes in the mucosal microvasculature can be useful for distinguishing non-malignant from malignant lesions.[54,55] It has a reported sensitivity of 93.2% for the detection of laryngeal cancer in comparison with 68.5% for white light endoscopy.[56]

Remarks

The panel provided several justifications for the strong recommendation of this statement. First, a practitioner stated that flexible laryngoscopy could give a closer look at the lesion; however, the evidence showed no statistically significant difference between rigid and flexible laryngoscopy in detecting a laryngeal lesion. Second, it was clarified that both methods are considered standard of care and are accessible in clinics, although rigid laryngoscopes can be more readily available. Third, identifying the laryngeal lesion would warrant further workup and a treatment plan that would be beneficial to the patient.

3. Among patients suspected of having laryngeal cancer, what is the cost-effective method of obtaining tissue samples for biopsy?

3. We recommend direct laryngoscopy with microlaryngeal surgery under general anesthesia to obtain tissue samples for biopsy.
Moderate certainty of evidence, Strong recommendation

Key Findings

For glottic lesions, a surgical microscope is used to view the larynx through a transorally placed laryngoscope. This precise microsurgical method is used for the biopsy and staging of early and advanced malignant tumors of the glottis.[57]

The European CPG (EHNS-ESMO-ESRO) strongly recommended that examination and biopsy are best carried out using an endoscopic route under general anesthesia for pharyngolaryngeal tumors.[8]

In a systematic study done by Owusu-Ayim and Ranjan et al. regarding the diagnostic accuracy of in-office biopsies (IOB) for patients with laryngopharyngeal lesions, the median sensitivity of the IOB was 73% and specificity was 96.7%. Although it has the advantages of cost-effectiveness, reduced waiting times, and the avoidance of general anesthesia, available evidence suggests clinicians should remain cautious when interpreting negative biopsy results, especially in the context of strong suspicion, and should conduct confirmatory testing in such scenarios.[58]

Remarks

No consensus issues arose.

4. Among patients with suspected or proven laryngeal cancer, what imaging tests are necessary for pre-treatment assessment and staging?

4.1. What are the roles of computed tomography (CT) and magnetic resonance imaging (MRI)?

4.1. We recommend the use of contrast-enhanced (CE) computed tomography (CT) scan and/or magnetic resonance imaging (MRI) to detect local invasion and nodal involvement. *Moderate certainty of evidence, Strong recommendation*

Key Findings

Three-dimensional imaging, such as CT and MRI, following a clinical examination can better assess the extent of involvement of the deep laryngeal spaces. In a study by Thabet et al.,[59] CT was 88% accurate in staging transglottic and 68% accurate in supraglottic involvement compared with pathologic findings alone. Another study found that clinical or endoscopic evaluation alone yielded only a 57.5% staging accuracy compared with the addition of CT or MR imaging, which resulted in a significantly higher staging accuracy of 80% and 87.5%, respectively.[60] In another study[61], specificity and accuracy using T1-weighted MR images in predicting pre-epiglottic space invasion were 84% and 90%, respectively. A more recent prospective study[62] also showed high sensitivity (89%) and specificity (97%) rates of MRI in assessing pre-epiglottic space invasion. On the other hand, Banko and colleagues[63] demonstrated a 100% accuracy rate in determining anterior commissure involvement by MRI. MRI is considered superior in evaluating muscle and cartilage invasion, with 89 to 94% sensitivity and 74 to 88% specificity for thyroid cartilage invasion in laryngeal cancer.[64]

Paratracheal lymph node metastasis in laryngeal carcinoma indicates a worse prognosis. These nodes are hard to evaluate preoperatively, both clinically and by ultrasound. CT has a 70% sensitivity and 36% specificity, while MRI has a 50% sensitivity and 71% specificity for diagnosing paratracheal lymph node involvement.[65]

Contrast-enhanced CT and/or magnetic resonance imaging were mainly recommended to assess the primary tumor and regional lymph nodes.[8,46]

Remarks

Due to the moderate certainty of evidence, the panel voted for a strong recommendation.

4.2. What is the role of positron emission tomography-computed tomography (PET-CT)?

4.2 We recommend the use of PET/CT, if available in a high-resource setting, in the following situations:

6. in the evaluation of laryngeal cancer with equivocal CT or MRI findings
7. to accurately detect regional or distant metastases and second cancers or synchronous primary tumors
8. in advanced laryngeal cancer when definitive treatment is needed.

Moderate certainty of evidence, Strong recommendation

Key Findings

A PET/CT is a combination of two imaging modalities done in a single procedure on one machine. This combination makes it superior to a CT scan alone because, aside from the information that may be gleaned from CT, PET will show the absorption of certain radioactive tracers that will show cancerous cells not apparent by a CT scan. It was proven with the study of Senft et al., [66] which shows a higher sensitivity of the combined research in detecting tumors.

In a meta-analysis of 24 articles on detecting cervical nodal metastases, the pooled per-patient, per-neck-side, and per-neck-level sensitivities and specificities of FDG-PET/CT were 0.91/0.87, 0.84/0.83, and 0.80/0.96, respectively, which were higher than those of conventional neck-level imaging.[67] A systematic review that included two meta-analyses also showed that FDG-PET/CT could diagnose head and neck squamous cell carcinoma with a higher level of accuracy. The calculated pooled sensitivity of PET/CT is 89.3%, while pooled specificity is 89.5%, compared to 71.6% and 78.0%, respectively, for standard conventional imaging.[68]

Regarding the detection of distant metastasis and second cancers, Kim et al.[69] recommended using FDG-PET/CT as a primary staging method because of its high sensitivity (97.5%) and specificity (92.6%). A meta-analysis of 12 studies from 2001 to 2011 showed a calculated pooled sensitivity of 88.8% and a pooled specificity of 95.1%.[70]

PET/CT is the recommended in advanced stages of the disease when definitive treatment is needed “or in those with equivocal findings on a CT or MRI scan” [46,71]

Remarks

Due to the moderate certainty of evidence, the consensus panel opted for a strong recommendation despite the availability issue in low-resource settings.

3.3.2. Primary and Adjuvant Treatment

5. What are the treatment options for in-situ and early-stage laryngeal cancer?

5.1. We recommend endoscopic resection or radiotherapy for cases of carcinoma-in-situ.
Moderate certainty of evidence, Strong recommendation

Key Findings
The World Health Organization (WHO) considers carcinoma in situ a premalignant lesion.[72,73] It is an intraepithelial neoplasia in which the entire thickness of the squamous epithelium exhibits the cellular features of carcinoma without invasion into the basement membrane.[52]

Since it has a high risk of progression to invasive carcinoma, an intervention, preferably endoscopic resection, is recommended.[14,46,52] Other approaches for the removal of visible lesions are microlaryngoscopic, such as CO2 lasers or vocal cord stripping.[74]

Another treatment option is radiotherapy.[14,46] This modality is useful in infrequent occasions of high-grade dysplastic lesions with poor access.[75] According to Kerr et al., the voice quality of patients who underwent endoscopic resection may be poorer than that of those who received radiotherapy.[76] But the 5-year disease-specific, disease-free, and total laryngectomy-free survival were comparable between the treatment modalities.[77]

Remarks
There were no comments on the recommendation.

5.2.1. We recommend transoral laser microsurgery or open partial laryngectomy for early-stage laryngeal cancer (T1-T2 N0).
Moderate certainty of evidence, Strong recommendation

5.2.2.We recommend external beam radiotherapy (EBRT) in the treatment of early-stage laryngeal cancer (T1-T2 N0).
High certainty of evidence, Strong recommendation

Key Findings
Transoral microsurgery achieves acceptable oncologic and functional outcomes in patients with T1/T2 glottic cancers. This may also be a treatment option for T1/T2 glottic cancer with anterior commissure involvement, as long as adequate resection margins are obtainable. Another surgical option is open partial laryngectomy in cases of T1/T2 glottic cancer with limited extension into adjacent subsites or the anterior commissure.

Transoral microsurgery can be easily repeated and affords a more available retreatment option for local recurrence compared to initial radiotherapy or open partial laryngeal surgery.[78] Transoral laser microsurgery (TLM) is currently considered the standard of care for early glottic cancer; however, transoral robotic surgery (TORS) is also being used to treat early-stage glottic

carcinomas, despite the limited data. These minimally invasive surgical treatments are usually done as a single-modality treatment for early-stage laryngeal cancers.[79,80]

According to a review article by Chow[81], although surgery and EBRT have not been compared in randomized trials, these treatments provide similar locoregional control and survival outcomes. The SEOM clinical guideline stated that a multidisciplinary team should select the treatment based on the characteristics and wishes of the patient and the potential functional outcomes of the treatment to avoid morbidity.

An updated meta-analysis on the role of EBRT fractionation on head and neck cancers showed that for stage I and II disease, EBRT can be given alone without any induction or concurrent chemotherapy. For Stage I, a standard fractionation RT with 2 Gy/fraction and a total primary tumor dose ranging from 66 to 70 Gy in 6-7 weeks is recommended, depending on the tumor volume and location.

For Stage II, via hyperfractionated or superfractionated RT with a slightly higher total tumor dose given in twice-a-day fractions in 6-7 weeks or via moderately accelerated RT with a similar total RT dose (66-70 Gy) in 5.5-6 weeks.[82]

Remarks

There were no comments on the recommendation for surgical procedures for early-stage laryngeal cancer. Both statements garnered strong recommendations due to moderate-to-high certainty of evidence. The second recommendation does not cover advanced techniques such as intensity-modulated radiation therapy (IMRT), helical tomotherapy, volumetric-modulated arc therapy (VMAT), and image-guided RT (IGRT) due to insufficient evidence on benefits in terms of survival.

6. What are the treatment options for locally advanced laryngeal cancer?

6.1. We recommend concurrent chemoradiation or RT alone for the following:
   a. Patients with no to minimal aspiration and without cartilage invasion
   b. Patient with unresectable laryngeal cancer and who are medically unfit or refuses surgery
   High certainty of evidence, Strong recommendation

Key Findings

Among patients with advanced-stage tumors where laryngeal preservation is suitable and desired, concurrent chemotherapy with radiation therapy is recommended.[14,46,83] In this setting, there is no further surgical plan after the concurrent chemotherapy and radiation therapy, and surgery will be reserved for salvage. The intergroup trial RTOG 91-11[84,85] is the basis for this recommendation. Intergroup trial RTOG 91-11 enrolled stage III and IV (non-metastatic) laryngeal cancer patients and compared three treatment regimens: 1) induction chemotherapy (cisplatin + 5-fluorouracil) followed by radiation therapy (70 Gy/ 7 weeks or 2 Gy/fraction), 2) concurrent radiation therapy (70 Gy/ 7 weeks or 2 Gy/fraction) and high dose chemotherapy (cisplatin 100

mg/m2 days 1, 22, 43), and 3) single agent radiation therapy (70 Gy/ 7 weeks or 2 Gy/fraction). It found that concurrent chemotherapy and RT have a statistically significant higher 2-year laryngeal preservation (local control) rate of 88% compared to the two other regimens (74% for induction chemotherapy followed by RT and 69% for single agent RT). This trial excluded T2 and high-volume T4 (tumor extending more than 1 cm into the base of the tongue or tumor penetrating through cartilage) primary lesions. Long-term follow-up of the Intergroup trial RTOG 91-11 showed that laryngeal preservation was better in concurrent chemotherapy and RT than in the two other treatment regimens.[84] Long-term follow-up showed no overall survival difference in all treatment regimens.

Remarks

The panel defined the qualification of good laryngeal function as having no to minimal aspiration and without cartilage invasion. The panel also deemed it critical to perform a modified barium swallow to check the laryngeal function.

6.2. We recommend surgery and adjuvant radiation +/- chemotherapy in patients with aspiration and with cartilage invasion.
High certainty of evidence, Strong recommendation

Key Findings

Patients T4b, N0-3, or unresectable nodal disease, or who are unfit for surgery are recommended to receive the following based on their performance status. A performance status of 0-1 has the option to receive either concurrent chemotherapy and radiation therapy or induction chemotherapy followed by either radiation therapy or concurrent chemotherapy and radiation therapy. [14] Performance status 2 has the option to receive either RT alone or concurrent chemotherapy and radiation therapy. [14] Those with poor performance status have the following options: palliative radiation therapy, single-agent systemic therapy, or best supportive care. The option of enrolling in a clinical trial is recommended regardless of performance status.[14]

Remarks

There were no other comments aside from specifying poor laryngeal function (i.e., with aspiration and cartilage invasion) in the recommendation statement.

6.3. We recommend induction chemotherapy with response assessment in selected locally advanced and potentially resectable laryngeal cancer after a multidisciplinary team consensus.
Moderate certainty of evidence, Strong recommendation

Key Findings

Induction chemotherapy may be given at various stages aside from T1-2, N0 glottic, and supraglottic cancer.[14] Induction chemotherapy used may be a combination of cisplatin or carboplatin, 5-fluorouracil, and/or docetaxel.[14] Response assessment should be done after induction chemotherapy.[14] If the primary site achieves a complete response, it is recommended to proceed with definitive radiation therapy.[14,84] If the primary site achieves a partial response, it

is preferred to proceed with radiation therapy.[14,84] Another option after a partial response to induction chemotherapy is concurrent chemotherapy and radiation therapy.[14,86-88] After receiving recommended treatments for a complete or partial response to induction chemotherapy, patients will be reassessed in 4-8 weeks.[14] If there is residual primary, persistent disease or progression, patients will be evaluated with imaging (CT, MRI, or FDG PET/CT) for the extent of disease and metastasis. After a multidisciplinary meeting, subsequent treatment recommendations will be based on disease status, resectability, and performance status.

If the response achieved after induction chemotherapy is less than partial, surgery (laryngectomy) is recommended. In cases of partial response to induction chemotherapy who had laryngectomy, surgical histopathology will be checked for adverse features (extranodal extension, close or positive margins, pT4, pN2, or pN3, perineural, vascular, or lymphatic invasion). Such cases will be treated as in the adjuvant or post-operative setting, wherein recommended treatment will be based on adverse features present. In cases of extranodal extension, combined chemotherapy and radiation therapy are the preferred adjuvant therapies. Among those with close or positive margins, surgical re-resection is preferred. However, in cases where surgical treatment is not an option, adjuvant radiation therapy should be provided for those with close or positive margins. For those having other adverse features (pT4, pN2, or pN3, perineural, vascular, or lymphatic invasion), radiation therapy is recommended.[14]

Remarks

The panel examined the long-term effects of induction chemotherapy and concluded that, in terms of survival, this treatment is not superior to concurrent chemoradiation, the standard of care.

7. What is the appropriate surgical management for advanced laryngeal cancer?

7.1. What is the extent of surgery for the primary?

7.1. We recommend total laryngectomy as the primary surgical modality for T3/T4 glottic cancers.
Low certainty of evidence, strong recommendation

Key Findings

Total laryngectomy is recommended for most advanced-stage and resectable laryngeal cancers. It is also preferred in patients with cartilage erosion, tongue base involvement, and patients who are poor candidates for laryngeal preservation, which includes the following:

1. Poor functional status
2. Severe airway compromise requiring tracheostomy and/or enteric feeding
3. Arytenoid fixation
4. Invasion of the posterior commissure
5. Subglottic extension of >5 mm posteriorly and 5-10 mm anteriorly or to the upper border of the cricoid cartilage

6. Cricoid cartilage invasion and major thyroid cartilage invasion (T4)
7. Massive pre-epiglottic space involvement
8. Positive margins in the frozen section
9. Extralaryngeal spread.

Advanced-stage laryngeal cancer resulting in larger defects, such as those with pharyngeal extension, may require primary reconstruction.

Remarks
There was no discussion of total laryngectomy as the primary surgical modality for T3/T4 glottic cancers.

7.2. Which reconstructive procedures can be performed following total laryngopharyngectomy +/- esophagectomy among patients with advanced-stage laryngeal cancer?

7.2.1. We recommend primary soft tissue flap reconstruction with or without gastric pull-up following tumor resection not amenable for primary closure.
Moderate certainty of evidence, Strong recommendation

7.2.2. We recommend tracheo-esophageal fistula with or without voice prosthesis (as an option for voice rehabilitation) be performed at the time of total laryngectomy (primary) or later stage (secondary).
Low certainty of evidence, Strong recommendation

Key Findings
Flap reconstruction for pharyngectomy defects following laryngectomy is not routinely necessary.[8,52] The best functional outcome can be achieved if the neopharynx can be created through primary closure. In extended resections (e.g., laryngopharyngectomy) that result in defects beyond primary repair, using soft tissue flaps such as the radial forearm and anterolateral thigh free flaps is necessary. Free flaps are primarily considered based on better quality of life (voice rehabilitation and swallowing). A well-vascularized reconstruction is essential to establishing a radiation-resistant reconstruction.[8,52]

A voice prosthesis may be inserted at the time of total laryngectomy (primary) or later. A primary prosthesis provides almost immediate and satisfactory voice rehabilitation.[89,90]

Other options for voice rehabilitation, including esophageal speech, electrolarynx, and tracheoesophageal speech with a voice prosthesis, should be offered to patients who have undergone total laryngectomy based on the adopted guideline.[52]

Remarks
The panel suggested specifying the types of flaps for reconstruction that will serve as options for

those institutions with the capacity and resources. Variations in practice evident in other clinical practice guidelines were also considered by the panel in formulating the recommendation statement on primary soft tissue flap reconstruction. In addition, it was emphasized that capacity development for this procedure must be bolstered in order to increase the number of skilled clinicians.

They recommended a tracheo-esophageal fistula with the option of a voice prosthesis for those patients who might prefer it because of the reported increase in quality of life associated with their ability to return to work. However, the panel also acknowledged the scarcity of resources in a variety of contexts across the nation (i.e., distributors of voice prostheses, clinical expertise in restoration procedures, and additional costs), so this was included only as an option.

7.3. What is the extent of the neck dissection?

7.3.1. We do not recommend elective neck dissection in T1N0 and T2N0 glottic cancers.
Moderate certainty of evidence, Strong recommendation

7.3.2. We recommend the following neck dissection to all surgically managed laryngeal cancer:
1. If clinically N0, do selective neck dissection (levels II-IV) for the following:
    a. T1-T2, supraglottic and/or subglottic cancer
    b. T1-T2, laryngeal cancer primarily managed with partial laryngectomy
    c. T3-T4, glottic cancer
2. If clinically N+, do modified radical neck dissection
    a. Any T, N1-N2b glottic cancer
    b. T3-T4 supraglottic and/or subglottic cancer
    c. extra-laryngeal extension and/or extracapsular nodal extension (ENE)

Moderate certainty of evidence, Strong recommendation

7.3.3. We recommend bilateral neck dissection in glottic cancers that cross the midline, all supraglottic, subglottic, and transglottic cancer, and N2c-N3 laryngeal cancer.
Moderate certainty of evidence, Strong recommendation

Key Findings
The decision to perform elective neck dissection should depend on the risk of occult metastasis in the appropriate lymph node basin and it is justifiable when the risk exceeds 15%. Neck dissection should be performed as indicated when the primary site is treated surgically.

The rate of occult nodal metastasis was 14% (*n* = 11): levels IIa and/or III were affected in 9 cases (11.5%) compared with single cases of IIb and IV involvement (1.3% each).[91] The rate of occult nodal metastasis was significantly lower among patients operated on for recurrent disease after radiotherapy than in patients who never had any radiotherapy of the cervical lymph nodes (0% vs. 16.7%, *P* = 0.03).[91]

Elective neck dissection is not recommended for early glottic cancer (T1N0-T2N0) because of the

low likelihood of lymph node metastasis (0-8.6%) or rare nodal recurrence during follow-up. However, for advanced glottic cancer there is 14.3-23.4% neck recurrence rate; hence, neck dissection is acceptable. Since the lymphatic spread of glottic cancer has a predictable pattern along the jugular chain, ipsilateral selective neck dissection of levels II, III, and IV is sufficient.[14,52]

Neck management of supraglottic cancer requires a different approach because the lymphatic system is involved at a much earlier disease phase and neck nodal metastases are much more common. Occult metastases were observed in 0% of pT1, 26% of pT2, 46% of pT3, and 26% of pT4 cases.[52,92] In a prospective case-control study, Djordjevic et al. found a significant difference in the occurrence of regional metastases after surgery, with a rate of 4.15% in the group that underwent elective neck dissection compared to 11.8% in the group that did not receive immediate treatment and was observed over time.[52,93]

In patients with T1–2 node-negative cancer of the supraglottic larynx, lymph node dissection is associated with greater OS.[14,94]

There are few studies on the recommended levels of neck dissection for patients with glottic cancer with a clinically positive node, as the procedure is typically tailored to the extent of the disease. Advanced glottic cancers often involve ipsilateral levels II, III, and IV in the neck. If levels I or V are affected, it usually means that levels II, III, or IV are also affected. Hence, neck dissection at levels I or V may be necessary, depending on the patient's individual nodal status.[52,95]

Appropriate cervical lymph node treatment is an important aspect of therapy for patients with supraglottic cancer, as the nodal status has prognostic significance. The presence of clinically palpable cervical lymph node metastasis is associated with an approximately 50% reduction in overall survival. Candela et al. retrospectively reviewed 247 consecutive patients with supraglottic cancer who underwent comprehensive neck dissection. For patients in whom clinical nodal disease is evident on preoperative imaging, via nodal fine needle aspiration cytology, or at the time of surgery, surgical resection via comprehensive node dissection might reduce the risk of recurrence and, possibly, mortality.[52,96]

Remarks

Other than the clarification on the certainty of the evidence for the statement against elective neck dissection in T1N0 and T2N0 glottic tumors, the panel had no further comments.

Clarifying whether an ipsilateral or bilateral neck dissection, lymph node assessment, and appropriate dissection procedures should be performed on a particular laryngeal site arose during the discussion of neck dissection in all other laryngeal cancer cases with surgical management.

8. What adjuvant treatments can be offered after surgical management?

8. We recommend the use of adjuvant or postoperative therapy depending on the adverse feature seen on a surgical histopathological report.
   - In cases with extranodal extension, combined chemotherapy and radiation therapy is the preferred adjuvant therapy.
   - Among those with close or positive margins, surgical re-resection is preferred. However, when surgical treatment is not an option, adjuvant chemoradiation should be provided for those with close or positive margins.
   - Radiation therapy is recommended for those with other adverse features, specifically pT4, pN2, or pN3, perineural, vascular, or lymphatic invasion.

   High certainty of evidence, Strong recommendation

Key Findings

Adjuvant or post-operative treatment (surgery, radiation therapy, or chemotherapy) is necessary for patients with any adverse feature seen on the surgical histopathologic report.[14] These adverse features include extranodal extension and close or positive margins.

A clear margin is defined as having no tumor within the distance from the invasive tumor to the resected margin. By measurement, this is the absence of a tumor in the resection margin of 5 mm or more. For a close margin, the distance of the margin from the invasive tumor is 2-5 mm. However, for glottic cancers, a 1- to 2-mm margin is already adequate. For a positive margin, there is carcinoma in situ or invasive carcinoma in the margin of resection.

Other adverse features as defined by the American Joint Committee on Cancer (AJCC) 8th edition staging for laryngeal cancer are defined as follows:

- T4 primary tumor or moderately advanced or very advanced local disease
- Pathologic N2 or metastasis in a single ipsilateral lymph node with a size of 3 cm or less without extranodal extension
- Pathologic N3 nodal disease or metastasis in a lymph node, larger than 6 cm in greatest dimension and no extranodal extension; or metastasis in any lymph node with clinically overt extranodal extension

According to the RTOG 91-11study, among resected patients with extranodal extension, combined chemotherapy and radiation therapy is the preferred adjuvant treatment.[37,84,97-100] A tumor-free margin is essential for decreasing the risk of local recurrence. With close or positive margins, the risk of local recurrence may necessitate post-operative treatment.[97] Surgery or re-resection may be done to achieve a clear margin from the tumor in cases of close or positive margins. Another option is to provide adjuvant therapy in the form of chemotherapy or radiation therapy.[14] For cases with other adverse features (pT4, pN2, or pN3, perineural, vascular, or lymphatic invasion), radiation therapy is the preferred treatment modality. [37,84,97-100]

Remarks
After clarification of the included evidence, the panel unanimously approved this recommendation statement. No other issues arose.

Post-operative chemoradiotherapy was highlighted as the preferred treatment for those with extranodal extension, close margins, or positive margins, supported by two randomized controlled trials, due to its benefit of decreasing the risk of locoregional recurrence. The panel, which specializes in radiation oncology, questioned the use of Forastiere's trial due to the absence of a surgical arm.

3.3.3. Follow-up/Surveillance

9. Among patients with laryngeal cancer who received primary or definitive treatment, what is the interval for history and physical examination during surveillance or follow-up?

9. We recommend the following consultation intervals for patients with laryngeal cancer who have received primary or definitive treatment.
    - First year of monitoring: every 1-3 months
    - Second year of monitoring: every 2-6 months
    - Third to fourth year of monitoring: every 4-8 months
    - Beyond 5 years of monitoring: annually

    Moderate certainty of evidence, Strong recommendation

Key Findings
History and physical examination (H&P), specifically including mirror and fiberoptic examination, should be done at the following intervals:

- First year of monitoring: every 1-3 months
- 2nd year of monitoring: every 2-6 months
- Years 3-5 of monitoring: every 4-8 months
- Beyond 5 years of monitoring: annually. [14]

Most laryngeal cancer recurrences occur within the first two years after treatment. This is seen in the more frequent monitoring within the first year of adjuvant treatment.[14]

Remarks
The panel strongly recommends follow-up consultations and the aforementioned intervals for patients with laryngeal cancer who have received primary or definitive treatment. There were no issues with this statement.

10. Among patients with laryngeal cancer, what are the evaluation methods during surveillance?

10.1. What is the role of endoscopy during surveillance?

10.1 We recommend rigid or flexible laryngoscopic examination to check for local recurrence.
Low certainty of evidence, Strong recommendation

Key Findings
Laryngoscopic examinations should be carried out alongside history and physical examinations during the aforementioned follow-up interval. Laryngoscopy or stroboscopy with the use of either a rigid telescope or a flexible video or fiberscope provides better accuracy (100% for both methods) than history and physical examination (33%).[51]

Narrow-band imaging reportedly has a true-positive laryngeal cancer lesion detection rate that is 18% higher than that of conventional white-light endoscopy. It features both high accuracy as well as the ability to differentially diagnose abnormal regions from postradiotherapy or chemoradiotherapy inflammatory and/or cicatricial changes.[101-103]

Patients who have undergone extended resection via transoral laser surgery require regular laryngeal examinations every 4 to 8 weeks during the first year after surgery, as the risk of locoregional recurrence remains high.[104]

Second look microlaryngoscopy is still considered somewhat controversial, but may be adapted for uncertain (close or altered for iatrogenic artifacts) surgical margins, granulomas, web formation, other post-excision abnormal tissue growth at the level of the primary resection site (despite appropriate medical and voice therapy), or the involvement of certain laryngeal subsites (anterior commissure, ventricle, subglottis) [105-107].

Remarks
Other than the clarification on the timing of the laryngoscopic examination to check for local recurrence, there were no other comments during the panel discussion. The members voted strongly due to the observed standard of practice.

10.2. What is the role of imaging studies during surveillance?

10.2.1.a. We recommend FDG PET/CT scan 3 months after completion of definitive therapy to assess treatment response.
Moderate certainty of evidence, Strong recommendation

10.2.1.b. We recommend CT scan or MRI within 6 months after treatment to serve as baseline imaging.
Moderate certainty of evidence, Strong recommendation

Key Findings
It was stated in the NCCN that the optimal time frame for performing FDG PET/CT after definitive radiation or systemic therapy/RT to evaluate the efficacy of treatment and detect any residual tumor is between 3 and 6 months. [45,71,108,109]

Clinical relevance demands that earlier detection of recurrence with surveillance imaging demonstrates improved salvage outcomes. Kao et al. report that 2-year overall survival rates were significantly different between patients who had a negative versus positive PET/CT result within 6 months of completing radiation therapy (100% vs. 32%, $P < 0.001$).[108,110]

Likewise, CT and/or MRI should be obtained within 3 to 4 months after surgical treatment for patients with locoregionally advanced disease as a baseline assessment for future comparisons. For those patients with an incomplete response, a CT or MRI scan may be done as early as 4–8 weeks after treatment or even immediately, depending on the clinical situation. CT scans or MRIs can be done after 2–3 cycles of induction chemotherapy prior to the definitive treatment. [14,111,112]

Remarks
It was clarified that both tests must be done, as seen in other guidelines. The panel voted strongly to recommend both tests, which serve two different purposes. They recognized the importance of imaging studies in individual cases, especially if symptoms occur or abnormalities are found during the clinical examination during surveillance.

The discussion also brought up concerns regarding the accessibility of resources in low-resource settings and the financial burden that patients may incur if both tests are done.

10.2.2.a.	We recommend FDG PET/CT scan 3 months after completion of definitive therapy to accurately detect regional or distant metastasis. *Moderate certainty of evidence, Strong recommendation*
10.2.2.b.	We recommend ultrasound among patients suspected of having neck lymph node recurrence. *Moderate certainty of evidence, Strong recommendation*

Key Findings
Numerous studies have demonstrated that PET-CT shows an accuracy rate of nearly 100% in detecting distant metastasis among individuals with cancer. [113-115]

It was found that a PET after 1 year will reveal a recurrence or second primary cancer in about 10% of treated patients, and an FDG PET/CT done on asymptomatic patients revealed lesions at distant sites. [108,116]

According to the European guideline, neck ultrasound is also deemed valuable for nodal surveillance due to its availability, safety, efficiency, affordability, and relatively high accuracy in

detecting suspicious nodal disease.[117] Research shows that ultrasound has 97.5% accuracy in detecting enlarged lymph nodes.[118] Other studies also revealed that ultrasound and ultrasound-guided biopsy provide critical information for detecting neck node recurrences.[119-121] However, ultrasound is very user-dependent. Ultrasound-guided FNAC requires both expertise and experience and has very high specificity rates (98%) in diagnosis. It should be noted that there are no absolute ultrasound characteristics for differentiating benign from malignant disease. [71]

Remarks

The panel recommended the utilization of FDG PET CT owing to its reported accuracy. Ultrasound was suggested as an alternative in resource-limited settings where PET CT is not available.

10.3. What is the role of thyroid-stimulating hormone (TSH) monitoring during surveillance among laryngeal cancer patients after definitive treatment?

10.3 We recommend that TSH be evaluated among patients who had a total thyroidectomy and/or after neck irradiation to screen for hypothyroidism. TSH should be monitored every 6-12 months.
Moderate certainty of evidence, Strong recommendation

Key Findings

The levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in the blood are measured to evaluate thyroid function. Patients who have undergone neck radiation or a total thyroidectomy should undergo serum thyroid-stimulating hormone screening to monitor the presence of hypothyroidism. [14,122-124]

Neck radiation can disrupt thyroid hormone production, leading to biochemical hypothyroidism in at least 50% of patients. Radiotherapy-induced fibrosis can decrease thyroid function by reducing blood flow to the thyroid and causing fibrosis of the entire gland.[52,125] Moreover, a definitive initial surgery that removes part of the thyroid gland can also increase the risk of hypothyroidism. [52 126] During neck dissection, the vascular structures near the thyroid gland might be iatrogenically damaged or intentionally sacrificed, thus affecting the blood supply and eventual function of the gland. A review of 147 total laryngectomy patients found that 19.9% developed hypothyroidism by year 3 of follow-up. By years 6 and 10, 38.6% and 93.3% of the patients had developed hypothyroidism, respectively.[52,127] These findings emphasize the need for regular thyroid evaluations for at least 10 years after undergoing treatment for laryngeal cancer.[52]

Remarks

This statement, which received unanimous approval, took a partial thyroidectomy with neck irradiation to screen for hypothyroidism into consideration.

3.4. Nasopharyngeal Cancer

3.4.1. Screening, Diagnosis, and Pretreatment Evaluation

1. Is screening for NPC recommended among asymptomatic individuals in the Philippines?

1. We suggest against screening for NPC among asymptomatic individuals in the Philippines.
   Low certainty of evidence, Weak recommendation

Key Findings

Limited studies and reports have delved into the screening procedures for asymptomatic nasopharyngeal carcinoma. To date, only two articles and a select guideline have explored the screening of asymptomatic NPC, which has primarily focused on high-risk populations and endemic areas.

In the included RCT[128] and two reviews[129,130], EBV testing, either via serology (IgA) or DNA, was associated with the screening of NPC. In the RCT, which involved a total of 16 towns from Southern China and a total of 70,296 participants, the use of EBV IgA as a screening method yielded high early diagnostic rates of approximately 45% without changes in NPC-specific mortality. Despite the results, the study included a high-risk population from areas where NPC was endemic. This notion is also supported by the two reviews, which emphasize that screening for early NPC is only applicable and warranted in endemic regions with a high incidence of NPC and among high-risk populations. Similarly, in 2020, the ESMO-EURACAN Clinical Practice Guidelines[131] recommended that screening for NPC is only necessary in endemic areas and among those considered high-risk using plasma EBV DNA.

The certainty of evidence was low due to indirectness, risk of bias, and imprecision. No other efficacy and safety outcomes with regard to screening in the studies were reported.

Remarks

The prevalence of nasopharyngeal cancer based on the data of Western countries and some Asian countries is different, with the latter exhibiting a comparatively increased burden. However, the panel weighed the certainty of evidence and endemicity in the various regions of the country heavily, with a particular focus on Luzon. Data on prevalence in Visayas and Mindanao were also scarce. The panel also suggested against it after considering the screening tests (i.e., plasma Epstein-Barr virus DNA) used in the evidence.

2. What clinical findings would make you suspect NPC in a patient?

2. We recommend to look for the following signs and symptoms of NPC:
   a. Cervical lymphadenopathy
   b. Nasal obstruction
   c. Epistaxis
   d. Conductive hearing loss or ear fullness
   e. Ptosis
   f. Diplopia

   Moderate certainty of evidence, Strong recommendation

Key Findings

Recognition of the signs and symptoms associated with nasopharyngeal cancer is crucial in facilitating early diagnosis and averting poor prognosis in patients. Late NPC diagnosis might result from ignoring or misdiagnosing unspecific symptoms that, in the early stages, may appear to be an upper respiratory tract infection.[132]

Two narrative reviews[133,134], two narrative reports [132,135], two retrospective studies [136,137] and two case reports[138,139] showed clinical manifestations of patients with NPC. The latter two study categories included a total of 1,090 patients diagnosed with nasopharyngeal cancer. The case reviews were performed for an average span of 8 years. Three of the four case reviews recruited nasopharyngeal cancer patients. The fourth case review included all patients with nasopharyngeal masses with a sub analysis for comparing symptoms between benign and malignant conditions (including nasopharyngeal cancer and lymphoma).

Outcomes of measures for these eight descriptive studies included six specific clinical findings attributed to nasopharyngeal cancer namely epistaxis, nasal obstruction, ear problems, neck masses, headache and cranial nerve palsies. Some mentioned studies in the literature reviews, and two of the four case reviews explained that nasal and otic symptoms are earlier findings whereas neck mass is a late finding.

Cervical lymphadenopathy

In a retrospective study in Nigeria (n = 73), neck mass or swelling was listed as the second most common presenting symptom (64.4%) among patients with NPC, of whom the majority presented stage 3 or 4 disease at first presentation.[136]. In another 8-year retrospective study (n = 1,647), neck mass was found in 205 patients with nasopharyngeal masses who underwent biopsies (12.44%).[137] Of these, 29 (37.5%) had a unilateral and 176 patients (85.9%) had a bilateral, cervical lymphadenopathy. No palpable cervical lymph nodes were found in 87.56% (n = 1442) of the study population.[137] The incidence of neck mass in these patients with malignant disease was significantly higher than in those with benign disease ($P < 0.0001$). [137]

Nasal obstruction or congestion

Nasal obstruction or congestion was listed as in the most common presenting symptom in the two retrospective studies. In Nigeria, 63% of patients with NPC had nasal congestion.[136] Nasal

obstruction was was the most common complaint among patients with nasopharyngeal pathologies and was present in 49.3% of patients with NPC. The difference in the incidence of nasal congestion of patients with and without NPC was statistically significant.[137]

Epistaxis

Epistaxis was listed as the second most prevalent symptom in early nasopharyngeal cancer in an Indonesian study.[136] The Nigerian study listed epistaxis as the most common presenting symptom (67.1%). However, there is no significant difference between benign and malignant conditions ($p>0.05$). [137]

Ear problems (fullness, tinnitus, discharge)

Unilateral ear problem was noted to be the earliest sign of nasopharyngeal cancer presenting months prior to diagnosis in one cohort study.[136] While not among the top three, noted ear problems were noted in the Nigerian study including hearing impairment or loss (23.3%), ear fullness (17.8%), ear discharge (16.4%) and tinnitus (15.1%).[137] Otitis media was found in 15.36% of the study population (unilateral 9.48% and bilateral 90.52%) with significant difference in the incidence of benign and malignant conditions ($P = 0.0645$). However, there was no significant difference for tinnitus between benign and malignant conditions ($P > 0.05$).[137]

Ptosis and Diplopia

While not among the top presenting symptoms, the Nigerian study noted that 12.3% of its sample presented with cranial nerve palsies.[136] Visual problems like diplopia and squint ranked fifth (10.7%) among the top five presenting symptoms in a retrospective study of 5020 patients in Hong Kong. A Turkish study observed neuro-ophthalmic symptoms in 25% of its sample.[134] Though commonly in the lower relative frequency, two studies from Nigeria and Malaysia showed a cranial nerve palsy frequency of 60% and 33.9%, respectively.[134]

Most of the evaluated descriptive studies only noted the frequency of symptoms present in their sample, and did not include measures of statistical significance. Only one retrospective study compared the statistical difference of presenting symptoms between benign and malignant conditions presenting with a nasopharyngeal mass.[137] No adverse outcomes were reported as only the clinical profiling of patients were included in all evaluated studies.

Certainty of evidence

The observational studies were marked as moderate as they are considered formal descriptive studies appropriate for clinical profiling of patients and their presenting symptoms

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
United Kingdom National	Nasopharyngeal carcinoma is more common in men than in women (3:1), with a median age at	Noted as part of clinical

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Multidisciplinary Guidelines Released on 2016	presentation of 50 years. The most common symptoms are: ● Nasal obstruction ● Epistaxis ● Conductive hearing loss secondary to otitis media with effusion (OME) due to eustachian tube orifice obstruction ● Cranial nerve neuropathies secondary to skull base invasion (cranial nerves III, IV, V and VI) ● Neck lumps and swellings due to cervical lymph node metastasis, which is usually in the upper levels of the neck and often bilateral due to the midline lymphatic drainage of the tumour.	presentation but no stated recommendation
ESMO-EURACAN Clinical Practice Guidelines Released on December 25, 2020	No enumeration of clinical findings but listed medical history and physical examination as the first in diagnostic workup of nasopharyngeal cancer.	Noted medical history and physical examination in diagnostic work up but no stated recommendation

Remarks

Apart from clarifying the visual problem specific to nasopharyngeal carcinoma, there was no further discussion.

3. Among individuals suspected of having NPC after a complete history and physical examination, what initial diagnostic tests are necessary?

3. We recommend the following baseline examinations:
   - Nasopharyngoscopy (flexible or rigid) (High CoE)
   - Tissue biopsy of nasopharyngeal mass or cervical lymphadenopathy (High CoE)
   - EBER staining if clinically indicated (High CoE)
   - Panendoscopy or examination under anesthesia if clinically indicated (Low CoE)

   Low to High certainty of evidence, Strong recommendation

Key Findings

Nasopharyngoscopy and Tissue Biopsy

Three cross-sectional studies [140-142], one meta-analysis[143], and one prospective cohort study[144] evaluated the diagnostic accuracy of nasopharyngoscopy in the visualization and biopsy of nasopharyngeal cancer using pathologic assessment as the gold standard. One observational studies[140] compared NBI and white-light (WL) mode endoscopy. They concluded that NBI mode

(Sn 100%, Sp 98.96%, PPV 0.96, and NPV 1) is superior to WL mode (Sn 82.6%, Sp 0%, PPV 0.17, and NPV 0) in detecting early stage nasopharyngeal malignancies because it can differentiate early vascular changes. In another cross-sectional study, 78% (43/55) patients were diagnosed with NPC using NBI endoscopy (40/43) and WL endoscopy (18/43).[141]
In these studies, nasopharyngoscopy was also used to obtain tissue samples for pathologic assessment.

Another observational study compared endoscopy and ultrasonography for detecting early NPCA.[142] Both US and endoscopy achieved a good diagnostic accuracy for NPC with AUC values of 0.929 and 0.938, respectively. Moreover, there was no statistically significant difference in the diagnostic accuracy for NPC between US and endoscopy (Z=0.36, P=0.72).[142] In a meta-analysis of observational studies, the diagnostic odds ratio of narrowband imaging was 77.5 (95% CI 37.4 to 160.7). The NBI shows a relatively high diagnostic accuracy. Its sensitivity, specificity, and negative predictive value were 0.871 (95% CI 0.808 to 0.915), 0.905 (95% CI 0.816 to 0.953), and 0.955 (95% CI 0.906 to 0.979), respectively.

In a prospective cohort study, nasopharyngeal MR imaging had a lower specificity for the detection of NPC than endoscopy or endoscopic biopsy (92% versus 94% and 100%, respectively); the difference was statistically significant between MR imaging and endoscopic biopsy (P=0.002), but not between MR imaging and endoscopy (P=0.617).[144]

EBV testing (EBV-DNA and EBER)
Evidence involving EBV testing consisted of one case-control[145], one cohort[146], one systematic review[147], and three meta-analyses[148-151]. One case-control study (n = 357)[145] compared the detection rate of EBV-DNA, anti EBV antibodies and EBV-mRNA in NPC and a control group. Plasma EBV-DNA loads were significantly higher in NPC patients compared to controls. Plasma EBV-DNA also increases with more advanced stages. There is moderately good to excellent test-retest reliability (ICC 0.837-0.998) achieved by tested plasma anti-EBV antibodies. Among the plasma miRNAs, plasma EBV-miR-BART7-3p levels were higher in NPC compared to population controls.

The cohort study evaluated the use of plasma EBV DNA and determined a PPV of 11% in an asymptomatic population (n = 300). One meta-analysis compared the sensitivity, specificity, positive likelihood and negative likelihood of EBV DNA and anti-EBV antibodies.[149] The highest sensitivity was EBNA1-IgA (0.86), and the highest specificity were EBV-DNA (0.96) and EA-IgA (0.96).[149] Another meta-analysis compared detection rate of EBV DNA in plasma and serum and found that the accuracy of detection by plasma for NPC (0.86) was higher than in serum (0.81), with largest areas under the SROC of 0.97 and 0.91, respectively.

One meta-analysis also compared the sensitivity and specificity of HPV and EBV DNA in NPC and controls. Among the studies reviewed for EBV testing, EBV DNA testing in plasma samples of NPC patients was shown to have the best sensitivity and specificity compared to anti EBV antibodies and EBV MRNA. Though detectable, HPV DNA had a lower detection rate than EBV-DNA.

Safety outcomes

Only one of the five reviewed studies for nasopharyngoscopy (with endoscopically guided biopsy) mentioned a bleeding complication for tumors located in the pharyngeal recess. However, no frequency data or computed likelihood was collected, computed or reviewed in the study. None of the studies on EBV and HPV testing explored safety outcomes.

Certainty of evidence

Reviewed studies on nasopharyngoscopy have a high certainty of evidence since the study designs included were meta-analysis, cross sectional, and prospective cohort. Due to the study design of the latter two, no randomization was conducted.

Recommendations of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
ESMO-EURACAN Clinical Practice Guidelines (accessed on April 30, 2023)	Definitive diagnosis is made by endoscopic-guided biopsy of the primary nasopharyngeal tumour [II, A]; diagnostic neck biopsy and/or neck nodal dissection should be avoided. Determination of EBV on the histological specimen by ISH is indicated [III, B]. In regions where NPC is endemic, the use of plasma EBV DNA, coupled with endoscopic examination and MRI, can be recommended for detecting early, asymptomatic NPC [III, A].	Strong Recommendation
United Kingdom National Multidisciplinary Guidelines (accessed on April 30, 2023)	Patients with NPC should be assessed with rigid and fibreoptic nasendoscopy (R) Nasopharyngeal biopsies should preferably be carried out endoscopically (R)	Strong Recommendation
NCCN Guidelines Version 1.2023	Recommended workup includes: Nasopharyngeal fiberoptic examination Biopsy of primary site or FNA of the neck Consider Epstein-Barr virus (EBV)/DNA testing	Strong Recommendation

Remarks

The types of tissue biopsy (e.g., incision, core-needle, and fine-needle aspiration) arose in the deliberation. The recommendation statement was left unspecified after consideration of practice variations in performing tissue biopsy.

The panelists particularly believed that the certainty of evidence of EBER staining in the baseline assessment was high. This is one of the ancillary tests requested when pathologists are dealing with carcinomas of unknown origin. Given the appropriate morphologic context, the reactivity to the test is used as a basis for classifying the carcinoma as nasopharyngeal in origin. Due to high CoE in most of these baseline examinations, this statement garnered a strong recommendation.

4. Among individuals diagnosed with NPC, what further tests are necessary for staging?

4. We recommend the following examinations:
- MRI with contrast of the NP and neck is preferred for locoregional staging.
- CT with contrast of the nasopharynx and neck is complementary.
- FDG PET-CT is the preferred method to evaluate distant metastases.
- CT of the chest (with contrast as clinically indicated) and upper abdomen, and bone scan are alternatives.

High certainty of evidence, Strong recommendation

Key Findings

Once diagnosed, NPC needs to be staged like any other malignant tumor using the AJCC 8th edition staging classification using the TNM (tumor, node, metastasis) system. Numerous diagnostic modalities have been proposed to accurately diagnose and stage nasopharyngeal tumors. Most notable among them are MRI, CT, and FDG PET CT scans.

Clinical practice guidelines and scientific studies support the use of MRI for characterizing the primary tumor and defining its extent, CT or FDG PET CT for assessing lymph node status, and FDG PET CT for detecting distant metastases in newly diagnosed NPC.[14,152,153]

MRI

Two meta-analysis presented evidence on using MRI in determining the stage of NPC. In one meta-analysis of cohort studies [154], gadolinium-enhanced nasopharynx MRI demonstrates high pooled sensitivity (98.1%, 95% CI 95.2 to 99.3%; n = 9 studies, I^2 = 26.7%) and pooled specificity (91.7%, 95% CI 88.3 to 94.2%; n = 9 studies, I^2 = 45.4) as well as positive LR (11.9, 95% CI 8.35 to 16.81; n = 9 studies, I^2 = 0%) and negative LR (0.02, 95% CI 0.01 to 0.05, n = 9 studies, I^2 = 43.2%). All studies in this meta-analysis included patients suspected of having nasopharyngeal carcinoma due to positive EBV serology, middle ear effusion, blood-stained epistaxis or rhinorrhea, cervical nodal metastasis, or other clinical features and only one cohort included patients with proven or suspected NPC. The reference standard was either endoscopic biopsy or histopathology. The findings provide evidence in favor of utilizing MRI as a primary diagnostic modality for assessing the lesions, in conjunction with its well-established function in assessing the extent of disease within a specific region. If employed before conducting an endoscopic biopsy, it has the potential to enhance the effectiveness of the biopsy or assist in determining whether a biopsy is unnecessary for patients with a low likelihood of having the disease.[154]. These results, particularly in terms of sensitivity of MRI in T staging, is aligned with the results of previous meta-analysis which examined the diagnostic utility of MRI compared to that of CT and FDG PET-CT.[155]

CT

In the aforementioned meta-analysis with the comparison of the three modalities and CT was found to have a good performance in determining diagnosis of N stage.[155] The pooled sensitivity and specificity of CT (n = 4 studies) in N stage was 92% (95% CI 88 to 95%) and 93% (95% CI 76 to 99%), respectively whereas the sensitivity and specificity of MRI (n = 10 studies) was 88% and 95%, respectively. The reference standard in these studies were histology and pathology biopsy or nasoscope.

FDG PET-CT

In the same meta-analysis, the combined sensitivity of FDG PET-CT (82%) is higher than that of MRI (80%) and CT (53%) when used in M classification. All the studies relied on the reference standard of clinical follow-up. In another meta-analysis that assessed the diagnostic utility of FDG PET-CT among patients with newly diagnosed NPC, it showed a good accuracy in N and M but not T classification.[156] The combined sensitivity estimate for FDG PET-CT in T classification was 77% (95% CI 59 to 95%). For N classification, the pooled sensitivity was 84% (95% CI 76% to 91%) and the specificity was 90% (95% CI 83% to 97%). For M classification, the combined sensitivity estimate was 87% (95% CI 74% to 100%) and a specificity of 98% (95% CI 96% to 100%).

Certainty of Evidence

Reviewed studies have a high certainty of evidence since these are systematic reviews of studies with meta-analyses.

Recommendations of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
United Kingdom National Multidisciplinary Guidelines (accessed on June 27, 2023)	Multislice CT scan of head, neck and chest should be carried out in all patients and MRI where appropriate to optimize staging. Staging investigations should include multislice computed tomography (CT) scan of the head, neck and chest. Magnetic resonance imaging (MRI) scans of the skull base are useful especially in locally advanced tumors. The use of positron emission tomography computed tomography (PET–CT) should be reserved for patients with a suspected occult primary tumor in the nasopharynx and should be carried out before diagnostic procedure.	Strong
SEOM clinical guidelines for the treatment of head and neck cancer (2020) (accessed on June 27, 2023)	-Imaging diagnosis before a large biopsy avoids false diagnosis from anatomy distortion. -Cervical computed tomography (CT) or magnetic resonance (MR). Imaging MRI is superior to CT for evaluation of tongue, perineural spread, skull base invasion and intracranial extension. Regarding	Strong

	lymphatic dissemination, defining extracapsular nodal extension is of prognostic value. -CT of chest preferably, or X-ray in early stages. -Positron emission tomography-CT (PET-CT) is very useful in diagnosis of node (N) and metastases (M) and synchronous primary tumors. It is recommended in patients with stage III–IV disease when definitive treatment is indicated or in those with equivocal findings on CT or MRI scan	
NCCN Guidelines Version 1.2023 (accessed on June 27, 2023)	• MRI with contrast of skull base to clavicle ± CT of skull base/neck with contrast to evaluate skull base erosion • Imaging for distant metastases with FDG-PET/CT and/or chest CT with contrast	Strong
Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up (accessed on June 27, 2023)	Routine staging procedures include a medical history, physical examination with cranial nerve examination, CBC, serum biochemistry (including liver and renal function tests and LDH), nasopharyngoscopy and radiological imaging. • MRI is the most accurate way of defining local and nodal tumor staging and it should be preferred whenever available and according to the centre's expertise [III, B]. • FDG-PET adds further accuracy in nodal staging, is the best imaging method for detecting distant metastases and is recommended at least in locally advanced disease [III, B].	Strong
Pan-Asian adaptation of the EHNS-ESMO-ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck (accessed on June 27, 2023)	Rigid head and neck endoscopy, head and neck contrast-enhanced computed tomography (CE-CT) and/or magnetic resonance imaging (MRI) and chest imaging (with CT and/or [18F]2-fluoro-2-deoxy-Dglucose-positron emission tomography (FDG-PET) are strongly recommended [IV, A].	Strong

Remarks

The lack of FDG PET-CT necessitated consideration of the contrast for chest CT. The use of contrast is suggested if there is suspicion of the presence of pathologic lymph nodes. However, it can impose a financial burden on patients, especially in resource-constrained settings.

The examinations were still strongly recommended based on the certainty of the evidence, the standard of practice, and the potential to enhance the preparedness of government hospitals in accordance with the National Integrated Cancer Control Act.

5. Among individuals diagnosed with NPC who have completed staging work-up, what additional procedures are necessary to request prior to the start of definitive treatment?

5. We recommend the following pretreatment evaluation procedures:
   - Baseline audiogram
   - Dental clearance
   - Nutrition consult and assessment for enteral feeding
   - Thyroid function test

   High certainty of evidence, Strong recommendation

Key Findings

The clinical practice guidelines included and reviewed recommended a list of pretreatment procedures and assessments.[14,131,157] These include obtaining the patient's medical history and conducting a physical examination, performing blood counts and chemistry tests, conducting a nasopharyngoscopy, obtaining a tumor biopsy, and obtaining imaging scans such as a CT scan or MRI, or FDG PET-CT or CT imaging. Other recommended assessments include baseline audiometry, dental examination, evaluation of nutritional status, ophthalmological assessment, endocrine evaluation, determination of plasma EBV DNA levels, and quality of life (QoL).

Several meta-analyses highlighted the side effects of NPC management on dental health, nutrition, mastication, and hearing that affect activities of daily living and overall quality of life. Therefore, it is imperative to conduct baseline pretreatment procedures to determine the pretreatment status and assess the patient's prognosis.

Baseline Audiogram

In one meta-analysis of 11 RCTs (n = 2801), the risk of acute and late toxicities of CRT and RT in patients with NPC was investigated. The treatment of NPC, particularly concurrent chemoradiotherapy was significantly associated with higher incidence of severe late toxicity, such as hearing loss (RR 1.46, 95% CI 1.04 to 21.01).[158]

Dental Clearance

One of the goals of the pre-RT oral or dental evaluation stipulated in the NCCN guidelines is examining and providing treatment plan for patients with head and neck cancer.[14] Examination includes radiographs of all teeth and risk assessment for caries and periodontal disease. [14] In the NCCN guidelines, the plan of care also ensures removal of potential sources of infection, extractions at least 2 weeks before the start of RT, treatment of active dental caries or periodontal disease, use of silicone guards for radiation, prescription of potent topical fluoride used daily, scheduling re-evaluation, and evaluation for oral candidiasis with appropriate treatment.[14]

Nutrition Consult and Assessment for Enteral Feeding

One meta-analysis of 10 cohort studies (n = 3,458) examined the overall survival of head and neck cancer patients treated with radiotherapy (CRT and IMRT).[159] Six of the studies included patients with NPC. The analysis shows that these head and neck cancer patients with lower nutritional status measured by prognostic nutritional index had higher risk of mortality (HR 1.97, 95% CI 1.64 to 2.37; I^2 = 22.6%), worse distant metastasis-free survival (HR 1.96, 95% CI 1.6 to 2.4; I^2 = 0), and worse progression-free survival (HR 1.5, 95% CI 1.21 to 1.84; I^2 = 0%. The identification of suboptimal nutritional status presents an opportunity to improve the patient's nutritional status prior to undergoing radiotherapy. [159]

Thyroid Function Test

No direct evidence on the diagnostic accuracy and efficacy outcomes of the thyroid function test for patients with nasopharyngeal cancer was found, apart from an observational study on the incidence of thyroid dysfunction among those who underwent RT. Immanuel and colleagues conducted a one-year prospective cohort analysis on 82 patients with histopathologically confirmed head and neck cancer who underwent radiotherapy targeting the neck area. The results revealed a 19.5% incidence rate of thyroid dysfunction and an increasing trend in the mean TSH levels at 3 months, 6 months, and 12 months. Monitoring the thyroid function can help in detecting thyroid dysfunction among patients undergoing radiation or chemoradiation before it progresses to clinical hypothyroidism.[160]

Certainty of Evidence

Evidence were graded with high certainty since these recommendations were derived from systematic reviews and meta-analyses of high-quality cohort and/or randomized controlled trials.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
National Comprehensive Cancer Network (NCCN) Guidelines for Patients – Nasopharyngeal Cancer: Head and Neck Cancers Series (2019)	▪ Health care that are needed before NPC treatment includes medical history, physical examination, and other as needed tests or procedures such as speech and swallowing examination, nutritional assessment, dental examination and X-rays, hearing or vision tests.	▪ The guideline discussed that NPC treatment may have an effect on the vision, hearing, swallowing, and nutrition of patients with NPC. However, there was no mention of the level of evidence and strength of recommendation.
ESMO-EURACAN Clinical Practice Guidelines (2020)	▪ Routine staging procedures include a medical history, physical examination with cranial nerve examination, CBC, and serum biochemistry. ▪ Baseline audiometric testing, dental examination, nutritional status evaluation and ophthalmological and endocrine evaluation should be carried out as appropriate.	▪ There were no discussion in the guideline on the recommendation for routine staging procedures (e.g., CBC) and other procedures (e.g., audiometry, dental examination, etc.). Moreover, the level of evidence and strength of recommendations were not mentioned. ▪ Level of Evidence: III Grade of Recommendation: B

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
	▪ Pre-treatment QoL scales may be suggested to better delineate the individual risk and to prompt medical or physical support before the start of treatment [III, B].	
Radiation Oncology Physicians Branch of the Chinese Medical Doctor Association and the Radiation Oncology Branch of the Chinese Medical Association (2021)	▪ The patient's status should be fully assessed before treatment and the following tests should be performed according to clinical indications: ophthalmological assessment (specialist assessment recommended).	▪ The guideline discussed that NPC may cause compression of the optic nerve and lead to diplopia and other ocular manifestations. The treatment may also affect the optic nerve and lead to ocular symptoms. However, there was no mention of the level of evidence and strength of recommendation.

Remarks

The tests listed above hold paramount importance for the consensus panel in pretreatment evaluations. Assessments by ophthalmologists and speech pathologists were initially considered as they pertain to different carcinoma-related clinical indications; however, these are not required, as additional pretreatment test procedures are resource-draining for the patients and could delay the treatment of urgent clinical problems.

This recommendation statement merits a disagreement from one member, as the speech-language pathologist believes that assessing swallowing function, initiating preoperative and pre-radiation exercises, and providing counseling are also essential.

3.4.2. Treatment

6. What is the appropriate management for patients with T1-2N0 NPC?

6.1. We recommend definitive radiotherapy using intensity-modulated radiotherapy (IMRT) technique for T1-T2N0 NPC.

High certainty of evidence, Strong recommendation

6.2.1. We do not recommend concurrent chemotherapy for T1N0 disease.

High certainty of evidence, Strong recommendation

6.2.2. We do not recommend concurrent chemotherapy for T2N0 unless with bulky disease.

Moderate certainty of evidence, Strong recommendation

6.3. We recommend 69.96 to 70.0 Gy in 33 to 35 fractions (2.0 to 2.12 Gy per fraction) delivered over 6 ½ to 7 weeks, once daily, five times per week, to the primary tumor and involved lymph nodes.

High certainty of evidence, Strong recommendation

6.4. We recommend 59.4-63.0 Gy in 1.8-2.0 Gy per fraction be given to sites of intermediate risk target volume, and 50-56 Gy in 1.6-2.0 Gy per fraction may be given to sites of low-risk target volume.

High certainty of evidence, Strong recommendation

Key Findings

Several medical professional groups recommend definitive RT alone for patients with early-stage NPC.[152,161-165] The NCCN guidelines specifically recommend definitive RT to nasopharynx and elective RT to the neck for T1N0M0 NPC.[14]

Aside from the clinical practice guidelines, other available evidence on the use of radiotherapy in early-stage NPC looked into outcomes such as overall survival, locoregional recurrence, and distant metastasis. No randomized controlled trials specifically comparing treatment options for T1N0 patients were found.

In one retrospective cohort study among 506 biopsy-proven nonmetastatic NPC patients who received IMRT as the primary treatment, outcomes such as 5-year overall survival and patterns of failure (e.g., local recurrence, distant metastasis) were examined.[166] It is important to take note that in this study, only 110 were staged with N0 disease. After the completion of RT, all patients were followed up every 1-3 months during the first 2 years, every 6 months in years 2 to 5 annually thereafter. Thirty-eight patients (7.5%) developed locoregional recurrence, 74 patients (14.6%)

had distant metastasis, and 81 patients died. Of the 110 N0 patients, 3 developed local recurrence (one had T2N0 and 2 patients had T4N0 disease). Four of the 110 N0 patients developed distant metastasis. In T1N0 disease, the OS rate was 97.8% and the distant metastasis-free survival rate was 96.6%.[166]

In another retrospective cohort of 106 patients with biopsy-proven nasopharyngeal cancer treated by definitive radiotherapy in Iran, 9 patients had T1N0 NPC. Patients underwent radiotherapy with a median dose of 70 Gy (IQR 70-70).The 5-year OS rate for stage I was 88%.[167]

Another observational study looked into the use of late-course accelerated hyperfractionation radiotherapy alone among Stage I-II NPC patients and revealed a 5-year OS of 83.3% for Stage I patients, which accounted for only 18 out of the 158 patients in the cohort. The study included the use of a unique dosing regimen that involved, for the first two-thirds of the treatment, giving 2 daily fractions of 1.2 Gy to the primary lesion, 5 days per week, for a total dose of 48 Gy in 40 fractions over a period of 4 weeks. In the 5th week, an accelerated hyperfractionation schedule was carried out. Two daily fractions of 1.5 Gy were given, for a total dose of 30 Gy/20 fractions over 2 weeks. Thus, the total dose was 78 Gy in 60 fractions in 6 weeks.[168]

Another retrospective analysis examined the treatment outcomes of patients with nasopharyngeal carcinoma (NPC) who underwent intensity-modulated radiation therapy (IMRT). Out of the total 865 NPC patients, 52 were classified as Stage I. The analysis revealed that these Stage I patients had a 5-year OS rate of 93.8%, a progression-free survival rate of 100%, and a distant metastasis-free survival rate of 100%. The authors observed favorable results among those who received IMRT as the sole treatment for early-stage nasopharyngeal carcinoma.[169]

A retrospective study conducted in China examined the outcomes of patients with predominantly WHO grade II early stage NPC who underwent IMRT with or without chemotherapy. Out of the total 69 patients, 17 were classified as stage I. The study found that patients with stage T1-2N0 and T1N1 had a 3-year overall survival (OS) rate of 100% and a 3-year local recurrence-free survival (LRFS) rate of 100%. These rates were significantly higher compared to patients with stage T2N1, who had a 3-year OS rate of 74.5% and a 3-year LRFS rate of 81.8%.[170]

The aforementioned studies were also aligned with observational study done in older adults with NPC. Data of 147 adults who aged 70 years old and above were analyzed. This study revealed that there was a strong trend showing the RT was associated with higher median and 5-year OS among those older adults who survived 1 year or more (n = 96).[171] Another study that involved a national database for analysis of practice patterns is the sole study that provides a direct comparison of results of those who received RT alone and combined RT and chemotherapy. All patients with T1N0 NPC (n = 396) received curative-intent radiation therapy, while 37% of them also received chemotherapy in conjunction with RT. There was no significant difference observed in the 5-year OS rates between the group receiving RT alone (77%) and the group receiving CRT (75%). However, it should be noted that this comparison was conducted in a non-prospective, non-randomized setting with small sample size.[172]

Safety Outcomes

Late complications were reported in one study.[170] Xerostomia was the most common late complication, with 35% of patients experiencing Grade 2 it. Dental caries (Grade 2 = 27%) and hearing loss (Grade 2 = 10%) were also commonly seen. Seventeen (10.8%) had cranial nerve palsy. Patients Another outcomes study showed that 52.2% of experienced grade 1, 46.4% experienced grade 2, and there were no grade 3 or 4 toxicities. Surprisingly, dermatitis was the most common acute toxicity (58.0% grade 1), followed by mucositis (50.8% grade 1) and dysphagia (65.2% grade 1).

Certainty of Evidence

There is agreement among all guidelines cited, including a high-quality guideline from the NCCN, that for Stage I (T1N0) NPC patients, radiotherapy alone, given as IMRT, is strongly recommended as chemotherapy does not confer any benefit at this stage. Studies that support this recommendation were marked by moderate certainty of evidence due to selection bias.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
American College of Radiology (ACR) Appropriateness Criteria for Nasopharyngeal Cancer, 2016	• Early-stage NPC (Stage I) is curable with RT alone, wih a 5-year overall survival close to 90% • Even though a noted improvement in outcome in recent years can be attributable to better staging modalities and stage migration, an improvement in radiation planning and delivery techniques likely explains at least some of this improvement. • It is unclear if adjuvant or neoadjuvant systemic therapy would offer any benefit to patients with early-stage NPC, as very few patients with stage I or early stage II disease have been included in clinical trials examining this question.	Strong
Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines, 2016	Patients with early disease can be treated with RT alone, resulting in disease free survival rates of 90 and 84 per cent. The dose to the primary tumour should be equivalent to 70 Gy in 2 Gy fractions and at least 50 Gy in 2 Gy fractions to the bilateral neck and other sites of potential microscopic spread. Intensity modulated radiotherapy techniques should be used. Evidence of benefit from the addition of chemotherapy to RT in early disease is lacking.	Strong
Indian clinical practice consensus guidelines for the management of nasopharyngeal cancer, 2020	Early nasopharyngeal carcinoma (T1, N0, M0) • Patients with early-stage disease can be treated with definitive RT alone including both sides of the neck and retropharyngeal	Strong

	nodes. The prognosis of patients with stage I disease is extremely good with RT alone.	
Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2012	Radiation therapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC. Stage I disease is treated by RT alone	Strong
The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma	T1N0 – No chemotherapy (evidence 2A)	Grade I recommendation
Does East meet West? Towards a unified vision of the management of Nasopharyngeal carcinoma	For treatment, all guidelines are consistent with the recommendation of RT alone for stage I disease.	Strong
National Comprehensive Cancer Network Guidelines, Version 2.2023	For T1N0M0 (Stage I) NPC • Definitive RT to nasopharynx and elective RT to the neck	Category 2A recommendation

Remarks

Other than clarifying that the definitive treatment does not include chemoradiotherapy, no further concerns on the recommendation statement 6.1 were mentioned.

The panel believes that radiotherapy alone is the standard treatment for T1-T2N0. As mentioned by a specialist in the panel, withholding chemotherapy to treatment of selected patients with T2N0 disease is still debatable among nasopharyngeal carcinoma experts. Despite this division, this recommendation against concurrent chemotherapy was strong due to the moderate certainty of evidence.

Concurrent chemotherapy is indicated for those T2N0 cases with high-risk features (i.e., high level of plasma EBV DNA and increased tumor volume). The panel opted to use ‘bulky disease’ instead since the local capacity to detect plasma EBV-DNA among patients with NPC is limited.

No further discussion on statements 6.3 and 6.4 apart from the clarification on the specific dosages.

7. What is the appropriate management for patients with T1-2N1 and T3N0 NPC?

7.1. We recommend definitive concurrent chemoradiation in patients with T1-T2N1 and T3N0 NPC.

High certainty of evidence, Strong recommendation

7.1.1. We recommend 69.96 to 70 Gy in 33-35 fractions (2.0 to 2.12 Gy per fraction) delivered over 6.5-7 weeks, once daily, 5x per week to the primary tumor and involved lymph nodes.

High certainty of evidence, Strong recommendation

7.1.2. We recommend that simultaneous integrated boost (SIB) or sequential boost be offered.

High certainty of evidence, Strong recommendation

7.1.3. We recommend that elective nodal coverage for NPC should cover the bilateral retropharyngeal lymph nodes and levels II to V.

High certainty of evidence, Strong recommendation

7.2. We recommend that concurrent chemotherapy be offered for T1-2N1 patients.

High certainty of evidence, Strong recommendation

(continued on page 88)

Early-stage NPC was characterized as Stage I and II by AJCC staging system, and definitive RT alone is considered to be standard of care.

For Stage II NPC, there has been debate as to whether patients with Stage II NPC would need multimodal treatment (a combination of radiation therapy and chemotherapy). Initial trials during the 2D-conventional RT era have shown improvement in OS and PFS with the addition of chemotherapy. It has been shown in later studies that included patients treated with IMRT that Stage II NPC patients treated with the said advanced RT modality did not have improved outcomes with the addition of chemotherapy.

Key Findings

Two (2) RCTs and 2 meta-analyses were included comparing radiotherapy alone versus chemoradiotherapy. Outcomes of measures of the studies included overall survival, local relapse/recurrence free survival, nodal relapse free survival, and distant metastasis-free survival.

In one meta-analysis (16 studies, n = 3,038), overall survival was slightly higher (RR 1.04, 95% CI 1.01 to 1.06) and locoregional failure-free survival (RR 1.05; 95% CI 1.02 to 1.07) among

patients with stage II NPC who underwent CRT and RT compared to those who had RT alone.[173] There were 6 studies that investigated addition of chemotherapy to conventional RT (n = 1,084) and 10 studies on CRT combined with IMRT (n = 1,954) There was also little to no effect on progression-free survival (RR 1.05, 95% CI 1.00-1.10) and no effect in terms of distant metastasis failure-free survival (RR 1.00, 95% CI 0.97 to 1.03). However, subgroup analysis showed that chemoradiation could significantly improve OS (RR 1.09, 95% CI 1.03 to 1.15), PFS (RR 1.20, 95% CI 1.08 to 1.35), and locoregional failure-free survival (RR 1.09, 95% CI 1.04 to 1.14, but no conclusive result on DMFS when compared to conventional RT. However, compared with IMRT alone, CRT did not significantly improve the rate of the said outcomes. The results were similar with another meta-analysis (6 trials, n = 1218 patients) on IMRT plus concurrent therapy versus IMRT alone in stage II NPC patients.[174] Newer studies comparing the two interventions (CRT versus RT alone), on the other hand, have conflicting results that may be due to the type of RT employed. Patients who received 2D RT with a therapeutical accumulative dose of 68-70 Gy given to the primary tumor and 60-62 Gy to the involved neck regions while those in the CCRT group received cisplatin on a weekly regimen at dose 30 mg/m^2.[175] Statistically significant improvements in incidence rates of overall survival, progression-free survival, and cancer-specific survival between the two groups was found, with increased rates in CCRT. These benefits were primarily seen in the T2N1 population.[175] In a small randomized phase II trial, stage II patients (2010 AJCC) were randomly assigned to either IMRT alone or IMRT plus concurrent cisplatin, concomitant chemotherapy with IMRT did not significantly improve survival outcomes.[176]

Safety Outcomes

In the study conducted by Huang et al., it was observed that patients who underwent chemoradiotherapy without the use of IMRT experienced a negative impact on their bone marrow function. In another trial, the outcomes of chemoradiotherapy were examined in relation to 2D RT alone. The study findings did not indicate any significant increase in toxicities. Both meta-analyses demonstrated that the inclusion of chemotherapy alongside radiotherapy resulted in increased incidences of acute and late toxicities.

Certainty of Evidence

The certainty of is deemed high as a result of incorporating two trials and two meta-analyses. The conflicting results can be attributed to the disparity in outcomes observed between studies conducted during the two-dimensional (2D) era and studies conducted during the period of IMRT.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
American College of Radiology (ACR) Appropriateness Criteria for Nasopharyngeal Cancer, 2016	Patients with stage II NPC (T1N1, T2N0–1), especially those with node-positive disease, have a substantial rate of distant metastases, and therefore concurrent chemotherapy and RT is recommended	Strong

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines, 2016	Intermediate stage II disease can be treated with RT alone (T2N0M0), but most cases are treated with combination chemoradiotherapy. Intensity modulated radiotherapy should be considered mandatory.	Strong
Indian clinical practice consensus guidelines for the management of nasopharyngeal cancer, 2020	Locally advanced nasopharyngeal carcinoma (T1, N1-3; T2-4, any N) Concurrent chemotherapy and radiotherapy (CT/RT) • In locally advanced disease, surgical treatment is quite challenging due to complex anatomy and it must be reserved for patients where chemoradiotherapy (CTRT) is failed or for patients who are not suitable for CTRT. Hence, concurrent CT/RT followed by adjuvant CT should be the standard of care for advanced nasopharyngeal carcinoma.[567] It includes weekly cisplatin or carboplatin + RT followed by adjuvant cisplatin plus 5-FU every 4 weeks for three cycles.	Strong
Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2012	Stage II – Concurrent chemoradiotherapy (I,B)	Grade IB recommendation
The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma, 2021	T2N0 Grade I recommendation Radiotherapy alone [101] (evidence 2B) Grade II recommendation Concurrent chemoradiotherapy [102, 103] (with poor prognostic factors, such as large tumor volume or high EBV DNA copy number) (evidence 2A) T1-2N1 Grade I recommendation Concurrent chemoradiotherapy [102, 103] (evidence 2A) Grade II recommendation Radiotherapy alone (evidence 2A)	Evidence strength 2A-2B
Does East meet West? Towards a unified vision of the management of Nasopharyngeal carcinoma, 2019	There is some heterogeneity for Stage II disease, with some advocating RT alone, while others having CCRT as an option in the presence of adverse risk factors (significant nodal disease, parapharyngeal tumor extension, and high plasma EBV level (SEOM)), and others recommending CCRT outright.	Strong

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
National Comprehensive Cancer Network Guidelines, Version 2.2023	For T2N0M0 (Stage II) NPC • Definitive RT +/- concurrent systemic therapy if with high risk features (bulky tumor volume, high serum EBV DNA copy number) For T0 (EBV+)-2N1M0 or T3N0M0 • Concurrent systemic therapy/RTj,k • Consider induction or adjuvant chemotherapy if high-risk features (bulky tumor volume, high serum EBV DNA copy number)	Category 2A recommendation

Remarks

The recommendations on definitive concurrent chemoradiation in patients with T1-T2N1 and T3N0 NPC received approval from the panel without further comments. The discourse only clarified that the high-quality evidence for the elective nodal coverage for NPC excludes level Ib. Apart from these, no further discussion or comments on statement 7.2.

…continuation

7.3. We recommend concurrent chemotherapy for T3N0 disease.

High certainty of evidence, Strong recommendation

7.4. We recommend adjuvant or induction chemotherapy for T1-2N1 and T3N0 with bulky disease.

Moderate certainty of evidence, Strong recommendation

7.5. We recommend giving cisplatin either triweekly or weekly.

High certainty of evidence, Strong recommendation

7.6. We recommend radiotherapy alone for patients ineligible to receive any systemic agent provided that patient understands that inferior outcome of this monotherapy.

High certainty of evidence, Strong recommendation

Stage III disease is defined by either bony involvement or cervical lymph node involvement. For locally advanced NPC (Stage III and IVA) disease, a combined modality approach consisting of chemotherapy and radiotherapy is recommended in the available literature, which includes multiple randomized controlled trials for both endemic and non-endemic NPC, and this has held in spite of the move to more conformal, intensity-modulated radiation therapy. The subset of Stage III NPC patients,

Stage T3N0, is unique in that they have been excluded from randomized trials assessing the benefit of chemotherapy in the induction and adjuvant settings with chemoradiotherapy.

Key Findings

Four (4) retrospective studies and one (1) review were included comparing radiotherapy alone versus chemoradiotherapy.

Outcomes of measures for these five (5) studies included overall survival, local relapse/recurrence-free survival, nodal relapse-free survival, and distant metastasis-free survival.

Two retrospective studies did not find a benefit to adding induction chemotherapy (one study: 4-year OS 91.7% vs. 92.6%, p = 0.794), LRFS (92.7% vs. 96.8%, P = 0.138), DMFS (93.5% vs. 94.3%, P = 0.582), or PFS (87.5% vs. 91.1%, P = 0.223). Another induction chemotherapy study showed that among patients with T3N0M0 disease, the 5-year LRFFS, DFS, and OS rates were remarkably lower in the IC+CCRT group than the CCRT group (88.6% vs. 96.6%, P = 0.006; 81.0% vs. 92.7%, P = 0.002; 89.5% vs. 96.7%, P = 0.010). DMFS was similar between the two groups (92.1% vs. 96%, P = 0.204).

In one retrospective study that compared chemoradiotherapy (CCRT) with RT alone, no significant survival differences were observed between patients who received IMRT alone (n = 49) and CCRT (n = 114), including LRFS, DMFS, DFS, and OS (P > 0.05). In a SEER database analysis, the survival benefit of chemotherapy was insignificant for patients with node-negative stage III (T3N0M0) NPC. In crude Kaplan-Meier analysis, there was no difference in ACM for patients treated with chemotherapy versus those without (5-year ACM rate: 41.5% vs. 41.6%, P = 0.618, Fig. 3E; crude HR: 0.87, 95% CI [0.51–1.50], Table 2). IPTW procedures conducted in a node-negative cohort generated a well-balanced weighted population (Table S1 and Fig. S1). IPTW-adjusted Kaplan-Meier analysis yielded similar results (5-year ACM rate: 41.9% vs. 42.5%, P = 0.746, Fig. 3F; IPTW-adjusted HR: 0.89, 95% CI [0.45–1.76].

The literature review cited in this evidence review noted that the role of concurrent chemotherapy with radiation therapy is still being tested in a randomized trial, and none of the randomized trials and retrospective studies conducted in the IMRT era seemed to confer a benefit for T3N0. In terms of adjuvant and induction chemotherapy, their roles in T3N0 NPC patients appear limited.

Safety outcomes
In one retrospective study on induction with concurrent chemotherapy, the IC group experienced higher rates of grade 3–4 hematological toxicities (grade 3–4 leucopenia (P < 0.001) and neutropenia (P < 0.001)). Another induction study showed significantly more grade 3–4 hematologic side-effects occurred in the IC + CCRT group than the CCRT group (Anemia: 10.3% vs. 1.4%, P = 0.002; Thrombocytopenia: 16.4% vs. 1.4%, P < 0.001; Neutropenia: 43.8% vs. 6.9%, P < 0.001). Grade 1–2 impaired liver function and grade 1–2 impaired kidney function were significantly more frequently seen in the IC + CCRT group than the CCRT group, at 30.8% vs. 7.4% (P < 0.001) and 12.3% vs. 1.0% (P < 0.001), respectively.

The addition of chemotherapy to IMRT alone in the chemoradiotherapy versus radiotherapy retrospective study showed patients treated with CCRT experienced more hematological AEs, including leukopenia (11.6% vs. 1.2%, P = 0.005), neutropenia (7.4% vs. 0.0%, P = 0.012), and thrombocytopenia (4.8% vs. 0.0%, P = 0.045), than those treated with IMRT alone, except for anemia (2.1% vs. 0.0%, P = 0.186). Moreover, a higher incidence of mucositis was observed in the CCRT group compared with the IMRT alone group (50.5% vs. 19.5%, P < 0.001), while no statistical differences were observed in xerostomia, dermatitis, nausea/vomiting, or hepatoxicity between the two groups (P > 0.05).

Certainty of Evidence

The level of certainty regarding the effectiveness of chemoradiotherapy compared to radiotherapy alone is currently considered weak. To address this, a randomized trial is currently underway to investigate the role of concurrent chemoradiotherapy in the treatment of T3N0 nasopharyngeal carcinoma (NPC).

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
American College of Radiology (ACR) Appropriateness Criteria for Nasopharyngeal Cancer, 2016	Treatment for stage III or IV (advanced) disease • Concurrent chemotherapy and radiation is the backbone of treatment of locally advanced NPC.	Strong (but considers Stage III as a single entity together with Stage IV)
Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines, 2016	Stages III and IV • Concurrent chemoradiotherapy is the standard of care for advanced nasopharyngeal cancers. This improves OS by up to 6 per cent at five years compared with radical RT.	Strong (but considers Stage III as a single entity together with Stage IV)
Indian clinical practice consensus guidelines for the management of nasopharyngeal cancer, 2020	Locally advanced nasopharyngeal carcinoma (T1, N1-3; T2-4, any N) Concurrent chemotherapy and radiotherapy (CT/RT) • In locally advanced disease, surgical treatment is quite challenging due to complex anatomy and it must be reserved for patients where chemoradiotherapy (CTRT) is failed or for patients who are not suitable for CTRT. Hence, concurrent CT/RT followed by adjuvant CT should be the standard of care for advanced nasopharyngeal carcinoma.[567] It includes weekly cisplatin or carboplatin + RT followed by adjuvant cisplatin plus 5-FU every 4 weeks for three cycles.	Strong (but considers Stage III as a single entity together with Stage IV)

Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2012	Stage III – Concurrent chemoradiotherapy +/- adjuvant chemotherapy (I,A)	Grade IA recommendation
The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma, 2021	T3N0 Grade I recommendation Concurrent chemoradiotherapy (evidence 2A) Grade II recommendation Induction chemotherapy + concurrent chemoradiotherapy (evidence 1B) Concurrent chemoradiotherapy + adjuvant chemotherapy (evidence 1B)	Evidence strength 1B
Does East meet West? Towards a unified vision of the management of Nasopharyngeal carcinoma, 2019	For locally advanced disease, CCRT is a consensus. For stages II to IV, the recommendation of the use of ACT is likewise heterogenous. PMH advocates ACT, the UK, ESMO, and Malaysian guidelines only recommend CCRT, while the rest leave ACT as an option. The regimens for concurrent chemotherapy are either Cisplatin 100 mg/m2 every 3 weeks, or 40 mg/m2 weekly. NACT, however, is not systematically recommended, mainly because high level evidence has only recently been published. The NCCN guidelines advocate CCRT with either NACT or ACT (category 2A), with CCRT alone classified as category 2B. It is worth noting, however, that variations in recommendations may be the result of differences in selecting evidence and interpreting data.	Moderate (Heterogeneity in recommendation)
National Comprehensive Cancer Network Guidelines, Version 2.2023	For T0 (EBV+)-2N1M0 or T3N0M0 • Concurrent systemic therapy/RT • Consider induction or adjuvant chemotherapy if high-risk features (bulky tumor volume, high serum EBV DNA copy number)	Category 2A recommendation

Remarks

There was no further discussion on the statement on T3N0 patients receiving concurrent chemotherapy.

The panel clarified the certainty of the evidence for statement 7.4, which was initially high due to high-quality practice guidelines used as a basis. The panel still opted for a strong recommendation, as treatments were given as options for those with bulky diseases with moderate-certainty evidence. The administration of adjuvant chemotherapy, while subject to debate among experts in the field of nasopharyngeal carcinoma, is still offered as an option to T1-2N1 and T3N0 patients, particularly those with bulky disease who are presumed to undergo a concurrent regimen (i.e., systemic therapy and radiotherapy).

For statement 7.5, there was no further discussion on the frequency of cisplatin administration among patients receiving chemotherapy. For those cisplatin-ineligible or intolerant patients, carboplatin was discussed as an alternative. However, due to the lack of evidence showing benefit in comparison to cisplatin specifically for patients with NPC and the potential for toxicity, the panel opted to withdraw the recommendation on carboplatin.

8. What is the appropriate management for patients with T1-2N2, T3N1-2, any T4, or any N3?

8. We recommend concurrent chemoradiation with induction or adjuvant chemotherapy for T1-2N2, T3N1-2, any T4, and any N3 NPC.

High certainty of evidence, Strong recommendation

Definitive chemoradiation, with or without adjuvant chemotherapy, has been regarded as the standard treatment for locally advanced nasopharyngeal cancer as per Intergroup 0099.[177] However, over the years and with the development of more sophisticated techniques in radiotherapy, this protocol was refined with clinical trials that defined who would benefit from adjuvant chemotherapy and who would be best suited for induction chemotherapy prior to definitive chemoradiation.

Key Findings

There are five international clinical practice guidelines that define the current management for locally advanced (i.e. T1-2N2, T3N1-2, any T4, or any N3) NPC[14,131,178-180]. All 5 CPGs recommended concurrent chemoradiation with induction or adjuvant chemotherapy for locoregionally advanced NPC based on multiple randomized controlled trials that provided high certainty of evidence and strong strength of recommendation.

Some are from the biggest oncology groups and consensus panels in oncology: NCCN[14], ASCO-CSCO (i.e., American and Chinese collaboration)[178], and ESMO[131], while the others are national guidelines from Spain[179] and India[180].

All five CPGs recommended a combined modality approach with concurrent chemoradiation with either induction or adjuvant chemotherapy for locoregionally advanced NPC.

In 1998, the phase III clinic trial Intergroup 0099[177] established the benefit of concurrent chemoradiation followed by adjuvant chemotherapy compared to radiotherapy alone in locally advanced NPC after showing superior PFS and OS. The 3-year PFS rate was 24% versus 69%, respectively ($P < .001$). The median survival time was 34 months for the radiotherapy group and not reached for the chemoradiation group, and the 3-year survival rate was 47% versus 78%, respectively ($P = .005$). This became the standard for several years.

The benefit of concurrent chemoradiation alone was shown by one meta-analysis on chemotherapy.[181] This meta-analysis included 1834 patients with nasopharyngeal carcinoma in 7 trials in which concurrent chemotherapy during RT (without induction or adjuvant chemotherapy) was compared with RT alone. At a median follow-up of 7.7 years, compared with RT alone, concurrent chemotherapy improved both 10-year OS (59% versus 51%, HR 0.80, 95% CI 0.70 to 0.93) and 10-year progression-free survival (52% vs. 44%, HR 0.81, 95% CI 0.7 to 0.92).[181]

Induction chemotherapy followed by concurrent chemotherapy is the preferred approach for patients with locally advanced NPC, except for selected T3N0 disease. Patients with T3-4 or N0 disease were excluded from most trials investigating induction chemotherapy. This approach is supported by three large RCTs in an endemic region.

One trial evaluated the role of induction chemotherapy using gemcitabine and cisplatin followed by concurrent chemoradiation by comparing it with chemoradiation alone among patients with nonkeratinizing nasopharyngeal carcinoma.[182] This study showed a 3-year relapse-free survival of 85.3% vs. 76.5% (HR 0.51, 95% CI: 0.34-0.77, p = 0.001) and 3-year overall survival of 94.6% and 90.3% (HR 0.43; 95% CI, 0.24 to 0.77), both favoring the induction chemotherapy arm.[182]

Another RCT evaluated the role of induction chemotherapy using cisplatin, fluorouracil, and docetaxel followed by concurrent chemoradiation by comparing it with chemoradiation alone among patients with nonkeratinizing nasopharyngeal carcinoma.[183] After a median follow-up of 45 months, 3-year failure-free survival was 80% (95% CI 75 to 85%) in the induction chemotherapy plus concurrent chemoradiotherapy group and 72% (95% CI 66 to 78%) in the concurrent chemoradiotherapy alone group (HR 0.68, 95% CI 0.48 to 0.97; *P* = 0034).[183]

Another study evaluated the role of induction chemotherapy using cisplatin and fluorouracil followed by concurrent chemoradiation by comparing it with chemoradiation alone among patients with nonkeratinizing nasopharyngeal carcinoma.[184] After a median follow-up of 82.6 months, the 5-year DFS rate was 73.4% (95% CI 67.7 to 79.1) in the IC followed by CCRT group and 63.1% (95% CI 56.8 to 69.4) in the CCRT alone group (p = 0.007). The 5-year DMFS rate was also significantly higher in the IC followed by CCRT group (82.8%, 95% CI 77.9 to 87.7) than in the CCRT alone group (73.1%, 95% CI 67.2 to 79.0, *P* = 0.014). The updated analysis revealed that IC has benefit on 5-year OS: 80.8% vs. 76.8% (*P* = 0.040).[184]

For patients receiving adjuvant chemotherapy, three cycles of adjuvant cisplatin plus fluorouracil are used. For those with contraindications to cisplatin, alternatively, three cycles of adjuvant carboplatin plus fluorouracil may be given, which was noninferior to adjuvant cisplatin plus fluorouracil in a randomized trial. Adjuvant capecitabine may improve failure-free survival and OS in randomized phase III trials.[14,131,178]

Safety outcomes

There is a noted increase in toxicity with the addition of chemotherapy to radiation alone. Specifically, there is an increase in grade 3 to 4 episodes of neutropenia and vomiting.

As regards radiotherapy, the fraction size of 2.0 to 2.12 Gy, five fractions per week, to a total prescribed dose of 70 Gy in 33 to 35 fractions was used in the Intergroup 0099110 and RTOG 0225 trials and demonstrated good efficacy with acceptable toxicity. The development of more sophisticated techniques (i.e., the use of IMRT) brought significantly fewer RT-related side effects when compared to the use of conventional and 3D conformal techniques.

For locally advanced NPC where induction or adjuvant chemotherapy is added to concurrent chemotherapy, there was a noted increase in grade 3 or 4 adverse events of neutropenia, thrombocytopenia, anemia, nausea, and vomiting, while there was no noted increase in late grade 3 to 4 adverse events.

Certainty of Evidence

All five CPGs have recommended concurrent chemoradiation with induction or adjuvant chemotherapy for T1-2N2, T3N1-2, any T4, or any N3 NPC. This is in reference to the above-mentioned clinical trials, which are phase III randomized, well-written clinical trials. One caveat that has been discussed is that the control arm for the induction chemotherapy trials used concurrent chemoradiation alone without adjuvant chemotherapy. To date, there has been no head-to-head comparison between induction chemotherapy followed by chemoradiation and chemoradiation followed by adjuvant chemotherapy. There is one study from China that shows there is no benefit of adjuvant chemotherapy and establishes chemoradiation alone as the standard regimen for locally advanced NPC in endemic regions.[185]

Nevertheless, overall, the certainty of the evidence is high.

Remarks

There was no further discussion on this statement during the *en banc* meeting.

9. What is the appropriate management for patients with M1 NPC?

9.1. We recommend systemic treatment for symptom palliation and best supportive care.
High certainty of evidence, Strong recommendation

9.2. We recommend consideration of local consolidation therapy (both to primary and metastatic sites) with radiotherapy if with good response after systemic treatment.
High certainty of evidence, Strong recommendation

Key Findings

Efficacy Outcomes

For efficacy outcomes, such as OS, PFS, local control, one meta-analysis comparing four chemotherapeutic regimens namely bleomycin plus cisplatin plus 5-fluorouracil (FP), gemcitabine plus cisplatin (GP), paclitaxel plus cisplatin (TP) and triplet combination regimen (TCP) [186] and one newer RCT [187] investigating GP, FP, TP and the two TCPs, such as paclitaxel plus cisplatin plus 5-fluorouracil (TPF), and bleomycin plus cisplatin plus 5-fluorouracil (BPF) were found. In the meta-analysis, of the four regimens, the triplet combination regimen demonstrated the best short-term efficacy with objective response rate (0.74, 95% CI 0.62 to 0.87), disease control rate (0.91, 95% CI, 0.87 to 0.95), and 6-month progression-free survival (0.83, 95% CI, 0.75 to 0.91).[186] However, when compared with those who received the TP regimen, the 1-year OS rate among patients with metastatic NPC who received the triplet combination seemed slightly lower (79% vs. 74%). [186] In one recent RCT (n = 822) among adult patients with histological confirmation of WHO type II (non-keratinising carcinoma) or WHO type III (undifferentiated carcinoma) NPC with radiologically-confirmed distant metastasis, statistically significant higher response rates in GP (71.1%) and TPF (74%) regimens compared to PF regimen (60%) were recorded.[187] However, it was noted that the overall survival rates, median PFS, and median OS were similar among the five groups.[187]

Safety Outcomes

Two clinical trials compared the safety profile of different chemotherapeutic regimens for metastatic NPC.[187,188] One RCT concluded that GP had a better safety profile and compliance rate than FP.[188] The drug-related adverse events was 3% (6/180 patients) in the GP group versus 8% (14/173) in the FP group. More patients in the FP group had muscosal inflammation (59/173 vs. 2/180) and decreased appetite (61/173 vs. 40/180) than the GP group. Overall treatment-related adverse events, such as hematological and non-hematological toxic events, were similar between the two groups. Another trial concluded that despite being the most efficacious, TCPs is the most toxic chemotherapeutic regimen. [187] In the TPF group (n = 154), NPC patients with distant metastatic lesions had grade 3/4 neutropenia and related infections, nausea or vomiting, thrombocytopenia, neuropathy, allergic reactions, and treatment-related mortalities (3%). Group

using BPF regimen, on the other hand, exhibited grade 3/4 oropharyngeal mucositis, allergic reactions, and pulmonary fibrosis, apart from grade 3/4 neutropenia and nausea or vomiting.

Two clinical trials evaluated the utility of adding radiotherapy to chemotherapy as first line treatment for mNPC.[189,190] However, only one documented that radiotherapy caused grade 3 toxicities and deemed it a relatively safe addition for mNPC patients with good performance status.[190]

Two RCTs and one clinical trial compared overall survival using different regimens in platinum pretreated mNPC. The RCTs found that pembrolizumab[191] and toripalimab [192] had manageable safety profiles compared to the chemotherapeutic regimen. Treatment-related adverse events of grade 3 to 5 occurred in 12 of 116 participants (10.3%) receiving pembrolizumab and 49 of 112 participants (43.8%) receiving chemotherapy. There were three treatment-related deaths: one with pembrolizumab (pneumonitis) and two with chemotherapy (pneumonia and cerebral hemorrhage).[191] Meanwhile, the incidence of grade 3 adverse events (AEs) (89.0 versus 89.5%), AEs leading to toripalimab/placebo discontinuation (7.5 versus 4.9%), and fatal AEs (2.7 versus 2.8%) were comparable between the two arms; however, immune-related AEs (39.7 versus 18.9%) and grade 3 irAEs (7.5 versus 0.7%) were higher in the toripalimab arm.

Following the failure of cisplatin-based chemotherapy, capecitabine in combination with nedaplatin provides a tolerable safety profile for patients with recurrent and metastatic nasopharyngeal cancer (n =48).[193] Neutropenia (8.4%), anemia (2.1%), diarrhea (4.2%), stomatitis (6.3%), and hand-foot syndrome (HFS) (4.2%) were among the grade 3/4 toxicities reported in this study. [193]

Certainty of Evidence

Reviewed studies have a high certainty of evidence since study designs included were meta-analysis and RCTs.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
ESMO-EURACAN Clinical Practice Guidelines (accessed on June 22, 2023)	In metastatic NPC, palliative chemotherapy should be considered for patients with adequate performance status. A treatment combination of cisplatin and gemcitabine is the first line choice and improves overall survival (I,A) In patients with newly diagnosed metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and ultimately overall survival (II, A)	Strong
United Kingdom National Multidisciplinary	Palliative chemotherapy is the central component of the treatment for metastatic disease	mentioned in evidence summary

Guidelines (accessed on June 22, 2023)		
NCCN Guidelines Version 1.2023 (accessed on June 22, 2023)	For oligometastatic disease: Induction chemotherapy followed by RT or cisplatin/RT (PS 0-1) Concurrent cisplatin and RT (PS 0-1) Systemic therapy (PS 0-2) Widely metastatic with good PS (0-2): systemic therapy. If with good or near clinical response, consider definitive RT to primary and regional lymph nodes and to oligometastates or continued systemic therapy. Wide metastatic with poor PS (3-4): best supportive care	Strong
Pan-Asian adaptation of the EHNS-ESMO-ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck	Pembrolizumab in combination with platinum/5-FU and pembrolizumab monotherapy are two approved regimens for patients with recurrent or metastatic squamous cell cancer in the head and neck (SCCHN) expressing PD-L1 (I, A) Platinum/5-FU/cetuximab remains the standard therapy for patients with recurrent or metastatic SCCHN not expressing PD-La (I,A) Nivolumab is both PDA and EMA approved for recurrent or metastatic patients who progress within 6 months of platinum therapy (I, A)	Strong

Remarks

There was no opposition to these recommendations. However, the panel expressed a need for further elucidation regarding the definition of best supportive care and additional information pertaining to oligometastasis, oligoprogression, and oligorecurrence.

3.4.3. Follow-up Care

10. What is/are the recommended follow-up strategy for patients who have completed treatment for NPC?

10.1. We recommend the following follow up schedule:
- Every 1 to 3 months for year 1
- Every 2 to 6 months for year 2
- Every 4-12 months for years 3 to 5
- Annually thereafter

High certainty of evidence, Strong recommendation

10.2. We recommend the following tests during follow-up:
- History and physical examination
- Nasopharyngoscopy
- MRI with contrast of the NP and neck and/or CT scan with contrast of the NP and neck should be done 10-12 weeks after completion of radiotherapy. MRI with DWI (if available) may be done at 4 weeks postradiotherapy.
- FDG PET/CT scan may be done at least 12 weeks after completion of treatment if there is need to restage.
- Baseline post treatment audiogram
- TSH should be requested every 6-12 months.
- Pituitary function must be evaluated periodically for those with signs of symptom.
- Refer to supportive care and rehabilitation services, such as
    a. Speech and swallowing evaluation and rehabilitation
    b. Nutritional evaluation and rehabilitation
    c. Ongoing surveillance for depression
    d. Smoking cessation and alcohol counselling
    e. Lymphedema evaluation and rehabilitation

High certainty of evidence, Strong recommendation

Key Findings

The NCCN guideline has a strong recommendation regarding the follow-up schedule while the ESMO-EURACAN CPG has a strong recommendation regarding the tests during follow-up.

Other reviewed studies in this summary included two retrospective analyses which observed previously diagnosed patients who responded to definitive treatment, and characterized recurrence rates, time, location, and stage.

One retrospective study in China showed that 9.3% (60/645) of patients with untreated, nondistant metastatic, and histologically confirmed NPC had recurrence, and 81.7% (49/60) of them occurred during the first three years of treatment.[194] One hundred thirteen (17.5%) had distant metastasis 5 years after treatment. In the 113 patients with metastasis, the size of the cervical lymph node, size, and the time of residual cervical lymph node complete response were found to be independent prognostic factors for distant metastasis-free survival ($P < 0.05$). The metastases were diagnosed using imaging results (CT, PET, or MRI) and pathological confirmation. The patients' follow-up evaluations occurred every 3 months during the first 3 years and every 6 months thereafter.

Another retrospective analysis that aimed to describe the clinical characteristics of patients who had relapse after conventional irradiation for NPC recorded that NPC patients (n = 351) had a median recurrence time of 26 months, wherein recurrent interval time less than or equal to 6 months, 7 months to 12 months, 13 months to 18 months, and 19 months to 24 months accounted for 6.0% (21/351), 17.4% (61/351), 11.4% (40/351), and 13.3%, respectively.[195] The majority of cases were confirmed through the use of a biopsy. Only cases with recurrence in areas that are difficult to access, such as the skull base, cavernous sinus, and intracranial area, were diagnosed based on radiologic features. To determine the relapse, patients were seen in follow-up 1 month postradiation, and then every 3 months in 3 years, and every 1 year thereafter. During every follow-up visit, disease status and treatment toxicity were assessed. Routine tests include complete physical and fiberoptic nasopharyngoscopy, indirect nasopharyngeal speculum examinations, biochemistry profiles, chest radiography, abdominal ultrasonography, and contrast-enhanced CT or MRI of the nasopharynx and cervical region. Further tests were requested as needed.[195]

None of the studies evaluated safety outcomes.

Certainty of Evidence

The recommendations were based on the clinical practice guidelines that were reviewed and contained strong recommendations. Incorporated studies on recurrence among patients with NPC were graded with moderate certainty.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
NCCN Guidelines Version 1.2023 (accessed on June 27, 2023)	History and physical exam (including a complete head and neck exam and mirror and fiberoptic examination): done during Year 1, every 1–3 months in Year 2, every 2–6 months in Years 3–5, every 4–8 months if >5 years, every 12 months thereafter	Strong

Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up (accessed on June 27, 2023)	Further follow-up for patients includes periodic (every 3 months in the first year, every 6 months in the second and third year, and annually thereafter for the first 5 years) examination of the nasopharynx and neck, cranial nerve function, and evaluation of systemic complaints to identify distant metastasis [V, B]. For T2-T4 tumors, MRI might be used on a 6-monthly basis to evaluate the nasopharynx and the base of the skull, at least for the first 3 years after treatment [V, B]. PET imaging may be used in cases of equivocal imaging results. Plasma EBV DNA is a promising marker for the diagnosis of recurrence [II, B] and should be evaluated at least every year [V, B]. In patients who have received RT to the neck, it is recommended to do so annually; pituitary function should also be evaluated periodically or in cases of signs and/or symptoms [V, B].	Strong
Pan-Asian adaptation of the EHNS-ESMO-ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck (accessed on June 27, 2023)	4a. Clinical follow-up, including head and neck examination by flexible endoscopy, should be carried out every 2-3 months during the first 2 years, every 6 months for years 3-5 and annually thereafter [III, A]. 4b. Imaging should be carried out if symptoms occur or in cases of abnormalities found at the clinical examination [III, A]. 4c. FDG-PET/CT is recommended 3 months after CRT for patients with node-positive disease to assess the necessity of neck dissection [I, A].	Strong

Remarks

No issues were raised during the discussion of recommendation statement 10.1. Recommendation statement 10.2 received unanimous approval after the suggestion of adding an audiogram, which was included in the pretreatment evaluation.

All of the evaluations on the list are recommended to be performed during the follow-up phase. In low-resource settings, a CT scan may serve as a viable alternative to MRI in cases where the latter is not accessible. If available, MRI with diffusion-weighted imaging is preferred at four weeks postradiotherapy due to its efficiency. During the follow-up period, it is important for the panel of stakeholders to monitor various aspects such as speech and swallowing function, nutrition status, mental health status, lymphedema, and lifestyle. These factors require referral to the appropriate services.

3.4.4. Treatment of Recurrent Disease

11. What diagnostic test/s are necessary to evaluate patients in the residual, persistent, or recurrent setting?

11.1. We recommend repeat biopsy for patients suspected to have recurrent disease (for either local or regional) for confirmation.

High certainty of evidence, Strong recommendation

11.2 We recommend complete recurrent TNM staging workup be done (see Recommendation 4).

High certainty of evidence, Strong recommendation

Recurrent disease refers to the occurrence of new lesions following a period of being free from the disease. This is distinct from 'residual disease,' which refers to the persistence of tumor despite treatment. Recurrent nasopharyngeal cancer may manifest in 15-58% of NPC cases. The recurrence of nasopharyngeal carcinoma indicates treatment failure and its detection can be challenging due to treatment-induced changes.[196]

Key Findings

Insufficient literature exists regarding the recommended diagnostic tests for patients suspected of having a recurrence of NPC. The majority of the literature discusses the tests used for monitoring and treatment options for the recurrent disease. [197,198]

According to a research paper, the gold standard for diagnosing the condition is to perform a biopsy on the new lesion.[199] Additionally, it is imperative to assess the resectability of the recurrence, as this will dictate the optimal course of treatment for the patient. The work-ups mentioned in the previous recommendation (i.e., MRI, CT, or FDG PET-CT) for assessing the tumor stage can be utilized to determine resectability.

Among the literature reviewed, there is no specific mention of diagnostic tests that are recommended for patients suspected of having a recurrence of NPC. Evidence stated that confirmation by biopsy is the gold standard for a diagnosis of recurrent NPC. The majority of the literature mentions recurrences that were detected either through rigid and/or fieroptic endoscopy or PETCT, CT, or MRI as part of the patient's surveillance, and therefore discusses more on the treatment options for recurrent NPCA.

Studies obtained have stated that FDG PET/CT scans are the best modality for detecting residual or recurrent disease, especially distant metastases. MRI also provides great accuracy, more

specifically in assessing local recurrences. These tests are important in determining the patient's stage.

The United Kingdom Multidisciplinary Guidelines for Nasopharyngeal Carcinoma recommend that a multislice CT scan of the head, neck, and chest be carried out in all patients and an MRI scan whenever possible, especially in advanced cases with suspected recurrence. However, there was no discussion on the selected tests.

There is no mention of diagnostics in the ESMO-EURACAN Clinical Guidelines, but it is mentioned that a definitive diagnosis is made by endoscopic guided biopsy of the nasopharyngeal tumor, with MRI being more accurate than CT scans and FDG-PET for more locally and distantly advanced disease.

The NCCN guidelines for nasopharyngeal carcinoma do not specify what diagnostic tests are recommended for suspected cases of recurrent NPCA; however, they establish the need to determine the resectability of a recurrent tumor in order to appropriately plan its treatment. It can be deduced that the patient should undergo the necessary tests recommended for staging as discussed in the diagnosis of NPCA to assess the resectability status of the tumor, which includes a biopsy of the primary site or FNA of the neck, an MRI, and a metastatic workup, either a PET-CT scan or a chest CT scan with contrast.

Certainty of Evidence

The selected literature exhibited a high certainty of evidence, as the recommendations were derived from reviews, systematic reviews, meta-analyses, or well-established clinical practice guidelines from Europe and the United States.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
United Kingdom National Multidisciplinary Guidelines Released on 2016	Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan whenever possible, especially in advanced cases with suspected recurrence	No discussion associated with this recommendation No mention on the level of evidence and strength of recommendation
ESMO-EURACAN Clinical Practice Guidelines Released on December 25, 2020	MRI is the most accurate way of defining local and nodal tumor staging and it should be preferred whenever avail- able and according to the centre's expertise. FDG-PET adds further accuracy in nodal staging, is the best imaging method for detecting distant metastases and is recommended at least in locally advanced disease.	III, B III, B
NCCN Guidelines Ver 2.2023	No specific recommendation	II, A

May 15, 2023	For advanced Head and Neck Cancer, which includes Recurrent Disease, determination of resectability is warranted	

Remarks

Both statements garnered unanimous approval from the panelists. The following warranted clarification from the panelists: (1) type of biopsy for patients suspected to have recurrent disease; (2) aspects of recurrent TNM staging. A core-needle biopsy can be done among patients with suspected recurrence. After the biopsy, further tests are done to complete the TNM staging workup of locoregional recurrence.

12. What is/are the management option/s for patients with locoregional recurrence of NPC?

For patients with resectable disease:

12.1.1. We recommend nasopharyngectomy be considered for highly selected patients, including but not limited to: (a) rT1, early rT2 (with minimal parapharyngeal extension); (b) select rT3 (i.e. involvement of the floor of the sphenoid); and (c) minimal skull base extension.

Moderate certainty of evidence, Strong recommendation

12.1.2. We recommend salvage neck dissection for patients with resectable regional recurrence.

High certainty of evidence, Strong recommendation

12.1.3. We recommend adjuvant reirradiation for patients with positive or close margins (≤ 2mm) to either local or regional site of recurrence.

Moderate certainty of evidence, Strong recommendation

12.1.4 We recommend concurrent chemotherapy with reirradiation for eligible patients.

Moderate certainty of evidence, Strong recommendation

12.1.5. We recommend salvage reirradiation for patients not amenable for surgical option.

Moderate certainty of evidence, Strong recommendation

For patients with unresectable disease and/or inoperable tumor recurrence:

12.2.1. We recommend salvage reirradiation, preferably with concurrent chemotherapy.

Moderate certainty of evidence, Strong recommendation

12.2.2. We recommend systemic therapy for patients not amenable to any local therapy.

Moderate certainty of evidence, Strong recommendation

Management of recurrent nasopharyngeal cancer can be challenging, with complex problems related to the radiation doses to various organs at risk, the primary course of treatment, individual intrinsic radiobiologic characteristics, and the extent and location of the recurrent tumor. Currently, management varies from one center to another; hence, international guidelines have been published to guide the management of locoregional recurrence.

Key Findings

All four CPGs recommended similar treatments for different scenarios.[14,131,180,200] Long-term survival can be achieved in patients with locoregionally recurrent nasopharyngeal carcinoma through the utilization of local therapies, including surgery and/or radiation therapy. Clinical investigation is currently being conducted on the addition of chemotherapy, immunotherapy, and new agents.

For patients with isolated regional failure, surgery is the standard approach. Selective neck dissection has similar OS, DFS, and regional recurrence-free survival compared to radical neck dissection. However, selective neck dissection has the advantage of decreasing postoperative morbidity.

The vast majority of patients with locoregionally recurrent NPC have previously received RT as part of therapy for their primary tumor; thus, surgery is the preferred salvage modality with the goal of achieving negative margins.

Nasopharyngectomy can be done by either an open or endoscopic approach, but regardless of the technique, essential components of an ideal surgical approach include adequate tumor visualization, complete surgical resection of negative margins, and the ability to identify and protect critical neurovascular structures, all while preserving a high degree of cosmesis and function. It is definitely anatomically challenging to perform such a procedure; hence, surgical expertise is a serious consideration.

Patient selection is the most important factor when planning surgery, and the surgeon must consider a variety of patient and disease factors. Generally speaking, most rT1, rT2, and some rT3 patients can be considered for nasopharyngectomy. Surgery is also preferred for small recurrent tumors, as this improves survival and decreases long-term toxicity.

Adjuvant chemotherapy and/or RT (including conventional RT, brachytherapy, radiosurgery, and concurrent chemoradiation) are sometimes used following surgical salvage. Patients who received adjuvant treatment had better outcomes, and that is significant for patients with stage III or IV disease at recurrence, and there are cases where patients had positive or close margins post-operation. The need for adjuvant irradiation after salvage nasopharyngectomy should be taken on a case-by-case basis, bearing in mind that adjuvant RT should not be taken as a replacement for careful case selection of eligible surgical candidates.

For most patients with local recurrences, radiotherapy is the only option to offer another chance at a cure. Compared to primary RT treatment, which can lead to 5-year local control rates of 80% to >90%, re-irradiation, even with IMRT, may lead to considerably lower short-term local control and survival rates. The potential for long-term survival with reirradiation has been demonstrated for such carefully selected patients. The 5-year PFS with reRT is about 72%, and the OS is at 41%.

The role of chemotherapy in this setting remains to be defined, but despite the lack of concrete evidence, guidelines would consider adding a systemic treatment to patients with at least T3 or N+ disease. In theory, this would help the eradication of micrometastasis and, if given in a concurrent setting, could potentiate RT's efficacy. Induction with or without concurrent chemotherapy is preferred. Induction in this setting is a good approach, especially if the recurrence occurs within 12 months.

In summary, for patients with resectable disease:

1. Nasopharyngectomy may be considered for highly selected patients, including but not limited to: (a) rT1, early rT2 (with minimal parapharyngeal extension); (b) select rT3 (i.e., involvement of the floor of the sphenoid); and (c) minimal skull base extension.
2. Salvage neck dissection should be considered for patients with resectable regional recurrence.
3. Adjuvant reirradiation is recommended for patients with positive or close margins (≤2mm) to either the local or regional site of recurrence.
4. Concurrent chemotherapy with reirradiation is recommended for eligible patients.
5. Salvage reirradiation may be considered for patients not amenable to a surgical option.
6. For patients with unresectable and/or inoperable tumor recurrence:
7. We recommend salvage reirradiation, preferably with concurrent chemotherapy.
8. Systemic therapy may be considered for patients who are not amenable to any local therapy.

Safety outcomes

Given that this is a recurrent setting, side effects are expected to be greater, and extra caution should be exercised when doing reirradiation.

Reirradiation is associated with significant acute and late toxicities since the RT dose that can be delivered safely is limited by previous RT treatments and the tolerance of normal tissues. Grade 3 to 4 late toxicity rates range between at least 5-20% and consist of temporal lobe necrosis, cranial nerve palsies, hearing loss, endocrine abnormalities, palatal fibrosis, trismus, chronic pain, and osteoradionecrosis. Lethal (grade 5) late complication rates with standard fractionation are as high as 30 to 40 percent in some studies and include nasopharyngeal necrosis and hemorrhage. Such reirradiation-related toxicities can counteract treatment benefits, demonstrating the need for more effective, safer radiation treatment schedules.

Certainty of Evidence

All four CPGs have similar recommendations for the management of recurrent nasopharyngeal cancer. Some CPGs have elaborated on their treatment recommendations. Most of the recommendations are based on retrospective data, institutional experiences, and the expert opinions of specialists in the field. There are limited randomized controlled trials in recurrent NPC to guide treatment decision-making; hence, multidisciplinary review is mandatory to select the treatment option with the best possible therapeutic ratio. Although there are limited studies in this setting, all four CPGs have similar recommendations; with this, the certainty of the evidence of the recommendations is moderate to high.

Remarks

There was no disagreement from the panelists for all the statements and strength of the recommendations. Comments were focused on the definition of 'close margins' and salvage reirradiation. In contrast to the close margins in other subsites, NPC patients with recurrent disease have narrower margins with increased therapeutic advantage. Radiation oncologists suggested that re-irradiation should not be done if the most recent radiation was performed less than a month ago. Salvage reirradiation using either the standard fractionated RT or stereotactic techniques was added to broaden the range of treatment options for patients who are not amenable for surgical intervention.

13.What are the management options for patients with distant failure?

13.1. We recommend systemic therapy for patients with distant metastatic disease.

High certainty of evidence, Strong recommendation

13.2. We recommend consideration of local therapy to the metastatic site for patients with oligometastatic disease.

Moderate certainty of evidence, Strong recommendation

Key Findings

Six out of the nine studies, which included RCTs and meta-analyses, support the utility and safety of platinum-based chemotherapy for distant failure. Two descriptive studies and one clinical trial showed that survival is better if radiation therapy is also given to the metastatic sites, provided that the patient has a good performance status.

One RCT[188] and one meta-analysis[186] compared different chemotherapeutic regimens for recurrent and metastatic NPCA. One RCT compared gemcitabine plus cisplatin (GP) and 5-fluorouracil plus cisplatin (FP) as first line treatment.[188] The median progression-free survival was 7 months in the GP group and 5.6 months in the FP group (HR 0.55, 95% CI 0.44 to 0.68).[188] The

meta-analysis compared four chemotherapeutic regimens namely FP, GP, taxanes plus cisplatin (TP) and triplet combination regimen (TCP).[186] Of the four regimens in this meta-analysis, the triplet combination regimen demonstrated the best short-term efficacy with objective response rate (0.74, 95% CI 0.62 to 0.87), disease control rate (0.91, 95% CI, 0.87 to 0.95), and 6-month progression-free survival (0.83, 95% CI, 0.75 to 0.91).[186] However, when compared with those who received the TP regimen, the 1-year OS rate among patients with metastatic NPC who received the triplet combination seemed slightly lower (79% vs. 74%).[186]

Two RCTs and one clinical trial compared overall survival using different regimens in platinum pretreated mNPC. The two RCTs evaluated monoclonal antibodies pembrolizumab[191] and toripalimab [192] while the clinical trial assessed a second line chemotherapeutic regimen[193] with capecitabine and nedaplatin. The trial on pembrolizumab and chemotherapy, the median OS was 17.2 months (95% CI 11.7 to 22.9 months) with pembrolizumab and 15.3 months (95% CI 10.9 to 18.1 months) with chemotherapy (HR 0.90, 95% CI 0.67 to 1.19). In the trial on toripalimab, there were two complete response (4.2%), 18 partial responses 37.5%) giving an overall response rate of 41.7% (95% CI 27.7 to 55.8). The median time to progression was 5.8 months (95% CI 3.9 to 7.8 months) and median overall survival was 12.4 months (95% CI 9.6 to 16.8 months). The third trial shows that addition of toripalimab to GP chemotherapy as a first-line treatment for patients with recurrent metastasis NPC provided superior outcomes in terms of progression-free survival compared to GP alone (HR 0.52, 95% CI 0.36 to 0.74).

Two descriptive studies[201,202] and one clinical trial[203] evaluated the utility of multimodality treatment for distant failures. One descriptive study [201] compared the overall survival (OS) of patients who received first line chemotherapy, combined chemo radiation, and first and second line chemotherapy. It shows that among patients with distant metastases generally who initiated first-line systemic therapy, the median OS was 28 months (95% CI 44.9 to 62.3). Median OS for patients with distant metastatic disease who received systemic therapy only was 23.0 months (95% CI: 18.0–32.0) and 2-year survival was 49.4% (95% CI: 39.1–59.8). In contrast, median OS was 32.0 months.[201] The other descriptive study[202] compared the OS of patients who received radiation therapy to distant metastases in addition to systemic chemotherapy, and those who did not. The clinical trial[203] evaluated the OS of patients with distant failure who underwent best supportive care, chemotherapy and multimodality treatment.

Safety Outcomes

Between the two platinum-based chemotherapeutic regimens, GP had a better safety profile and compliance rate than FP.[188] The drug-related adverse events was 3% (6/180 patients) in the GP group versus 8% (14/173) in the FP group. More patients in the FP group had muscosal inflammation (59/173 vs. 2/180) and decreased appetite (61/173 vs. 40/180) than the GP group. However, the overall treatment-related adverse events, such as hematological and non-hematological toxic events, were similar between the two groups.

Two RCTs and one clinical trial compared overall survival using different regimens in platinum pretreated metastatic NPC. The RCTs found that pembrolizumab[191] and toripalimab [192] had manageable safety profiles compared to the chemotherapeutic regimen. Treatment-related

adverse events of grade 3 to 5 occurred in 12 of 116 participants (10.3%) receiving pembrolizumab and 49 of 112 participants (43.8%) receiving chemotherapy. There were three treatment-related deaths: one with pembrolizumab (pneumonitis) and two with chemotherapy (pneumonia and cerebral hemorrhage).[191] Meanwhile, the incidence of grade 3 adverse events (AEs) (89.0 versus 89.5%), AEs leading to toripalimab/placebo discontinuation (7.5 versus 4.9%), and fatal AEs (2.7 versus 2.8%) were comparable between the two arms; however, immune-related AEs (39.7 versus 18.9%) and grade 3 irAEs (7.5 versus 0.7%) were higher in the toripalimab arm.

Following the failure of cisplatin-based chemotherapy, capecitabine in combination with nedaplatin provides a tolerable safety profile for patients with recurrent and metastatic nasopharyngeal cancer (n = 48).[193] Neutropenia (8.4%), anemia (2.1%), diarrhea (4.2%), stomatitis (6.3%), and hand-foot syndrome (HFS) (4.2%) were among the grade 3/4 toxicities reported in this study. [193]

Certainty of Evidence

The utility and safety of platinum-based chemotherapy for distant failure have been thoroughly examined through a review of studies. The evidence supporting these findings is of high certainty, as the studies primarily consisted of randomized controlled trials and meta-analyses. However, the existing body of research on multimodality treatment primarily comprises descriptive studies.

Recommendation of Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
ESMO-EURACAN Clinical Practice Guidelines (accessed on June 22, 2023)	In metastatic NPC, palliative chemotherapy should be considered for patients with adequate performance status. A treatment combination of cisplatin and gemcitabine is the first line choice and improves overall survival (I,A) In patients with newly diagnosed metastatic NPC, the addition of locoregional RT to systemic therapy improves locoregional control and ultimately overall survival (II, A)	Strong
United Kingdom National Multidisciplinary Guidelines (accessed on June 22, 2023)	Palliative chemotherapy is the central component of the treatment for metastatic disease	mentioned in evidence summary
NCCN Guidelines Version 1.2023 (accessed on June 22, 2023)	For oligometastatic disease: Induction chemotherapy followed by RT or cisplatin/RT (PS 0-1) Concurrent cisplatin and RT (PS 0-1) Systemic therapy (PS 0-2) Widely metastatic with good PS (0-2): systemic therapy. If with good or near clinical response,	Strong

	consider definitive RT to primary and regional lymph nodes and to oligometastates or continued systemic therapy. Wide metastatic with poor PS (3-4): best supportive care	
Pan-Asian adaptation of the EHNS-ESMO-ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck	Pembrolizumab in combination with platinum/5-FU and pembrolizumab monotherapy are two approved regimens for patients with recurrent or metastatic squamous cell cancer in the head and neck (SCCHN) expressing PD-L1 (I, A) Platinum/5-FU/cetuximab remains the standard therapy for patients with recurrent or metastatic SCCHN not expressing PD-La (I,A) Nivolumab is both PDA and EMA approved for recurrent or metastatic patients who progress within 6 months of platinum therapy (I, A)	Strong

Remarks

Apart from the initial sequence of presenting these recommendations, there was no disagreement from the panelists for both statements. In general, systemic therapy is given to patients with distant metastatic disease regardless of the spread. It was clarified by the oncologists in the panel that systemic therapy can still be given to patients with oligometastatic disease who received local therapy.

CHAPTER 4.

FACILITATORS AND BARRIERS TO THE APPLICABILITY AND RESEARCH GAPS OF THIS GUIDELINE

Research Gaps

During the process of searching for available evidence and discussing recommendations, certain gaps in research were identified. Clinical decision-making relies on well-conducted and reproduced randomized controlled trials. Unfortunately, although based on high-certainty guidelines, individual supporting data for diagnostic and surgical procedures (e.g., reconstruction procedures, local data on frozen sections) may be low-certainty due to a lack of direct comparative studies to determine the superior type of procedures. No comparative studies were identified regarding the use of rigid versus flexible endoscopy and the administration of local versus general anesthesia in nasopharyngoscopy. A comparison was made between the diagnostic accuracy of NBI and WL modes of endoscopy. However, no studies investigating the feasibility or cost-effectiveness of these modes were identified. Furthermore, a lack of studies exists pertaining to the documentation of complications associated with the procedures of endoscopy and endoscopic-guided biopsy of nasopharyngeal masses.

Insufficient evidence was also found for advanced techniques of radiation therapy (e.g., IMRT, helical tomotherapy, and VMAT); hence, it was not included in the recommendation statement. The evidence supporting the use of induction chemotherapy followed by chemoradiotherapy for T3N0 NPC disease is comparatively weaker than for other subsets of locally advanced NPC (Stages III–IV). Trials conducted during the era of intensity-modulated radiation therapy (IMRT) have provided evidence suggesting that the addition of concurrent chemotherapy to radiotherapy may not yield significant benefits and could potentially lead to increased toxicities. However, the majority of the revised guidelines recommend the utilization of a concurrent chemoradiotherapy approach as a minimum. In cases where there are high-risk characteristics like a large tumor volume and a high serum EBV DNA copy number, the other guidelines recommend the inclusion of induction or adjuvant chemotherapy in addition to CCRT.

No direct study testing on the surveillance schedule of head and neck cancer, or specifically NPC patients, was found. Recommendations were based on previous guideline recommendations and studies documenting recurrence rates and time in patient groups. Research gaps include the following: 1) number of tertiary institutions with MRI, CT, and PET CT capability for recurrence workup; 2) compliance rate of NPC patients with the follow-up regimen; and 3) barriers to compliance with the follow-up regimen.

The generalizability of results, particularly among patients with distant failure metastases, can be challenging due to the inclusion of those newly diagnosed in the population of studies for the clinical question of metastatic NPC. Studies evaluating the effectiveness of the chemotherapy regimen in this population are limited. Moreover, treatment modalities need to be stratified based on the extent and location of metastasis. Lastly, RCTs on multimodality treatment can also provide robust evidence for its use.

Research pertaining to the prevalence of the disease per site, disease presentation, identification of diagnostic and treatment resources, assessment of workforce requirements, cost-benefit

analysis, patient perspectives, and treatment outcomes for head and neck cancers can provide valuable insights to facilitate the future decision-making process of relevant stakeholders.

The aforementioned research endeavors would aid in the provision of comprehensive healthcare services for patients with head and neck cancer in the country.

Applicability Issues and Resource Implications

In the process of developing this clinical practice guideline, the TWG searched for evidence that showed improvement in outcomes and, if possible, was regarded as applicable in the local setting. Considerations regarding the applicability of diagnostic tests and therapeutic options were also raised during the consensus panel meeting. However, for the recommendations to be applicable in the local setting, barriers to implementation should be identified and addressed, while facilitators need to be recognized and utilized.

The availability of the recommended diagnostic tools, skilled medical personnel, services, and infrastructure would probably differ at the regional, provincial, or maybe even at the municipal/city level. These issues were especially relevant to recommendations on referral to head and neck cancer specialists, utilization of certain evaluation procedures (e.g., PET/CT, flexible laryngoscopy), and treatment (e.g., flap reconstructions, use of a voice prosthesis) to improve patient outcomes.

The cost of diagnostic tests and interventions for head and neck cancers was also an important consideration during the panel discussion and brought up by the stakeholders. Certain statements, such as those on the use of PET/CT and referral to a higher level of care, nevertheless warranted strong recommendations due to the perceived significant benefit to the patient and trust in the government to pay attention to the provision of needed services and infrastructure and coverage of national health insurance. As low-middle-income country, it is imperative to allocate and utilize our limited resources in an efficient manner. Health technology assessment should be a vital safeguarding approach to guarantee that all disbursements made by government via PhilHealth are economically viable.

A major factor that can help facilitate the implementation and dissemination of this CPG is the involvement of representatives belonging to organizations involved in head and neck cancer management in the TWG and the CP. They occupy lead roles within their respective organizations as officers or fellows responsible for policymaking or as trainers in clinical programs that can utilize these clinical guidelines. These individuals are also known clinicians who are looked up to in their respective fields of specialization and can influence practice. The active participation of the patient survivor in the consensus panel, who shared his real experience during the discussion, also helped to improve the applicability of the recommendations. Another facilitating factor is the participation of the program manager of the NICCP, including palliative and hospice care, of the Department of Health in the consensus-building process.

Through close collaboration between the CPG developers and the DOH Cancer Control Division, the following steps to address barriers to full and effective implementation may be put in place:

Table 14. Steps in addressing barriers to CPG implementation

STEP	LEAD/RESPONSIBLE ORGANIZATION	TIMELINE
1. Systematic dissemination of the DOH National Head and Neck CPG to users and stakeholders	Various specialty organizations Training programs	First 6 months
2. Establishment of baseline knowledge and practice across the country and monitoring of impact of the CPG	Various specialty organizations Training programs	1st year
3. Establishment of an integrated national head and neck cancer database	DOH NICCP including palliative and hospice care and Thyroid Disorders	1st year
4. Translation of feedback from the CPG dissemination into policy, such as PHIC packages for head and neck cancer	DOH NICCP PHIC	2nd year
5. Fund allocation to implement certain aspects of the recommendation (make diagnostic procedures and treatment available)	DOH	2nd year

CHAPTER 5.

DISSEMINATION, MONITORING, EVALUATION, AND UPDATING OF THE GUIDELINE

Dissemination

The following channels are available for the dissemination of the guideline: (a) webinars and scientific fora run by the collaborating specialty organizations; (b) websites of the collaborating specialty organizations; (c) lay fora organized by specialty societies; (d) publication in a reputable scientific journal; (e) incorporation of key recommendations in medical curricula; (f) training; and (g) social media platforms.

The draft of the final recommendations was presented at the 78th Annual Clinical Congress on December 7, 2022. This conference was organized by the Philippine College of Surgeons and was attended by various medical professionals practicing nationwide.

The draft of this CPG was also presented in the webinar titled “National Clinical Practice Guidelines: Head Neck Cancer Diagnosis and Management” held by the Philippine College of Surgeons and the Philippine Society of General Surgeons Metro Manila Chapter via Zoom on August 26, 2023.

Implementation, Monitoring, and Evaluation

Once approved by the quality review panel of the NGC, a department order may be issued to introduce this CPG to the different DOH hospitals for implementation. Likewise, the various organizations that contributed to the development of the CPG may cascade and endorse the recommendations for implementation in their respective healthcare units and assess adherence at least annually.

The SC will be responsible for monitoring the implementation of the CPG and the compliance of the stakeholders. Part of the monitoring and evaluation activities will include a survey to determine (a) baseline knowledge and practices of target users, (b) feedback on the guideline recommendations, and (c) an assessment of applicability and feasibility. These surveys will be regularly performed to determine if there are any changes in the knowledge and practices of the target users.

Updating of the guidelines

This CPG will be updated every three years. The SC and TWG will do quarterly reviews of available evidence that may affect the initial recommendations stated in the guideline. If new, high-certainty evidence on thyroid cancer diagnosis and management becomes available before the scheduled update, the TWG will evaluate the evidence, and the SC may convene the CP if there is a need to issue amendments to the recommendations. Feedback from the target users of the CPG will also be reviewed annually to guide implementors and policymakers on matters pertaining to the CPG.

Table 15. Steps in the monitoring, evaluation, and updating of the guideline

PROCESS	RESPONSIBLE UNIT/ORGANIZATION	FREQUENCY	TIMELINE
1. Review of current evidence relevant to head and neck cancer management	SC and TWG	Quarterly	2023-2025
2. Review of feedback on the 2022 Heads and Neck cancer CPG by end users	SC	Annual	2023-2025
4. Amendment to the recommendations if new strong evidence becomes available	SC, TWG, and CP	N/A	2024-2026
5. Major update of the 2022 Heads and Neck cancer CPG based on recent evidence and feedback obtained using the questionnaire	SC, TWG, and CP DOH	N/A	2026-2027

CHAPTER 7.

AUTHORSHIP AND CONTRIBUTIONS

Authorship and Contributions

The Steering Committee coordinated among various society representatives and committees, and held *en banc* meetings. The SC was also in charge of overall organization and management and is accountable for the quality of the final CPG manuscript.

Dr. Ida Marie T. Lim, Dr. Cristina S. Nieves, Dr. Anna Maria B. Fineza-Dela Cruz, Dr. Lance Isidore G. Catedral, Dr. Joy Grace G. Jerusalem, and Dr. Arsenio Claro A. Cabungcal.

The Technical Coordinator of UP Manila-National Institutes of Health provided technical expertise throughout the CPG development process.

Dr. Rodney Dofitas

The Technical Working Group undertook the extensive technical work in searching for guidelines, presenting the draft recommendations to the Consensus Panel, and writing the evidence summaries.

Oral Cavity Cancer: *Dr. Alfred Phillip O. de Dios, Dr. Maria Cheryl L. Cucueco, Dr. Orlino C. Bisquera Jr., Dr. Jeanette Marie S. Matsuo, Dr. Kenneth G. Samala, Dr. Cesar Vincent L. Villafuerte III, and Dr. Daniel Jose C. Mendoza.*

Laryngeal Cancer: *Dr. Milabelle B. Lingan, Dr. Helen Bongalon-Amo, Dr. Christine Susean S. Sagpao, Dr. Joanmarie C. Balolong-Garcia, Dr. Adrian F. Fernando*

Nasopharyngeal Cancer: *Dr. JC Kennetth M. Jacinto, Dr. Christelle Anne M. Almanon, Dr. Ryan U. Chua, Dr. Michael Ray Sebastian, Dr. Marwin Emerson V. Matic and Dr. Christine Joy Arquiza.*

The Consensus Panel shared their knowledge, experience, and expertise to weigh the available evidence, patients' values and preferences, and other relevant issues such as best practices, accessibility, feasibility, and equity in the healthcare system of the country.

Dr. Christine Jew V. Baldovino, Dr. Solidad L. Balete, Dr. Francis Angelo D. Basilio, Dr. Humphrey C. Bitun, Dr. Clarito U. Cairo, Jr., *Dr. Joseph E. Cachuela, Dr. Johanna Patricia A. Cañal, Dr. Jose M. Carnate Jr, Dr. Ann Margaret V. Chang, Dr. Josephine Contreras-Tolentino, Ms. Carla Krishan A. Cuadro, Dr. Vivian P. Enriquez, Dr. Neresito T. Espiritu, Mr. Leo M. Flores, Dr. Peter Julian A. Francisco, Dr. Ana Patricia P. Villanueva-de Grano, Dr. Mark Philip C. Guinocor, Dr. Rainer Yu Lutanco, Ms. Aileen Matalog, Dr. Rowald Rey G. Malahito, Dr. Michael Benedict A. Mejia, Dr. Cherry Lyn V. Montealto, Ms. Rosalynn Pangan, Dr. Jocelyn C. Que, Dr. Elias T. Reala, Mr. Mark Gil de la Rosa, Dr. Neil Martin D. Sese, Dr. Ryan Rainier D. Siscar, Dr. Rowena Sudario-Lumague, Dr. Veronica T. Vera Cruz, and Dr. Gemma Leonora B. Uy.*

The guideline developers were also assisted by the following supportive members: *Dr. Alfred Phillip O. de Dios*, *Dr. Cristina S. Nieves, and Dr. Anna Maria B. Fineza-Dela Cruz* who moderated the discussion of the consensus panel members; *Dr. Ryner Carillo*, methodologist who provided expertise in evidence preparation of the TWG; and *Ms. Myzelle Anne Infantado-Alejandro* who collated the draft recommendations and drafted the full-text CPG manuscript

APPENDICES

APPENDIX A: CPG ACTIVITY PLAN

APPENDIX B: DECLARATION OF CONFLICTS OF INTEREST

Steering Committee

The SC members spearheaded the development of the CPG on head and neck cancer and finalized plans for updating it. They formed ERE and CP, developed and finalized the clinical questions which contains population, intervention, comparator, outcome (PICO) with the ERE and CP, coordinated meetings with CP, approved adaptation of existing CPGs to be used, if applicable, and development of *de novo* evidence summaries. Furthermore, they designated a technical writer and manage the writing and finalization of the CPG.

Table 1. Summary of COI disclosure of the SC members

Steering Committee	Affiliated Institution/s	Profession/ Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Ida Marie T. Lim*	• Jose R Reyes Memorial Medical Center • USTH, Department of Surgery and Clinical Epidemiology • Philippine College of Surgeons • PCS Cancer Commission • Philippine Society of General Surgeons • Philippine Academy of Head and Neck Society Inc. • Surgical Oncology Society of the Philippines	Chairperson, Surgeon (Head and Surgical Oncology Specialist), Research and Development Management	NCR	Nil
Dr. Cristina S. Nieves†	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil

	• Jose R. Reyes Memorial Medical Center • Ospital ng Makati			
Dr. Anna Maria B. Fineza-Dela Cruz†	• Philippine College of Radiology • Philippine Radiation Oncology Society • Jose R. Reyes Memorial Medical Center • De La Salle University Medical Center	Chairperson, Radiation Oncologist	NCR	Nil
Dr. Lance Isidore G. Catedral	• Philippine College of Physician • Philippine Society of Medical Oncology • General Santos Doctors Hospital Medical Suites	Medical Oncologist	General Santos City	Nil
Dr. Joy Grace G. Jerusalem	• Philippine College of Surgeons • Philippine Society of General Surgeons • University of Perpetual Help Rizal Medical Center	Chairperson, Committee on Research	NCR	Nil
Dr. Arsenio Claro A. Cabungcal	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Univ. of the Philippines-Philippine General Hospital	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil

*Project Lead, facilitator of CP meetings
†Facilitator of CP meetings

Technical Working Groups

The TWG drafted the recommendations based on their evidence reviewed from adopted clinical practice guidelines. They declared no conflict of interest.

Table 2. Summary of COI disclosure of the TWG for oral cavity cancer

Technical Working Group	Affiliated Institution/s	Profession/ Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Alfred Phillip O. de Dios*	• Philippine College of Surgeons, Philippine Society of General Surgeons • Philippine Academy of Head and Neck Surgery Inc. • Jose R. Reyes Memorial Medical Center Reyes • Manila Adventist Hospital	General Surgeon / Head and Neck Surgeon	NCR	Nil
Dr. Maria Cheryl L. Cucueco	• Philippine College of Surgeons • Philippine Society of General Surgeons • Gat Andres Bonifacio Memorial Medical Center • University of Santo Tomas Hospital	General Surgeon	NCR	Nil
Dr. Orlino C. Bisquera Jr.	• Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Surgical Oncology Society of the Philippines • Rizal Medical Center • Univ. of the Philippines-Philippine General Hospital	General Surgeon / Surgical Oncologist /Head and Neck Surgeon	NCR	Nil

Dr. Jeanette Marie S. Matsuo	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Univ. of the Philippines-Philippine General Hospital • Philippine Academy Head and Neck Surgery Inc.	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil
Dr. Kenneth G. Samala	• Philippine Society of Medical Oncologist • Jose R. Reyes Memorial Medical Center Reyes • Our Lady of Lourdes Hospital	Medical Oncologist	NCR	Nil
Dr. Cesar Vincent L. Villafuerte III	• Philippine Radiation Oncology Society • Univ. of the Philippines-Philippine General Hospital • Manila Doctors Hospital	Radiation Oncologist	NCR	Nil
Dr. Daniel Jose C. Mendoza	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Rizal Medical Center • Jose R. Reyes Memorial Medical Center	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil

*Head/Facilitator of Consensus Panel meetings

Table 3. Summary of COI disclosure of the TWG for laryngeal cancer

Technical Working Group	Affiliated Institution/s	Profession/ Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Milabelle B. Lingan	• Philippine Society of Otorhinolaryngology-Head and Surgery • Jose R. Reyes Memorial Medical Center • Our Lady of Caysasay Medical Center	Otorhinolaryngologist-Head and Neck Surgeon	NCR / Central Luzon	Nil
Dr. Helen B. Bongalon-Amo	• Philippine College of Surgeons • Philippine Society of General Surgeons • Surgical Oncology Society of the Philippines • Jose R. Reyes Memorial Medical Center Reyes • Our lady of Lourdes Hospital	General Surgeon/Surgical Oncologist	NCR	Nil
Dr. Christine Susean S. Sagpao	• Philippine Radiation Oncology Society • Univ. of the Philippines-Philippine General Hospital • Jose R. Reyes Memorial Medical Center • Univ. of the Philippines-Philippine General Hospital	Radiation Oncologist	NCR	Nil
Dr. Joanmarie C. Balolong-Garcia	• Philippine Society of Medical Oncology			

	• Jose R. Reyes Memorial Medical Center • St. Luke's Medical Center	Medical Oncologist	NCR	Nil
Dr. Adrian F. Fernando	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Philippine Academy of Head and Neck Surgeon Inc. • Amang Rodriguez Memorial Medical Center • University of the East - Ramon Magsaysay Memorial Medical Center	• Otorhinolaryngology-Head & Neck Surgery • Head & Neck Oncologic & Reconstructive Microsurgery	NCR	Speakership – Merck Philippines, on thyroid, head and neck cancer (2018-present); UAP, on ENT (2020); SV More, on Propolis (2022); Bayer, on Loratadine (2021)

*Head

Table 4. Summary of COI disclosure of the TWG for nasopharyngeal cancer

Technical Working Group	Affiliated Institution/s	Profession/ Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. JC Kennetth M. Jacinto	• Philippine Radiation Oncology Society • University of Santo Tomas Hospital • Elizabeth Hospital Inc.	Radiation Oncologist	NCR / General Santos	Nil
Dr. Christelle Anne M. Almanon	• Philippine Academy Head and Neck Surgery Inc. • Manila Medical Center • Jose B. Lingad Memorial General Hospital	General Surgeon	NCR / Central Luzon	Nil
Dr. Ryan U. Chua	• Philippine Society of Otorhinolaryngology-Head and Surgery • Jose R. Reyes Memorial Medical Center • University of Santo Tomas Hospital	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil
Dr. Marwin Emerson V. Matic	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • St. Frances Cabrini Hospital & Medical Center • Asian Hospital and Medical Center	General Surgeon, Head and Neck Surgeon	Southern Tagalog	Nil
Dr. Michael Ray C. Sebastian	• Philippine Society of Medical Oncology			

	• Jose R. Reyes Memorial Medical Center • Chinese General Hospital and Medical Center	Medical Oncologist	NCR	Nil
Dr. Christine Joy S. Arquiza	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Univ. of the Philippines-Philippine General Hospital • St. Luke's Global	Otorhinolaryngologist-Head and Neck Surgeon	NCR	Nil

*Head

Consensus Panel

The Consensus Panel members listed below all declared possible conflict of interest prior to voting. The Oversight Committee continuously reviewed the conflict-of-interest form and credentials of the voting panel throughout the formulation of recommendations.

Table 5. Summary of COI disclosure of the CP members for oral cavity cancer

Panel Member	Affiliated Institution/s	Profession/ Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Clarito U. Cairo, Jr.†	DOH	Cancer Program Manager	NCR	Nil
Dr. Rainer Y. Lutanco	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Surgical Oncology Society of the Philippines • Rizal Medical Center • Chinese General and Medical Center	General Surgeon / Head and Neck Surgeon	NCR	Nil
Dr. Neresito T. Espiritu	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Jose B. Lingad Memorial General Hospital • Univ. of the Philippines-Philippine General Hospital	General Surgeon / Surgical Oncologist	NCR / Central Luzon	Nil
Dr. Cherry Lyn V. Montealto	• Philippine College of Surgeons		Region VII	Nil

	• Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Cebu Institute of Medicine	General Surgeon / Head and Neck Oncologist		
Mr. Mark Gil Q. de la Rosa	• Philippine Society for Parenteral and Enteral Nutrition, Inc • Arellano University	Nurse	NCR	Nil
Ms. Rosalynn L. Pangan	• Philippine Society for Parenteral and Enteral Nutrition, Inc • St. Luke's Medical Center	Pharmacist	NCR	Nil
Dr. Johanna Patricia A. Cañal	• Philippine Radiation Oncology Society • UP-PGH Dept of Radiology • Asian Hospital and Medical Center	Radiation Oncologist	NCR	Nil
Dr. Ana Patricia P. Villanueva-de Grano	• Philippine Association of Plastic, Reconstructive, and Aesthetic Surgeons • Mariano Marcos Memorial Hospital and Medical Center	Plastic and Reconstructive Surgeon	Ilocos Region	Nil
Ms. Aileen F. Matalog	• Philippine Association of Speech - Language Pathologists • V. Luna Medical Center • St. Luke's Global	SLP/Swallowing Rehabilitation Specialist	NCR	Nil
Dr. Jose M. Carnate Jr.	• Philippine Society of Pathologist • UP College of Medicine, Dept of pathology • The Medical City	Pathologist	NCR	Nil

Dr. Solidad L. Balete	• Philippine Society of Medical Oncology • Jose R. Reyes Memorial Medical Center	Medical Oncologist	NCR	Nil
Dr. Ryan Rainier D. Siscar	• Philippine Dental Association • Jose R. Reyes Memorial Medical Center	Dentist	NCR	Nil
Dr. Veronica T. Vera Cruz	• Philippine Radiation Oncology Society • Jose R. Reyes Memorial Medical Center • Chinese General Hospital & Medical Center	Radiation Oncologist	NCR	Nil
Dr. Elias T. Reala	• Philippine Society of Otorhinolaryngology-Head & Neck Surgery • Jose R. Reyes Memorial Medical Center	Otorhinolaryngologist – Head and Neck Surgeon	NCR	Nil
Dr. Humphrey C. Bitun	• Philippine Society of Pathologist • Jose R. Reyes Memorial Medical Center	Pathologist	NCR	Nil
Dr. Jocelyn C. Que	• Philippine Society of Anesthesiologists • Philippine Board of Pain Medicine • University of Santo Tomas Hospital	Anesthesiologist / Pain Management Specialist	NCR	Nil
Dr. Neil Martin D. Sese	• Philippine College of Radiology • Jose R. Reyes Memorial Medical Center	Radiologist	NCR	Nil
Dr. Peter Julian A. Francisco	• Philippine Academy of Family Physicians • Jose R. Reyes Memorial Medical Center		NCR	Nil

	• Manila Doctors Hospital	Family Medicine Specialist		
Dr. Vivian P. Enriquez	• Philippine College of Surgeons • Philippine Society of General Surgeons • Surgical Oncology Society of the Philippines • Jose R. Reyes Memorial Medical Center Reyes • Our lady of Lourdes Hospital	General surgeon/ Surgical oncologist	NCR	Nil
Dr. Francis Angelo D. Basilio	• Philippine College of Radiology • Chinese Hospital &Medical Center • Asian Hospital and Medical Center	Interventional Radiologist	NCR	
Dr. Rowald Rey G. Malahito	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Marikina Valley Medical Center	Otorhinolaryngologist-Head and Neck Surgeon	NCR	
Dr. Mark Philip C. Guinocor	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • VisayasMed Hospital	Otorhinolaryngologist-Head and Neck Surgeon	Region VII	Nil
Dr. Joseph E. Cachuela	• Philippine Society of Otorhinolaryngology-Head and Surgery	Otorhinolaryngologist-Head and Neck Surgeon	Davao City	Nil

	• Academy of Head and Neck Oncology of the Philippines • Davao Doctors Hospital			
Mr. Leo M. Flores		Patient Representative	NCR	Nil

†Non-voting panel member

Table 6. Summary of COI disclosure of the CP members for laryngeal cancer

Panel Member	Affiliated Institution	Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Clarito U. Cairo, Jr.†	DOH	Cancer Program Manager	NCR	Nil
Dr. Rainer Y. Lutanco	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Surgical Oncology Society of the Philippines • Rizal Medical Center • Chinese General and medical Center	Genera Surgeon / Head and Neck Surgeon	NCR	Nil
Dr. Neresito T. Espiritu	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Jose B. Lingad Memorial General Hospital	General Surgeon / Surgical Oncologist	NCR / Central Luzon	Nil

	• Univ. of the Philippines-Philippine General Hospital			
Dr. Cherry Lyn V. Montealto	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Cebu Institute of Medicine	General Surgeon / Head and Neck Oncologist	Region VII	Nil
Dr. Jose M. Carnate, Jr.	• Philippine Society of Pathologist • UP College of Medicine, Dept of Pathology • The Medical City	Pathologist	NCR	Nil
Dr. Solidad L. Balete	• Philippine Society of Medical Oncology • Philippine Society of Oncologist • Jose R. Reyes Memorial Medical Center • Chinese General & Medical Center	Medical Oncologist	NCR	Nil
Dr. Josephine Contreras-Tolentino	• Philippine Society of Medical Oncology • The Medical City	Medical Oncologist	NCR	Nil
Dr. Rowald Rey G. Malahito	• Philippine Society of Otorhinolaryngology-Head and Neck Surgery • Marikina Valley Medical Center	Otorhinolaryngologist-Head and Neck Surgeon	NCR	
Dr. Joseph E. Cachuela	• Philippine Society of Otorhinolaryngology-Head and Surgery	Otorhinolaryngologist-Head and Neck Surgeon	Davao City	Nil

	• Academy of Head and Neck Oncology of the Philippines • Davao Doctors Hospital			
Dr. Ann Margaret V. Chang	• Philippine Society of Pathology • St. Luke's Medical Center • St. Francis Cabrini Medical Center	Head and Neck pathologist	NCR	Nil
Dr. Humphrey C. Bitun	• Philippine Society of Pathologist • Jose R. Reyes Memorial Medical Center	Pathologist	NCR	Nil
Dr. Peter Julian A. Francisco	• Philippine Academy of Family Physicians • Jose R. Reyes Memorial Medical Center • Manila Doctors Hospital	Family Medicine Specialist	NCR	Nil
Dr. Ryan Rainier D. Siscar	JRRMMC	Dentist	NCR	Nil
Mr. Mark Gil Q. de la Rosa	• Philippine Society for Parenteral and Enteral Nutrition, Inc • Arellano University	Nurse	NCR	Nil
Dr. Christine Jew V. Baldovino	• Philippine Society for Parenteral and Enteral Nutrition, Inc • Philippine College of Physicians • Batangas Medical Center	Diet and Clinical Nutrition Specialist	Central Luzon	Nil
Dr. Gemma Leonora B. Uy	• Philippine College of Surgeon • Surgical Oncology Society of the Philippines • UP-PGH	General Surgeon /Surgical Oncologist	NCR	Nil
Dr. Rowena Sudario-Lumague	• Philippine Association of Plastic, Reconstructive, and Aesthetic Surgeons		NCR	Nil

	• Jose R. Reyes Memorial Medical Center • UP-PGH	Plastic and Reconstructive Surgeon		
Ms. Aileen F. Matalog	• Philippine Association of Speech - Language Pathologists • V. Luna Medical Center • St. Luke's Global	SLP/Swallowing Rehabilitation Specialist	NCR	Nil
Ms. Carla Krishan A. Cuadro	• Philippine Association of Speech - Language Pathologists • St. Luke's Medical Center	SLP/Swallowing Rehabilitation Specialist	NCR	Nil
Dr. Michael Benedict A. Mejia	• Philippine Radiation Oncology Society • University of Santo Tomas Hospital • Asian Hospital & Medical Center	Radiation Oncologist	NCR	Nil
Mr. Leo M. Flores		Patient Representative	NCR	Nil
Dr. Ana Patricia P. Villanueva-de Grano	• Philippine Association of Plastic, Reconstructive, and Aesthetic Surgeons • Mariano Marcos Memorial Hospital and Medical Center	Plastic Surgeon	Ilocos Region	Nil

†Non-voting panel member

Table 7. Summary of COI disclosure of the CP members for nasopharyngeal cancer

Panel Member	Affiliated Institution	Position	Geographical Location	Summary of Disclosure Type of Interest – Commercial Entity/Organization, Topic (Dates of Involvement)
Dr. Clarito U. Cairo, Jr.†	DOH	Cancer Program Manager	NCR	Nil
Dr. Rainer Yu Lutanco	• Philippine College of Surgeons			

	• Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Surgical Oncology Society of the Philippines • Rizal Medical Center • Chinese General and medical Center	Genera Surgeon / Head and Neck Surgeon	NCR	Nil
Dr. Neresito T. Espiritu	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Jose B. Lingad Memorial General Hospital • Univ. of the Philippines-Philippine General Hospital	General Surgeon / Head and neck Surgeon	NCR / Central Luzon	Nil
Dr. Cherry Lyn V. Montealto	• Philippine College of Surgeons • Philippine Society of General Surgeons • Philippine Academy Head and Neck Surgery Inc. • Cebu Institute of Medicine	General Surgeon / Head and Neck Surgeon	Region VII	Nil
Dr. Jose M. Carnate, Jr.	• Philippine Society of Pathologist • UP College of Medicine, Dept of pathology • The Medical City	Pathologist	NCR	Nil
Dr. Solidad L. Balete	• Philippine Society of Medical Oncology • Philippine Society of Oncologist	Medical Oncologist	NCR	Nil

	• Jose R. Reyes Memorial Medical Center • Chinese General & Medical Center			
Dr. Humphrey C. Bitun	• Philippine Society of Pathologist • Jose R. Reyes Memorial Medical Center • FEU-NRMF Medical Center	Pathologist	NCR	Nil
Dr. Peter Julian A. Francisco	• Philippine Academy of Family Physicians • Jose R. Reyes Memorial Medical Center • Manila Doctors Hospital	Family Medicine Specialist	NCR	Nil
Dr. Mark Philip C. Guinocor	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • VisayasMed Hospital	Otorhinolaryngologist-Head and Neck Surgeon	Region VII	Nil
Dr. Joseph E. Cachuela	• Philippine Society of Otorhinolaryngology-Head and Surgery • Academy of Head and Neck Oncology of the Philippines • Davao Doctors Hospital	Otorhinolaryngologist-Head and Neck Surgeon	Davao City	Nil
Dr. Ryan Rainier D. Siscar	• Philippine Dental Association • Jose R. Reyes Memorial Medical Center	Dentist	NCR	Nil
Ms. Rosalynn L. Pangan	• Philippine Society for Parenteral and Enteral Nutrition, Inc • St. Luke's Medical Center	Pharmacist	NCR	Nil

Mr. Mark Gil Q. de la Rosa	• Philippine Society for Parenteral and Enteral Nutrition, Inc Arellano University	Nurse	NCR	Nil
Dr. Christine Jew V. Baldovino	• Philippine Society for Parenteral and Enteral Nutrition, Inc • Philippine College of Physicians • Batangas Medical Center	Diet and Clinical Nutrition Specialist	Central Luzon	Nil
Dr. Gemma Leonora B. Uy	• Philippine College of Surgeon • Surgical Oncology Society of the Philippines • UP-PGH	General Surgeon /Surgical oncologist	NCR	Nil
Dr. Rowena Sudario-Lumague	• Philippine Association of Plastic, Reconstructive, and Aesthetic Surgeons • Jose R. Reyes Memorial Medical Center • UP-PGH	Plastic and Reconstructive Surgeon	NCR	Nil
Ms. Aileen F. Matalog	• Philippine Association of Speech - Language Pathologists • V. Luna Medical Center • St. Luke's Global	SLP/Swallowing Rehabilitation Specialist	NCR	Nil
Ms. Carla Krishan A. Cuadro	• Philippine Association of Speech - Language Pathologists • St. Luke's Medical Center	SLP/Swallowing Rehabilitation Specialist	NCR	Nil
Dr. Josephine Contreras-Tolentino	• Philippine Society of Medical Oncology • The Medical City	Medical Oncologist	NCR	Nil
Dr. Michael Benedict A. Mejia	• Philippine Radiation Oncology Society • University of Santo Tomas Hospital	Radiation Oncologist	NCR	Nil

	• Asian Hospital & Medical Center			
Mr. Leo M. Flores	-	Patient Representative	NCR	Nil

†Non-voting panel member

APPENDIX C: APPRAISAL USING AGREE-II

Appendix: Appraisal of CPGs using AGREE II

Guidelines for the Surgical Management of Oral Cancer: Korean Society of Thyroid-Head and Neck Surgery

No. of Appraisers: 3
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	18	21	-	91.6
2. Stakeholder Involvement	14	15	-	63.8
3. Rigour of Development	41	44	47	75
4. Clarity of Presentation	20	21	-	97.2
5. Applicability	10	22	-	50
6. Editorial Independence	8	14	-	64.3

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Oral cavity cancer management guidelines for low-resource regions

No. of Appraisers: 3
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	13	21	-	77.8
2. Stakeholder Involvement	11	13	-	50
3. Rigour of Development	28	41	43	61.1
4. Clarity of Presentation	21	21	-	100
5. Applicability	10	26	-	58.33
6. Editorial Independence	2	8	-	25

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Guideline: NCCN Guidelines Version 2.2022 Head and Neck Cancers

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	5	19	-	50
2. Stakeholder Involvement	8	21	-	63.8
3. Rigour of Development	31	42	56	72.9
4. Clarity of Presentation	13	21	-	77.8
5. Applicability	10	27	-	60.4
6. Editorial Independence	8	11	-	62.5

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers
[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)

No. of Appraisers: 3
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	18	21	-	91.7
2. Stakeholder Involvement	15	21	-	83.3
3. Rigour of Development	40	44	47	74.3
4. Clarity of Presentation	20	21	-	97.2
5. Applicability	15	26	-	68.8
6. Editorial Independence	14	14	-	100

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Indian clinical practice consensus guidelines for the management of oral cavity cancer

No. of Appraisers: 3
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	3	21		50
2. Stakeholder Involvement	6	13		36.1
3. Rigour of Development	23	33	11	29.9
4. Clarity of Presentation	17	21		88.9
5. Applicability	10	28		62.5
6. Editorial Independence	14	14		100

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Japanese Clinical Practice Guideline for Head and Neck Cancer

No. of Appraisers: 3
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
7. Scope and Purpose	13	15	-	61.1
8. Stakeholder Involvement	8	9	-	30.5
9. Rigour of Development	40	42	44	70.8
10. Clarity of Presentation	20	21	-	97.2
11. Applicability	6	22	-	41.7
12. Editorial Independence	2	8	-	25

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

German Guideline Program in Oncology: Evidence-based Guideline Oral Cavity Cancer

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	19	18	-	86.1
2. Stakeholder Involvement	20	21	-	97.2
3. Rigour of Development	42	47	56	84.0
4. Clarity of Presentation	20	18	-	88.9
5. Applicability	10	27	-	60.4
6. Editorial Independence	14	12	-	91.7

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Pan-Asian adaptation of the EHNS–ESMO–ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	13	17	-	66.7
2. Stakeholder Involvement	12	9	-	41.7
3. Rigour of Development	31	44	47	68.1
4. Clarity of Presentation	20	21	-	97.2
5. Applicability	18	22	-	66.7
6. Editorial Independence	14	14	-	100

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

SEOM clinical guidelines for the treatment of head and neck cancer (2020)

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	3	15	-	33.3
2. Stakeholder Involvement	6	9	-	25
3. Rigour of Development	23	20	31	34.7
4. Clarity of Presentation	20	19	-	91.7
5. Applicability	12	21	-	52.1
6. Editorial Independence	8	14	-	75

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNSeESMOeESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score[†], %
1. Scope and Purpose	3	9	-	16.7
2. Stakeholder Involvement	10	9	-	36.1
3. Rigour of Development	28	20	34	40.3
4. Clarity of Presentation	20	19	-	91.7
5. Applicability	12	22	-	54.2
6. Editorial Independence	14	14	-	100

[†]Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline

No. of Appraisers:
Appraisers:
1. CAMA
2. DJM
3. IML

Domains[a]	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	21	21	-	100
2. Stakeholder Involvement	10	21	-	69.4
3. Rigour of Development	28	50	56	76.4
4. Clarity of Presentation	20	21	-	97.2
5. Applicability	12	28	-	66.7
6. Editorial Independence	14	14	-	100

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

Reference

AGREE Next Steps Consortium (2009). The AGREE II Instrument [Electronic Version]. Retrieved June 3, 2022, from http://www.agreetrust.org

Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

No. of Appraisers: 3
Appraisers:

1. PGS
2. MBL
3. CSS

Domains	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	20	21	21	98.15%
2. Stakeholder Involvement	17	19	15	77.78%
3. Rigour of Development	47	56	50	89.58%
4. Clarity of Presentation	21	21	21	100.00%
5. Applicability	27	28	22	90.28%
6. Editorial Independence	13	13	8	77.78%

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

AHNS series: Do you know your guidelines? Guideline recommendations for recurrent and persistent head and neck cancer after primary treatment

No. of Appraisers: 3
Appraisers:
1.PGS
2.CSS
3. HBA

Domains	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	18	19	9	68.52%
2. Stakeholder Involvement	4	4	5	7.41%
3. Rigour of Development	8	22	12	12.50%
4. Clarity of Presentation	15	21	12	72.22%
5. Applicability	5	10	4	9.72%
6. Editorial Independence	2	7	2	13.89%

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers
[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

AHNS Series: Do you know your guidelines? Principles of treatment for locally advanced or unresectable head and neck squamous cell carcinoma

No. of Appraisers: 3
Appraisers:
1.PGS
2. MBL
3. AFF

Domains	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	20	20	21	96.30%
2. Stakeholder Involvement	4	15	21	57.41%
3. Rigour of Development	8	29	52	45.14%
4. Clarity of Presentation	16	17	21	83.33%
5. Applicability	7	16	25	50.00%
6. Editorial Independence	2	14	12	61.11%

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers
[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

AHNS Series: Do you know your guidelines? Review of current knowledge on laryngeal cancer

No. of Appraisers: 3
Appraisers:

1.JBG
2. HBA
3. CSS

Domains	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	17	14	15	68.52%
2. Stakeholder Involvement	7	6	10	25.93%
3. Rigour of Development	16	12	22	18.06%
4. Clarity of Presentation	15	15	20	75.93%
5. Applicability	11	4	4	9.72%
6. Editorial Independence	2	2	2	0.00%

†Domain Score: [Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

[a] Domain (No. of items): Scope & Purpose (3); Stakeholder involvement (3); Rigour of Development (8); Clarity of Presentation (3); Applicability (4); Editorial Independence (2)

AHNS Series - Do you know your guidelines? Principles of treatment for glottic cancer: A review of the National Comprehensive Cancer Network guidelines

No. of Appraisers: 3
Appraisers:

1.PGS
2. MBL
3. AFF

Domains	Score of Appraiser 1	Score of Appraiser 2	Score of Appraiser 3	Domain Score†, %
1. Scope and Purpose	18	21	21	94.44%
2. Stakeholder Involvement	4	11	20	48.15%
3. Rigour of Development	8	53	53	62.50%
4. Clarity of Presentation	17	21	20	90.74%
5. Applicability	7	17	23	48.61%
6. Editorial Independence	2	2	12	27.78%

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: Chemotherapy in Combination with Radiotherapy for Definitive-intent Treatment of Stage II to IVA Nasopharyngeal Carcinoma: CSCO-ASCO Guideline slides

Overall quality: 5
Recommedation: Yes, with modifications: use the unabridged version

Domains	Item	Item	Item	Total
1. Scope and Purpose	5 Objective stated in the introduction but it does not show health intent and expected benefit of outcome. Objective is not easy to find.	6 Clinical questions do not mention outcomes.	7	18
2. Stakeholder Involvement	6 The guidelines did not provide a description of each member's role.	2 The method to capture the patients' point of view was not described. However, one of the panel members included a patient representative.	5 The guideline lists the target audience clearly but it does not explain how the audience may use the guideline.	13
3. Rigour of Development	1 No electronic database, search terms, time period and search strategy mentioned.	1 No inclusion criteria noted.	1 No description of strengths and limitations.	9
	2 The guideline mentioned that recommendations were based on an expert panel consensus but did not detail	1 No supporting data per recommendation. No report of risks and benefits stated.	1 No supporting evidence listed.	

	the technique or methodology used.			
	1 No external review mentioned.	1 No procedure for updating the guideline is mentioned.		
4. Clarity of Presentation	6 There is no identification of intent or purpose.	7 Treatment options are specifically described some with indication to specific patient population.	6 The entir reference seems like a quick reference guide. Recommendations are grouped based on clinical question.	19
5. Applicability	7 Barriers listed in the patient and clinician communication section.	2 No additional tools but the entire reference is adequately simplified for understanding of the audience.	1 No potential resource implications noted.	11
	1 No monitoring and auditing criteria were listed.			
6. Editorial Independence	1 No funding body were listed.	1 No competing interests were listed.		2

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: Chemotherapy in Combination with Radiotherapy for Definitive-intent Treatment of Stage II to IVA Nasopharyngeal Carcinoma: CSCO-ASCO Guideline

Overall quality: 7
Recommendation: Yes

Domains	Item	Item	Item	Total
7. Scope and Purpose	5 Objective stated in the introduction but it does not show health intent and expected benefit of outcome. Objective is not easy to find.	6 Clinical questions do not mention outcomes.	7 Target population was properly indicated with disease and stage	18
8. Stakeholder Involvement	7 The guidelines provided a description of each member's role at the end,	6 The guideline lists the target audience clearly and describes the method on how they obtained the patient perspective.	7 The guideline included a list of the target audience. It was also able to elucidate how these people might use the guideline.	20
9. Rigour of Development	6 Electronic database, time period and search strategy were mentioned. Search terms were not mentioned.	7 Inclusion criteria was noted.	7 Guideline lists strengths and limitations in the disclaimer.	55
	7 The guideline mentioned that recommendations were based on an expert panel consensus and	7 There was supporting data per recommendation. Some had a report of risks and	7 There was supporting evidence listed.	

	detailed the technique or methodology used.	benefits stated.		
	7 External review was mentioned.	7 There was a a section on guideline implementation.		
10. Clarity of Presentation	6 There is no identification of intent or purpose.	7 Treatment options are specifically described some with indication to specific patient population.	7 Recommendations are grouped based on clinical question.	20
11. Applicability	7 Barriers listed after recommendation 5.3.	7 Section on additional tools listed.	7 Cost implications were noted.	28
	7 Guideline implementation noted monitoring and auditing criteria			
12. Editorial Independence	7 Funding came from CSCO.	7 Author disclosures were mentioned.		14

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up

Overall quality: 6
Recommendation: Yes, with modifications: more detail into the scope, target population and target audience.

Domains	Item	Item	Item	Total
1. Scope and Purpose	1 Overall objectives were not listed.	1 Health questions are not described.	1 Population is not described or listed.	3
2. Stakeholder Involvement	5 Some authors' sub specialties were not listed. Author contribution was not listed.	1 No patient representation noted.	1 Target users were not defined	7
3. Rigour of Development	2 The article only mentioned that relevant literature was selected by the authors.	1 No inclusion criteria were noted.	1 No strengths and limitations were noted.	24
	5 No methodology was outrightly explained in the article but it provided a link which detailed the process.	7 Supporting evidence including the risks and benefits were explained after each recommendation.	7 Each recommendation is linked to a body of data which support it.	
	1 No statement regarding external review was noted.	1 No statement on guideline update		
4. Clarity of Presentation	6 No identification of intent or purpose within the	7 Different treatment options at noted. It is also explained	7 There are summarized boxes and flowcharts. The	20

	recommendation but it is sometimes explained in the subsequent paragraph. No identification of relevant population was noted.	when these options are best used.	recommendations are grouped together.	
5. Applicability	1 No identification of barriers was noted.	3 Numerous tables and flowcharts facilitate easier understanding of the article but no summary guides were listed.	4 The article mentioned that funding came from ESMO central funds which took care of production costs. Not much detail was given into other forms of expenditure.	9
	1 No monitoring and auditing criteria.			
6. Editorial Independence	7 Statement saying no external funding was used.	7 Author disclosures provided possible competing interests of the authors		14

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: Indian clinical practice consensus guidelines for the management of nasopharyngeal cancer

Overall: 3
Recommendation: No

Domains	Item	Item	Item	Total
1. Scope and Purpose	1 No statement of objectives	1 No clinical questions stated	1 No target population listed	3
2. Stakeholder Involvement	6 No description of author contribution	1 No patient representative indicated	1 No target user defined	8
3. Rigour of Development	1 No methodology	1 No methodology	1 Body of evidence extremely concise. No mention of strengths and limitations.	14
	1 No methodology	2 Body of evidence is extremely concise. Health benefits and risks are mentioned only in some recommendations.	6 There is a link between supporting evidence and recommendations	
	1 No methodology	1 No methodology		
4. Clarity of Presentation	5 Recommendations are not stated outright. It is intermixed with the supporting evidence.	7 Treatment options listed with indications for each	2 Recommendations are not stated outright, and intermixed with the supporting evidence. No	14

			table showing key recommendations included.	
5. Applicability	1 No barriers listed	1 No summary tools, etc	1 No cost implications	4
	1 No auditing or monitoring criteria			
6. Editorial Independence	7 Funding source declared	7 Conflicts of interest declared		14

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: SEOM-TTCC clinical guideline in nasopharynx cancer (2021)

Overall: 5
Recommendation: Yes, with modifications

Domains	Item	Item	Item	Total
1. Scope and Purpose	1 Objectives were not stated.	1 Health questions were not stated.	1 Target population was not stated.	3
2. Stakeholder Involvement	2 All of the authors were medical oncologists. No description of the author contributions.	1 No patient representative was included.	1 No target users identified.	4
3. Rigour of Development	2 The journal mentioned that updated studies were used as references. There were no details on search strategy.	1 No criteria for selecting evidence described.	6 Supporting evidence and recommendations stratified by quality of evidence	24
	1 No methods on recommendation formulation included	5 Some recommendations include risks and benefits in their supporting data.	7 There is explicit link between the recommendations and supporting evidence.	
	1 No external review board mentioned.	1 No procedure for guidelines updates included		
4. Clarity of Presentation	4 The recommendati	6 Different therapeutic	7 Key recommendati	17

	ons are intermixed with the supporting evidence	options were listed. Some options list it's indications or specific target populations.	ons were summarized in a table.	
5. Applicability	1 No facilitators and barriers were listed.	5 Key recommendations were summarized in a table. Pertinent data can be found in table and algorithm format.	1 Cost implications were not listed.	9
	1 No monitoring and auditing criteria were listed.			
6. Editorial Independence	1 No funding body was listed	7 Conflicts of interest were declared.		8

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Guideline: SEOM-TTCC clinical guideline in nasopharynx cancer (2017)

Overall: 3
Recommendation: No, use the 2021 version

Domains	Item	Item	Item	Total
1. Scope and Purpose	1 No objectives mentioned.	1 No clinical questions stated.	1 No target population mentioned.	3
2. Stakeholder Involvement	2 All of the authors were medical oncologists. No description of the author contributions.	1 No patient representative was included.	1 No target users identified.	4
3. Rigour of Development	1 There were no details on search strategy.	1 No criteria for selecting evidence described.	6 Supporting evidence and recommendations stratified by quality of evidence	23
	1 No methods on recommendation formulation included	5 Some recommendations include risks and benefits in their supporting data.	7 There is explicit link between the recommendations and supporting evidence.	
	1 No external review board mentioned.	1 No procedure for guidelines updates included		
4. Clarity of Presentation	4 The recommendations are intermixed with the supporting evidence	6 Different therapeutic options were listed. Some options list their	3 No summary of key recommendations were placed. Some pertinent data	13

		indications or specific target populations.	were placed in table format.	
5. Applicability	1 No facilitators and barriers were listed.	2 Key recommendations were not summarized in a table. Pertinent data can be found in table and algorithm format.	1 Cost implications were not listed.	5
	1 No monitoring and auditing criteria were listed.			
6. Editorial Independence	1 No funding body was listed	7 Conflicts of interest were declared.		8

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines

Overall Rating: 3
Recommendation: Yes but with modifications

Domains	Item	Item	Item	Total
1. Scope and Purpose	1 No objectives mentioned.	1 No clinical questions stated.	1 No target population mentioned.	3
2. Stakeholder Involvement	4 The authors come from a variety of disciplines involved in treating nasopharyngeal cancer. No description of the author contributions.	1 No patient representative was included.	1 No target users identified.	6
3. Rigour of Development	1 There were no details on search strategy.	1 No criteria for selecting evidence described.	6 Supporting evidence and recommendations stratified by quality of evidence	23
	1 No methods on recommendation formulation included	5 Some recommendations include risks and benefits in their supporting data.	7 There is explicit link between the recommendations and supporting evidence.	
	1 No external review board mentioned.	1 No procedure for guidelines updates included		
4. Clarity of Presentation	4 The recommendations are intermixed with	6 Different therapeutic options were listed. Some	7 Key recommendations were	17

	the supporting evidence	options list their indications or specific target populations.	easily identifiable.	
5. Applicability	1 No facilitators and barriers were listed.	7 Key recommendations were emphasized. They were tables of data that facilitate understanding of the guideline.	1 Cost implications were not listed.	10
	1 No monitoring and auditing criteria were listed.			
6. Editorial Independence	1 No funding body was listed	1 Conflicts of interest were not declared.		2

†[Obtained score – Minimum possible score]/[Maximum possible score – minimum possible score]
Maximum possible score = 7(strongly agree) x No. of items x No. of appraisers
Minimum possible score = 1 (strongly disagree) x No. of items x No. of appraisers

APPENDIX D: Search Strategy for Evidence on Nasopharyngeal Cancer

NQ1. Is screening for NPC recommended among asymptomatic individuals in the Philippines?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	((((Nasopharyngeal Cancer) OR (Nasopharyngeal Carcinoma)) OR (Nasopharyngeal Neoplasm)) AND (Asymptomatic)) AND (Screening) Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	12 June 2023	4	2
PubMed	((((Nasopharyngeal Cancer) OR (Nasopharyngeal Carcinoma)) OR (Nasopharyngeal Neoplasm)) AND (Asymptomatic)) AND (Screen*) Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	12 June 2023	2	2
PubMed	((((Nasopharyngeal Cancer) OR (Nasopharyngeal Carcinoma)) OR (Nasopharyngeal Neoplasm)) AND (Early Stage)) AND (Screening) Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	12 June 2023	24	2
PubMed	((((Nasopharyngeal Cancer) OR (Nasopharyngeal Carcinoma)) OR (Nasopharyngeal Neoplasm)) AND (Early Stage)) AND (Screen*) Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	12 June 2023	8	1

Identification of studies via databases and registers			
Identification	Studies identified from: PubMed search(n=38) Selected Guidelines (n=3)		Duplicates removed (n = 9)
Included	Studies screened from PubMed (n=3) Other related studies (n=0) Guidelines screened(n=1)		Studies excluded (n=26) Guidelines excluded (n=2)

NQ2. What clinical findings would make you suspect NPC in a patient?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Google Scholar	nasopharyngeal cancer AND symptoms at presentation Filter: 2010 to 2023	April 9, 2023 1:00 PM	12,400	1
PubMed	nasopharyngeal cancer AND signs AND symptoms Filters: 2010 to 2023	April 9, 2023 1:00 PM	443	8

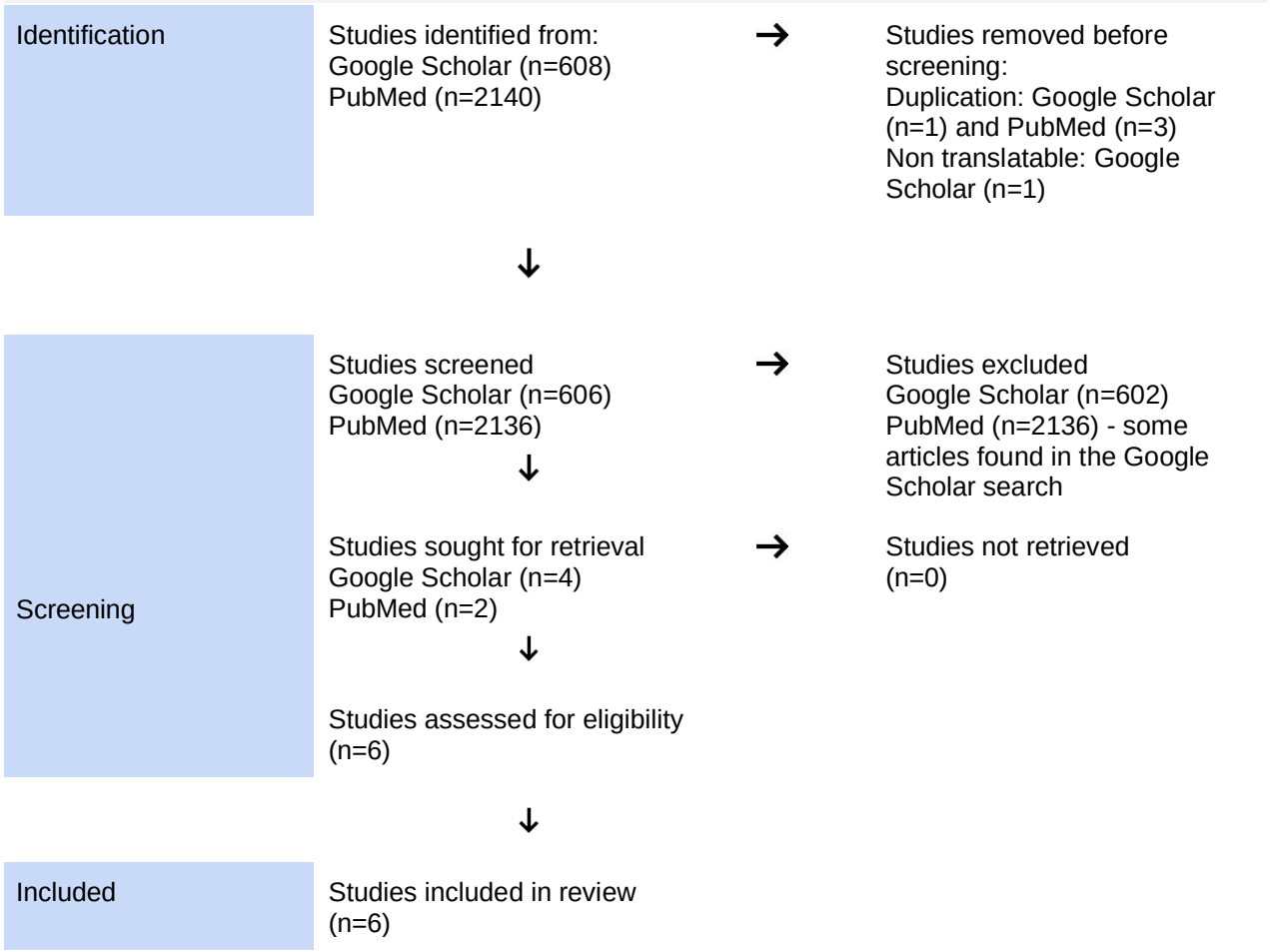
Identification of studies via databases and registers

Identification	Studies identified from: Google Scholar (n=12,400) PubMed (n=488)	→	Studies removed before screening: (n=0)
	↓		
Screening	Studies screened (n=12,488)	→	Studies excluded (n=12,479)
	↓		
	Studies sought for retrieval (n=9)	→	Studies not retrieved (n=1)
	↓		
	Studies assessed for eligibility (n=8)		
	↓		
Included	Studies included in review (n=8)		

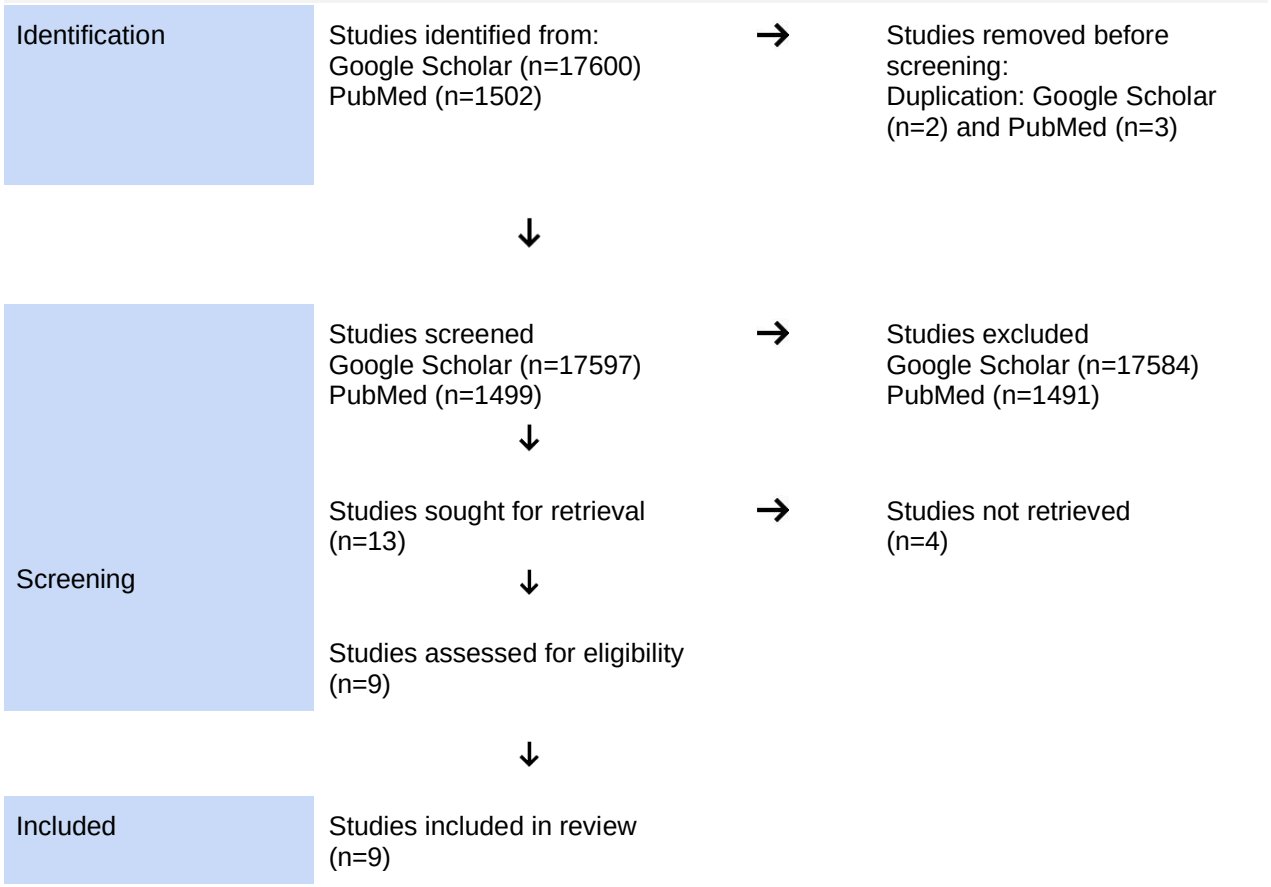
NQ3. Among individuals suspected to have NPC after complete history and physical examination, what initial diagnostic tests are necessary?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND (Diagnosis) AND ((Endoscopy) OR (Nasopharyngoscopy))) Filter: 2010 to 2022	July 7, 2022 8:30 AM	608	4
Google Scholar	((((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND (Diagnosis)) AND (Endoscopy)) OR (Nasopharyngoscopy) Filter: 2010 to 2022	July 13, 2022 8:30 AM	2,140	2
PubMed	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND (Diagnosis) AND ((HPV) OR (EBV) OR (EBER))) Filter: 2010 to 2022	August 1, 2022 8:30 AM	1,502	9
Google Scholar	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND (Diagnosis) AND ((HPV) OR (EBV) OR (EBER))) Filter: 2010 to 2022	August 11, 2022 3:00 PM	17,600	7

Identification of studies via databases and registers for **nasopharyngoscopy and biopsy**



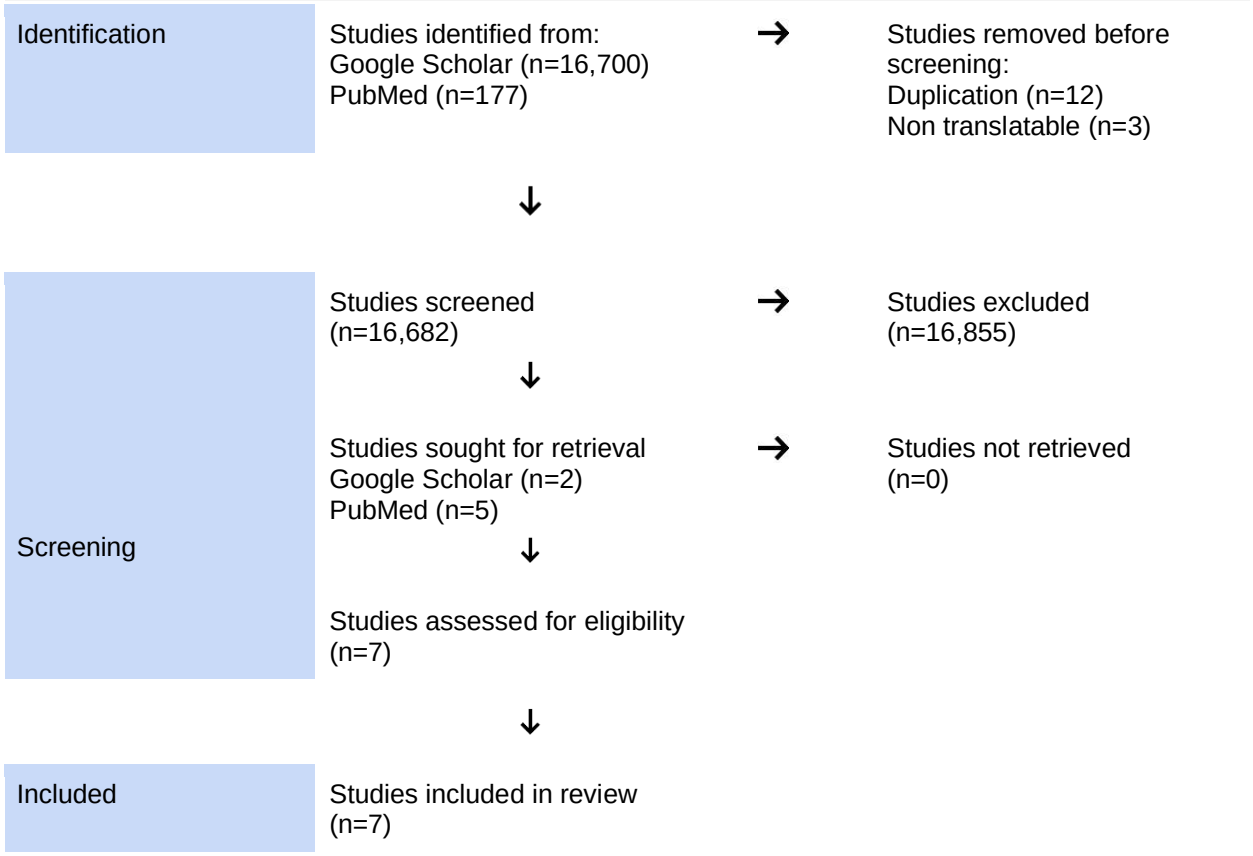
Identification of studies via databases and registers for **EBV and HPV testing**



NQ4. Among individuals diagnosed with NPC, what further tests are necessary for staging?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Staging AND Workup) Filter: 2012 to 2022	June 27, 2022 8:30 AM	177	2
Google Scholar	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Staging AND Workup) Filter: 2012 to 2022	July 27, 2022 8:30 AM	16,700	9

Identification of studies via databases and registers for **metastatic nasopharyngeal cancer**



NQ5. Among individuals diagnosed with NPC who have completed staging work-up, what additional procedures are necessary to request prior to the start of definitive treatment?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	((((Nasopharyngeal Cancer) AND (Nasopharyngeal neoplasm)) AND (pretreatment)) AND (assessment)) Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	12 June 2023	18	3
Google Scholar	"Nasopharyngeal Carcinoma" OR "Nasopharyngeal cancer" AND "pretreatment" AND "Quality of life" Filters: 10 years, reviews, systematic reviews, meta-analysis,	13 June 2023	258	7

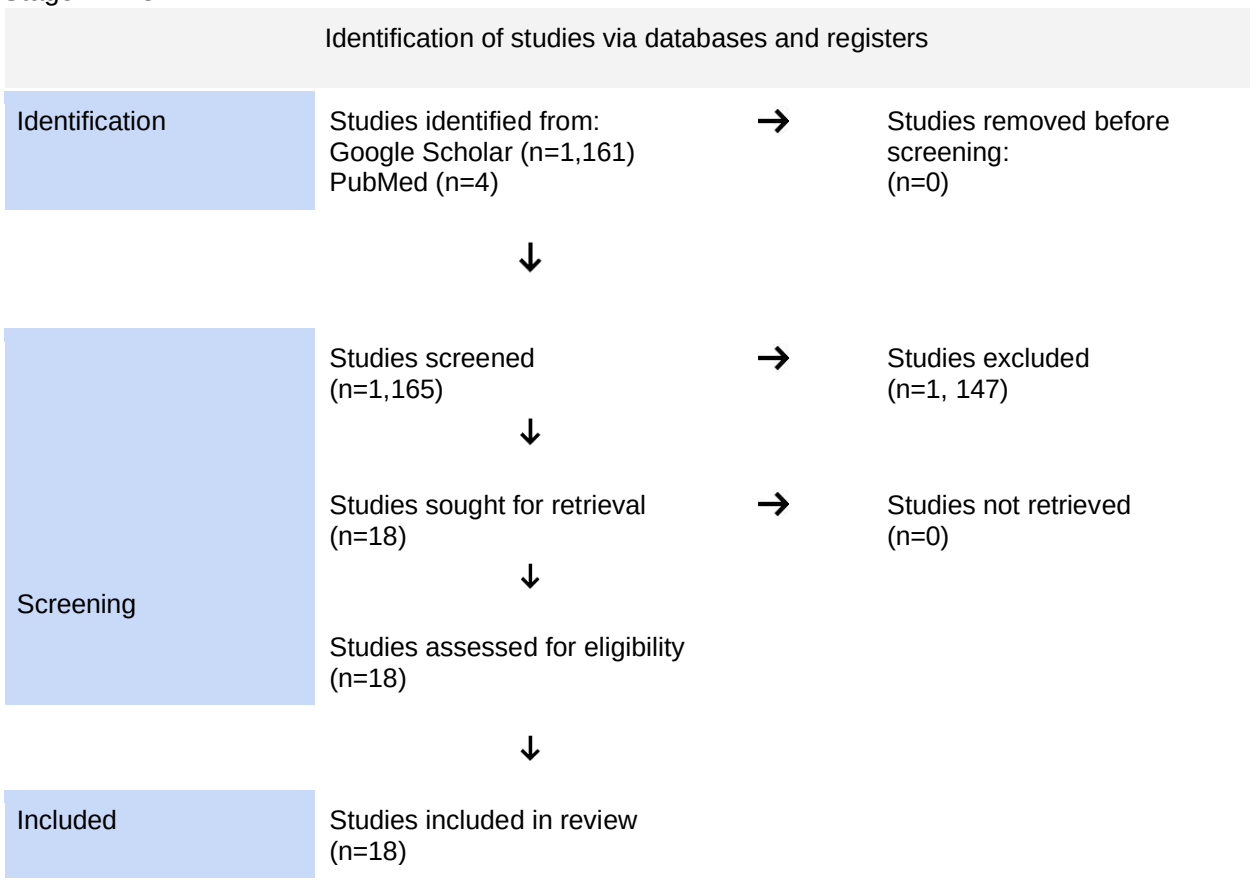
Identification of studies via databases and registers			
Identification	Studies identified from: PubMed search(n=18) Google Scholar search (n=258) Selected Guidelines (n=4)		Duplicates (n=52)
Included	Studies screened from Pubmed (n=3) Studies screened from Google Scholar (n=7) Other related studies (n=0) Guidelines screened (n=3)		Studies excluded (n=214) Guidelines excluded (n=1)

NQ6. What is the appropriate management for patients with T1-2N0 NPC?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Google Scholar	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND Stage I AND T1N0 Filters: 2013 to 2023	May 25, 2023 1:00 PM	1160	14
PubMed	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND Stage I AND T1N0 Filters: 2013 to 2023	May 25, 2023 1:00 PM	4	4

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Google Scholar	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND Stage II AND T2N0 Filters: 2013 to 2023	June 16, 2023 1:00 PM	2840	12
PubMed	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND Stage II AND T2N0 Filters: 2013 to 2023	June 16, 2023 1:00 PM	5	5

Stage I NPC

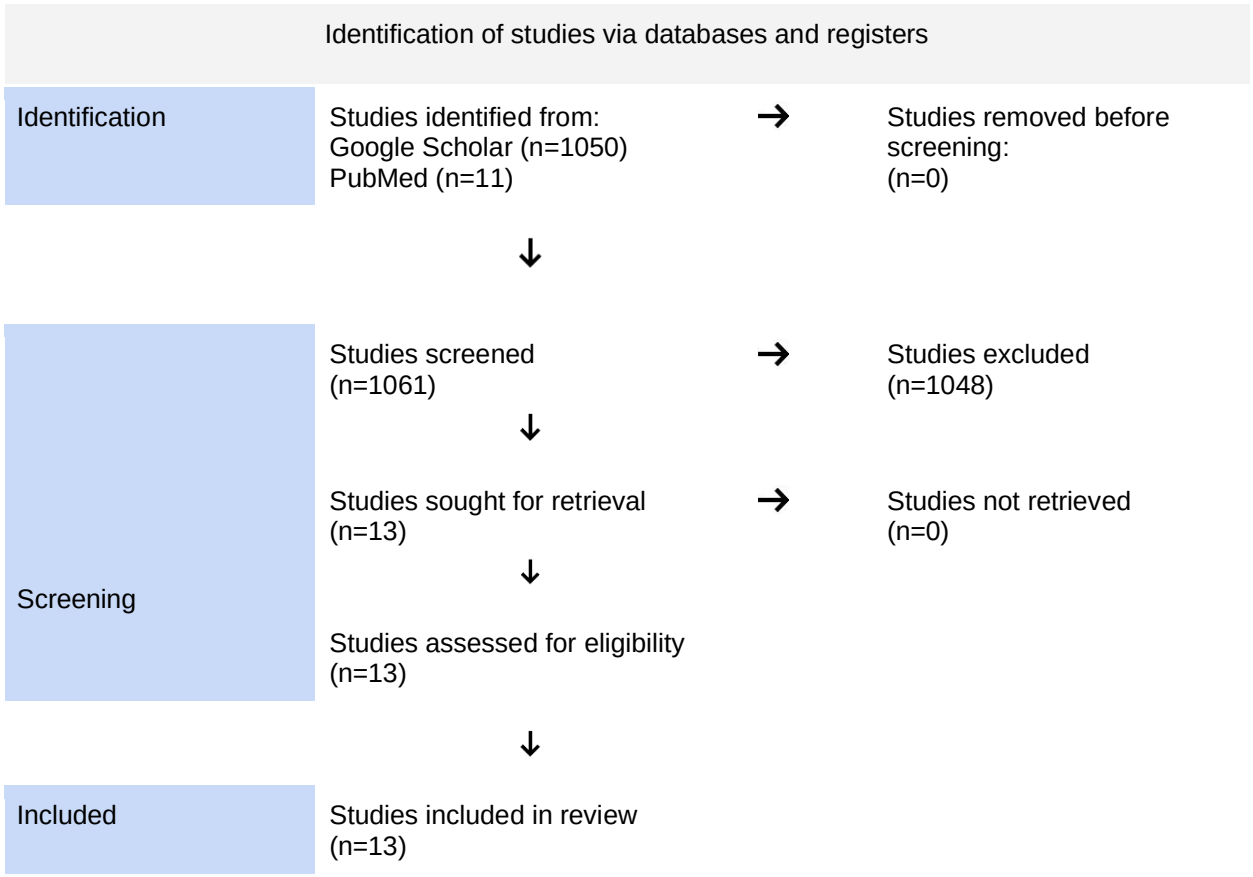


Stage II NPC

	Identification of studies via databases and registers		
Identification	Studies identified from: Google Scholar (n=2,840) PubMed (n=5)	→	Studies removed before screening: (n=0)
	↓		
Screening	Studies screened (n=2845)	→	Studies excluded (n=2832)
	↓		
	Studies sought for retrieval (n=12)	→	Studies not retrieved (n=0)
	↓		
	Studies assessed for eligibility (n=12)		
	↓		
Included	Studies included in review (n=12)		

NQ7. What is the appropriate management for patients with T1-2N1 and T3N0 NPC?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Google Scholar	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND T3N0 Filters: 2013 to 2023	June 21, 2023 1:00 PM	11	6
PubMed	nasopharyngeal cancer AND radiation therapy AND radiation AND chemotherapy AND T3N0 Filters: 2013 to 2023	June 21, 2023 1:00 PM	1050	4



NQ9. What is the appropriate management for patients with M1 NPC?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(Metastatic AND ((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Management) Filter: 2012 to 2022	June 21, 2022 8:30 AM	177	2
Google Scholar	(Metastatic AND ((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Management) Filter: 2012 to 2022	July 21, 2022 8:30 AM	16,700	9

Identification of studies via databases and registers for **metastatic nasopharyngeal cancer**

Identification	Studies identified from: Google Scholar (n=16,700) PubMed (n=177)	→	Studies removed before screening: Duplication (n=12) Non translatable (n=3)
	↓		
Screening	Studies screened (n=16,682)	→	Studies excluded (n=16,851)
	↓		
	Studies sought for retrieval Google Scholar (n=2) PubMed (n=9)	→	Studies not retrieved (n=0)
	↓		
	Studies assessed for eligibility (n=11)		
	↓		
Included	Studies included in review (n=11)		

NQ10. What is/are the recommended follow-up strategy for patient who completed treatment for NPC?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Recurrence Time) Filter: 2012 to 2022	July 28, 2022 8:30 AM	699	1
Google Scholar	(((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Recurrence Time) Filter: 2012 to 2022	August 28, 2022 8:30 AM	360	1

Identification of studies via databases and registers for **metastatic nasopharyngeal cancer**

Identification	Studies identified from: Google Scholar (n=360) PubMed (n=699)	→	Studies removed before screening: Duplication (n=5) Non translatable (n=0)
	↓		
Screening	Studies screened (n=1,054)	→	Studies excluded (n=1,052)
	↓		
	Studies sought for retrieval Google Scholar (n=1) PubMed (n=1)	→	Studies not retrieved (n=0)
	↓		
	Studies assessed for eligibility (n=2)		
	↓		
Included	Studies included in review (n=2)		

NQ11. What diagnostic test/s are necessary to evaluate patients in the residual, persistent or recurrent setting?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	nasopharyngeal cancer OR nasopahryngeal carcinoma AND recurrence AND diagnosis Filters: 10 years, reviews, systematic reviews, meta-analysis, trials	June 12, 2023	156	4

Identification of studies via databases and registers			
Identification	Studies identified from: PubMed search(n=156) Selected Guidelines (n=8)		
Included	Studies screened from Pubmed (n=4) Other related studies (n=3) Guidelines screened (n=3)		Studies excluded (n=152) Guidelines excluded (n=5)

NQ13. What are the management options for patients with distant failure?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(Distant) AND (Recurrence) AND ((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Management) Filter: 2012 to 2022	June 21, 2022 8:30 AM	699	
Google Scholar	(Distant) AND (Recurrence) AND ((Nasopharyngeal cancer) OR (Nasopharyngeal carcinoma)) AND Management) Filter: 2012 to 2022	July 21, 2022 8:30 AM	2,780	

Identification of studies via databases and registers for **metastatic nasopharyngeal cancer**

Identification	Studies identified from: Google Scholar (n=2,780) PubMed (n=699)	→	Studies removed before screening: Duplication (n=14) Non translatable (n=3)
	↓		
Screening	Studies screened (n=3,462)	→	Studies excluded (n=3,453)
	↓		
	Studies sought for retrieval Google Scholar (n=7) PubMed (n=2)	→	Studies not retrieved (n=0)
	↓		
	Studies assessed for eligibility (n=9)		
	↓		
Included	Studies included in review (n=9)		

APPENDIX E: Self-Evaluation (AGREE-II Checklist)

Fillable forms may be downloaded here: http://www.agreetrust.org/resource-centre/agree-reporting-checklist/

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☒ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	**p. 3** Section 1.2. Scope and Purpose: Overall objective
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	**p. 3** Section 1.2. Scope and Purpose: Health Questions; **pp. 21-109** Chapter 3 Evidence and Recommendations
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☒ Excluded populations (if relevant)	**p. 6** Section 1.2. Scope and Purpose: Population;
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☒ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☒ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	**p. 115,** Chapter 7: Authorship and Contributions. **p. 120,** Appendix B: Declaration of COIs
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups)	**p. 11** Section 2.3. Formulating Recommendations: Patients' Views and Preferences

	☒ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	**p. xiii,** Executive Summary; **pp. 6-7,** Section 1.3 Target Users
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	**pp. 10** Section 2.2 Evidence Synthesis- Search Methods and Strategies, **p. 170-182**, Appendix D
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☒ Context (if relevant)	**pp. 10** Section 2.2. Evidence Synthesis: Inclusion and exclusion criteria
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	**pp. 21-109** Chapter 3 Evidence and Recommendations
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered)	**pp. 11-12** Section 2.3 Formulation of Recommendations, **pp. 21-109**

reached. Specify any areas of disagreement and the methods used to resolve them.	☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	Chapter 3 Evidence and Recommendations
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	**pp. 21-109** Chapter 3 Evidence and Recommendations
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	**pp. 21-109** Chapter 3 Evidence and Recommendations
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	**pp. 13-20** Section 2.4 External Review

14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	**p. 114,** Chapter 5: Updating of the Guidelines
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	**pp. 21-109** Chapter 3 Evidence and Recommendations
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	**pp. 21-109** Chapter 3 Evidence and Recommendations
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	**p. xiv-xix,** Executive Summary - Summary of Recommendations **pp. 21-109** Chapter 3 Evidence and Recommendations
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography)	**p. 111**, Chapter 4- Applicability Issues and Resource Implications **pp. 21-109** Chapter 3 Evidence and Recommendations

	☒ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	**p. 114,** Chapter 5: Dissemination
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	**p. 111**, Chapter 4-Applicability Issues and Resource Implications
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	**p. 114,** Chapter 5: Dissemination
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	**p. v**; Acknowledgment
23. COMPETING INTERESTS *Provide an explicit statement that*	☒ Types of competing interests considered ☒ Methods by which potential competing	**p.9**; Section 2.1 Guideline

all group members have declared whether they have any competing interests.	interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	preparation **p. 120-139,** Appendix B: Declaration of COIs

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