CLINICAL PRACTICE GUIDELINES

2016 MOH/P/PAK/326.16(GU)

MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

Ministry of Health Malaysia

Malaysian Society of Otorhinolaryngologists Head & Neck Surgeons (MSO-HNS)

The Nasopharyngeal Carcinoma Society of Malaysia

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2016 and will be reviewed in 2020 or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

KEY RECOMMENDATIONS

The following recommendations were highlighted by the guidelines Development Group as the key clinical recommendations that should be prioritise for implementation.

✓ Clinical Presentations and Referral

Recommendation 1
- Patients presenting with any of the following symptoms should be referred to Otorhinolaryngologists **as soon as possible** to rule out nasopharyngeal carcinoma :
  - painless neck lump
  - blood-stained nasal discharge/saliva
  - unilateral ear block or hearing loss
  - unilateral headache
  - facial numbness
  - diplopia

✓ Investigations

Recommendation 2
- Nasopharyngeal carcinoma should be diagnosed by histopathological examination of the nasopharynx.
- In patients presenting with cervical lymphadenopathy, full head and neck assessment and fine needle aspiration cytological examination of the nodes should be done.

✓ Staging

Recommendation 3
- All nasopharyngeal carcinoma patients should be staged using the tumour node metastasis (TNM) system.

✓ Treatment

Recommendation 4
- Radiotherapy alone is the main treatment in Stage I nasopharyngeal carcinoma (NPC).
- Concurrent chemoradiotherapy should be offered in Stage II, III, IVA and IVB NPC.
- Intensity modulated radiotherapy is the preferred radiation technique in NPC.

Recommendation 5
- In recurrent nasopharyngeal carcinoma, nasopharyngectomy or re-irradiation may be offered.

Recommendation 7
- All nasopharyngeal carcinoma patients should have dental assessment prior to radiotherapy and treated accordingly.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these CPG were from the Ministry of Health (MoH) and Ministry of Education (MoE). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platform: Guidelines International Network (G-I-N), Medline via Ovid, Cochrane Database of Systemic Reviews (CDSR) and Pubmed. Refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all patients with nasopharyngeal carcinoma (NPC) regardless of study design. The search was limited to literature published in the last 20 years and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 22 January 2015 to 24 February 2016. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2016 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPGs namely Nasopharyngeal Cancer Treatment by Alberta Health Services published in 2013 and Diagnosis and Management of Head and Neck Cancer by Scottish Intercollegiate Guidelines Network published in 2006. The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to it being used as reference.

A total of 10 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 23 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval.

OBJECTIVES

The objectives of the Clinical Practice Guideline (CPG) are to provide evidence-based recommendations on the following:

i. diagnosis and staging of NPC
ii. treatment and follow-up of NPC

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

All patients with NPC

TARGET GROUP/USER

This CPG is intended to guide those involved in the management of NPC either in primary or secondary/tertiary care namely:

i. Medical officers and specialists in government and private practice
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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The draft CPG was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the CPG.

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ALGORITHM A : MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

- History taking
- Complete physical examination
- Nasopharyngeal examination & biopsy
- +/- FNAC of regional lymph nodes
- Baseline investigations (FBC, renal profile, random blood sugar, liver function test, chest X-ray and electrocardiogram)
- MRI of nasopharynx & neck (from base of skull to thoracic inlet) or CT with contrast
- PET-CT or CT thorax/abdomen or ultrasound and bone scan, as indicated
- Dental evaluation
- Nutritional evaluation

Determine disease stage

Stage I (T1N0M0)

Treatment with definitive radiotherapy (RT) to nasopharynx & elective RT to neck

- Definitive RT:-
  - **Primary site:** total of 66-70 Gy for 33-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
  - **Prophylactic neck**: 54-60 Gy for 30 fractions , treated one fraction/day for 6 weeks (1.8-2.0 Gy/fraction)
- **IMRT** recommended to minimise dose to critical structure

Stage II, III, IVA and IVB

Concurrent chemoradiotherapy

- Cisplatin + RT
- Conventional fractionation:
  - **Primary site:** total of 66-70 Gy for 33-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
  - **Neck**: 54-70 Gy for 30-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
- **IMRT** recommended to minimise dose to critical structures

Stage IVC (distant metastasis)

Palliative treatment

- Consider clinical trial if available
- Palliative chemotherapy to be considered in patients with good ECOG performance status (0-2)
- RT to palliate symptoms
- Referral to palliative care/ palliative home care

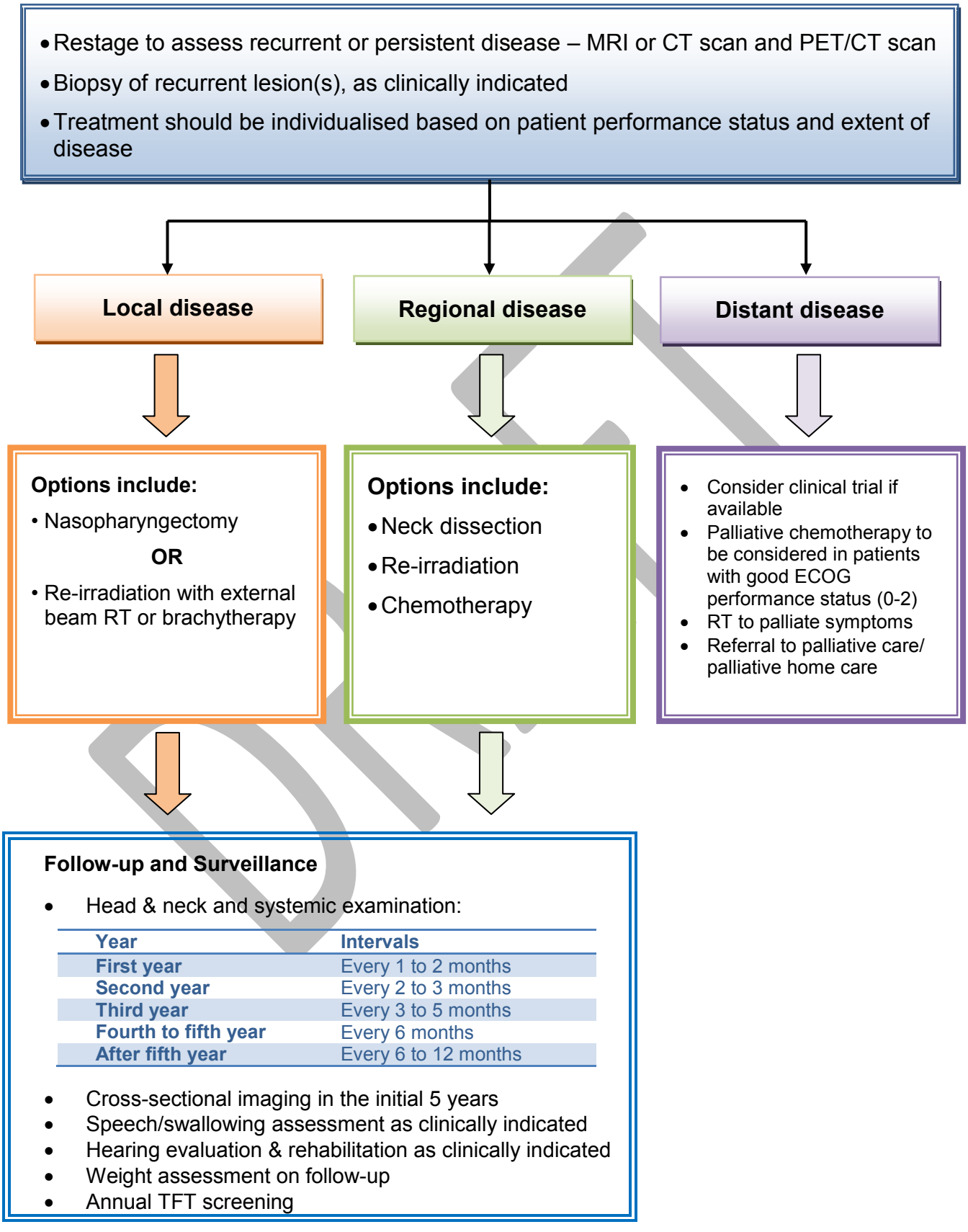
Follow-up and Surveillance

- Head & neck and systemic examination:

Year	Intervals
First year	Every 1 to 2 months
Second year	Every 2 to 3 months
Third year	Every 3 to 5 months
Fourth to fifth year	Every 6 months
After fifth year	Every 6 to 12 months

- Cross-sectional imaging in the initial 5 years
- Speech/swallowing assessment as clinically indicated
- Hearing evaluation & rehabilitation as clinically indicated
- Weight assessment on follow-up
- Annual thyroid function test (TFT) screening

ALGORITHM B : MANAGEMENT OF PERSISTENT DISEASE OR RECURRENT NPC



1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial malignant tumour of nasopharynx. It is most common among Chinese but constitutes only 0.7% of cancers worldwide.[1, level I] According to Global Cancer Statistic 2008, the incidence rate of NPC is 1 per 100,000 people and it was estimated that men are two to three times more likely to develop NPC than women.[2, level III] Geographically, Southeast Asia, Southern China, and North African countries have the highest prevalence of NPC compared with other parts of the world.

NPC is the fourth most common cancer among Malaysians (5.2% of all cancers).[3, level III] There are several risk factors associated with the disease. NPC is usually diagnosed late due to trivial presentation of painless neck lump, blood stained saliva or nasal secretion and unilateral mild ear block.[4-6, level III] In view of late presentation, its survival outcome is poor. The optimal management of NPC involves a multidisciplinary team. The main challenge for the team is for early diagnosis to prompt access to treatment such as radiation therapy. For those with intermediate or advanced disease, the aim is to minimise treatment side effects without compromising the outcome.

In view of high disease burden of NPC in Malaysia, variation in practice, resource implications as well as lack of local guidelines, the development of an evidence-based CPG for NPC is timely and essential to assist the healthcare providers in managing the disease locally.

2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

The number of new cancer cases is increasing worldwide. In 2012, there was an estimated of 86,700 new NPC cases with 50,800 deaths. Although NPC may be considered one of the rarer forms of cancer globally, the incidence is notably high in selected geographic and ethnic populations, such as in South-East Asia and Southern China.[7, level III]

In Malaysia, NPC is the fourth (5.2%) most common cancer among Malaysians and the third (8.4%) most common cancer among males.[3, level III] The male to female ratio is 3:1 for both newly diagnosed and recurrent cases.[4-6, level III] Most common age group at presentation is 40 to 60 years old.[4-6, level III] However, NPC may also occur in younger age group and the youngest case of NPC detected was in a 6 year old.[8, level III] NPC is predominant among Chinese (49%), followed by the natives of Sabah and Sarawak (28%) and Malay (22%).[4, level III] In Sarawak, high incidence of NPC is reported among Bidayuh (48.4%).[8, level III]

2.2 Risk Factors

Other risk factors for NPC are:

- **Infection** – increased risk of NPC in those tested positive for Epstein-Barr virus antibodies (RR of 3.5 to 32.8)[9, level II-2]
- **Family** – the risk of NPC among the first-degree relatives was 3.1 to 8.0 compared to those without family history [10-11, level II-2]
- **Lifestyle and environment**
  - ***Tobacco smoking*** is one of the important risk factors for NPC (OR=2.41, 95% CI 1.61 to 3.60).[12, level II-2] The risk rise by 1 - 2% with each pack-year of smoking.[13, level II-2]
  - Consumption of ***salted fish*** has higher risk of getting NPC in people who consume it since childhood (OR=2.45, 95% CI 2.03 to 2.94)[10, level II-2] and those who have it for three times or more in 1 month (OR=1.9, 95% CI 1.1 to 3.5).[14, level II-2]Exposure to

domestic wood cooking fires for more than 10 years (OR=5.8; 95%CI 2.5 to 13.6).[10, level II-2]

- Exposure to ***occupational solvents*** for 10 or less years (OR=2.6; 95%CI 1.4 to 4.8).[10, level II-2]
- Occupational exposure to ***wood dust*** (OR=1.63, 95%CI 1.02 to 2.61).[12, level II-2.]

2.3 Screening

Screening of NPC for general population in endemic area has been extensively studied. The methods used are Epstein-Barr virus (EBV) serology test and nasopharyngoscopy. The Health Technology Assessment (HTA) report by Ministry of Health (MOH) Malaysia published in 2011 concluded that there was insufficient evidence to recommend a population-based NPC screening programme as a public health policy.[15, level II-2] The findings of a recent Cochrane systematic review on NPC screening published in 2015 were consistent with the HTA report.[16, level I]

- Screening of NPC in general population could not be recommended due to insufficient evidence for its effectiveness and safety.

3. CLINICAL PRESENTATION AND REFERRAL

3.1 Clinical Presentation

Healthcare providers need to be aware that NPC patients often present with nonspecific symptoms and signs in the head and neck region. A proper clinical workup which begins with a detailed history of the presenting complaints is pertinent in diagnosing NPC.

The most common presenting symptoms of NPC are:[4-6, level III; 8, level III]

- neck lump/mass (42 - 80.8%) - always painless, can be unilateral or bilateral
- nasal symptoms (26 - 49.8%) - blood-stained nasal discharge or saliva, unilateral nose block, epistaxis or bad breath
- ear symptoms (11 - 48.4%) - ear block, deafness, tinnitus or pain; the symptoms are usually unilateral but can be bilateral as the disease progresses
- ophthalmo-neurologic symptoms (11 - 14.6%) - unilateral headache, facial numbness, diplopia, ptosis, trismus, dysphagia or hoarseness of voice. The most common cranial nerve involvement is 5th followed by 6th, 3rd, 4th and others.

The images of these symptoms can be viewed in **Appendix 3**.

Majority of NPC patients in Malaysia present with advanced stage (Stages III/IV) at the time of diagnosis (75 - 85%). This is due to lack of awareness of NPC symptoms and signs among patients and doctors.[4, level III; 6, level III; 8, level III]

3.2 Referral

There is no evidence retrieved on referral criteria for patients with NPC. In view of delayed in diagnosis of NPC, the CPG DG uses consensus method to address the importance of referral to Otorhinolaryngology services as soon as possible. Early referral is crucial in establishing diagnosis of NPC so that the patients could receive definitive treatment.

Recommendation 1

- Patients presenting with any of the following symptoms should be referred to Otorhinolaryngologists **as soon as possible** to rule out nasopharyngeal carcinoma :
  - painless neck lump
  - blood-stained nasal discharge/saliva
  - unilateral ear block or hearing loss
  - unilateral headache
  - facial numbness
  - diplopia

4. INVESTIGATION

4.1 Baseline Investigations

There is no retrievable evidence on baseline investigations for NPC patients. The established baseline investigations which include full blood count, renal profile, random blood sugar, liver function test, chest X-ray and electrocardiogram (ECG) are required to assess patient's general health.

4.2 Histopathology and Cytology

Biopsy of nasopharynx is mandatory in diagnosis of NPC. It is the preferred method for obtaining a definitive histological diagnosis as diagnostic sensitivity of nasopharyngeal cytology is limited (70 - 90%). Biopsies are taken from the gross lesions. In the absence of a gross lesion, multiple biopsies should be taken from nasopharynx for patients with high suspicion of NPC.[17] Fine needle aspiration cytological (FNAC) examination of enlarged cervical lymph nodes is useful in reaching a diagnosis of metastatic NPC, either for initial diagnosis or staging.

Histological grading of NPC is based on World Health Organization (WHO) Classification of Tumours, Pathology and Genetics of Head and Neck Tumours as outlined in **Table 1**.[17]

Table 1 : **Histopathological Classification of Nasopharyngeal Carcinoma**

WHO Classification 2005	WHO Classification 1991	WHO Classification 1978
Keratinizing squamous cell carcinoma (SCC)	Squamous cell carcinoma	WHO Type I (well-differentiated keratinized SCC
Non-keratinizing carcinoma • Differentiated • Undifferentiated	Non-keratinizing carcinoma • Differentiated • Undifferentiated	WHO Type II (differentiated keratinized non-SCC)
Basaloid squamous cell carcinoma	No synonym exists (recently described)	WHO Type III (undifferentiated carcinoma)

- In doubtful situation where the histological finding is unclear, ancillary tests such as immunohistochemical staining and EBV encoded early RNAs (EBER) in-situ hybridization will be performed.

Non-keratinizing carcinoma is the commonest histological subtype (75 - 99%) while the basaloid squamous cell carcinoma (SCC) is the least common (<0.2%).[17; 18, level III] Keratinizing SCC is more common in low incidence area of NPC.[18, level III] The histological type does not differ by gender.[19, level II-2]

There is no retrievable evidence on contraindication of lymph node biopsy in NPC. However, the CPG DG opines that full ENT assessment and FNAC is warranted before embarking on lymph node biopsy due to the possibility of extracapsular spread of the cancer cells.

Recommendation 2

- Nasopharyngeal carcinoma should be diagnosed by histopathological examination of the nasopharynx.
- In patients presenting with cervical lymphadenopathy, full head and neck assessment and fine needle aspiration cytological examination of the nodes should be done.

5. STAGING

Cancer staging plays an important role in determining the best treatment approach and prognosis of the disease. In this CPG, the latest edition of the American Joint Committee on Cancer or AJCC Cancer Staging Manual 2010 (7th Edition) is used to stage NPC.[20] The most clinically useful staging system is the Tumour Node Metastasis (TNM) System.

TNM staging consist of clinical examination, and pathological and radiological investigations. Clinical examination of nasopharynx, regional lymph nodes and distant metastatic sites (especially lung, liver and bone) is crucial for diagnosis and staging. Cranial nerves examination is vital as cranial nerve involvement may be the first and only presentation of NPC. Refer to **Appendix 4** for TNM Staging Diagram.

Primary Tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ

Nasopharynx	
T1	Tumour confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*
T2	Tumour with parapharyngeal extension*
T3	Tumour involves bony structures of skull base and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
*Note: Parapharyngeal extension denotes posterolateral infiltration of tumour.	

Regional Lymph Nodes (N) Nasopharynx

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis

N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa*
N3	Metastasis in a lymph node(s)* >6 cm and/or to supraclavicular fossa*
N3a	>6 cm in dimension
N3b	Extension to the supraclavicular fossa**
*Note: Midline nodes are considered ipsilateral nodes.	
**Note: Supraclavicular zone or fossa is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. All cases with lymph nodes (whole or part) in the fossa are considered N3b.	

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Radiological Staging

Imaging studies are essential in clinical staging of the NPC as it identifies the deep tumour infiltration and locoregional cervical lymph nodes involvement. It is mandatory to complete the staging process for further management of the disease.[20]

Magnetic resonance imaging (MRI) is superior to computed tomography (CT) scan in demonstrating soft tissue involvement. It is more sensitive than CT scan for skull base and intracranial tumour infiltration as well as identification of retropharyngeal lymph node metastasis (69.0% vs 52.1%, p<0.001). However, there is no significant difference in detection of the rest of the neck lymph node metastasis between MRI and CT scan.[21, level III] MRI is able to depict not only primary cancers that caused an obvious focal mass or infiltration outside the nasopharynx but also those early cancers that produced only mild thickening of the mucosa. It is also an accurate diagnostic test for patients with submucosal involvement which are not detected by endoscopy (sensitivity of 100% and specificity of 93%).[22, level III]

^{18}F-fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) has better sensitivity and specificity compared with other staging modalities (MRI or CT scan of head and neck, chest radiography, abdominal ultrasonography and skeletal scintigraphy) for N (pooled sensitivity of 84% and specificity of 90%) and M (pooled sensitivity of 87% and specificity of 98%) classifications, but not for T classification of newly diagnosed NPC.[23, level III]

In two systematic reviews, whole-body FDG PET or PET-CT demonstrated a good diagnostic performance in M staging of NPC compared to other conventional work-up (chest radiography, abdominal ultrasonography and skeletal scintigraphy). The pooled sensitivity ranged from 82% to 83% and the pooled specificity was 97%.[24-25, level III] A diagnostic study included in these systematic reviews showed that FDG PET-CT has better accuracy (96.2, 95% CI 89.3 to 98.7) in detecting distant metastasis compared with other imaging modalities which included CT scan of thorax and abdomen in combination with skeletal scintigraphy.[26, level III]

FDG PET is the best modality for diagnosis of local residual or recurrent NPC compared with CT and MRI with pooled sensitivity of 95% and specificity of 90%.[27, level III] However, the combined use of MRI and FDG PET-CT is more accurate (overall accuracy of 92.1, 95% CI 85.4 to 98.7) for tumour restaging than when either modality is used independently.[28, level II-2]

In local setting, CT scan is widely used to stage the disease in view of limited availability of MRI and FDG PET-CT. CT scan is also offered when there is contraindication for MRI such as the use of pacemaker. Some of the radiological images of NPC staging can be seen on **Appendix 5.**

Recommendation 3

- All nasopharyngeal carcinoma (NPC) patients should be staged using the tumour node metastasis (TNM) system.
- The preferred imaging modality is:
  - magnetic resonance imaging (MRI) for local and locoregional staging of NPC
  - ^{18}F-fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) for distant metastasis in NPC
- For restaging of residual and recurrence NPC, combination of MRI and FDG PET-CT should be used.
- When MRI and FDG PET-CT are not feasible, CT scan is an alternative imaging modality in NPC staging.

6. TREATMENT

Multidisciplinary team approach in the management of NPC cases is important to ensure optimum treatment planning. The main treatment for NPC is radiation therapy with or without chemotherapy.

6.1 Primary Cancer (Newly Diagnosed NPC)

Radiation therapy (RT) is the main treatment modality for non-disseminated NPC. Chemotherapy plays a role as adjunct treatment to RT. It can be given as concurrent, adjuvant or neoadjuvant setting.

NPC is radiosensitive and thus radiation therapy is the mainstay of treatment. Radical radiation therapy doses usually consist of 66 to 70Gy in 33-35 fractions, treated once daily over 6-7 weeks, usually 5 days a week with two rest days. Conventional 2-dimensional radiation therapy (2D-CRT) used to be the main technique. With the understanding about benefit of conformal radiation therapy and technological advancement, the therapy has evolved to 3-dimensional radiation therapy (3D-CRT) and more recently intensity modulated radiotherapy (IMRT).

IMRT has the potential to deliver higher doses of radiation to tumour cells near critical structures such as salivary glands, optic apparatus, spinal cord, brain stem and pituitary gland. IMRT improves local control and progression free survival (PFS) for both early and advanced stage NPC.[29, level II-2] A systematic review on IMRT to head and neck cancer showed significant reduction in grade 2-4 xerostomia (HR=0.76, 95%CI 0.66 to 0.87) without compromising loco-regional control and overall survival.[30, level I]

There is limited evidence on Stage II disease. In a cohort study of 362 patients on RT alone, the 5-years overall survival (OS) was significantly lower at 73.1% in T2N1 compared with T1N0 (96.6%).[31, level II-2] In a RCT conducted in 2011, concurrent chemotherapy improved the 5-year OS compared with RT alone (94.5% vs 85.8%) with a reduction of death by 70% (HR of death=0.30, 95% CI 0.12 to 0.76).[32, level I] Guidelines by National Comprehensive Cancer Network 2013 and European Society for Medical Oncology 2012 recommend CCRT in Stage II disease.[33-34]

There are strong evidences on chemotherapy added concurrently to RT in locoregionally advanced NPC (Stage III, IVA and IVB). Various combinations of chemotherapy were used with platinum-based being the commonest agent.

- In a meta-analysis of 1500 patients, pooled data showed an approximate 20% improvement in 2- to 4-year survival with the addition of chemotherapy to standard external beam radiation therapy. For the 4-year OS, the OR was 0.79 (95% CI 0.65 to 0.97). However, there was no report on quality assessment of the included primary studies.[35, level I]
- A Cochrane systematic review of eight RCTs in 2006 found that chemotherapy led to a small but significant benefit for 5-year OS with HR of death of 0.82 (95% CI 0.71 to 0.95). The concomitant trials showed a better treatment effect than induction trials or adjuvant trials [HR of 0.60 (95% CI 0.48 to 0.76), HR of 0.99 (95% CI 0.80 to 1.21) and HR of 0.97 (95% CI 0.69 to 1.38) respectively].[36, level I]
- A later updated meta-analysis of 19 RCTs in 2015 supported the findings of the above Cochrane review.[37, level I]
- In a 2015 network meta-analysis, both CCRT + AC and CCRT alone benefited OS significantly when compared with RT alone [HR of 0.64 (95% CI 0.53 to 0.76) and HR of 0.66 (95% CI 0.49 to 0.88) respectively]. The primary studies were of moderate quality.[38, level I]

The list of common chemotherapy drugs and the side effects is outlined in **Appendix 6**.

Neoadjuvant chemotherapy (NACT) is the administration of chemotherapy agents before a primary treatment. The aim is to reduce the size or extent of cancer. Based on three meta-analyses, NACT showed a benefit in disease free survival but not in OS and locoregional control.[37, level I; 39-40, level I] Strong evidence are required to establish the efficacy of NACT in locoregionally advanced NPC.

Adjuvant chemotherapy (AC) is chemotherapy given after primary treatment of NPC. Two meta-analyses showed that when compared with RT alone, AC + RT significantly lowered the risk of locoregional failure by 29 - 39% but not in OS.[37, level I; 40, level I] There were no significant differences in OS, locoregional recurrence free survival (LRFS) and distant metastasis free survival (DMFS) between CCRT + AC and CCRT alone. The primary studies used in these meta-analyses and network meta-analyses were of moderate in quality.[38, level I; 41, level I]

Common adverse events in chemotherapy include neutropaenia, mucositis, nausea and vomiting.[37-38, level I; 40, level I]

Due to limited evidence, efficacy of neoadjuvant and adjuvant chemotherapy in NPC has yet to be established.

Recommendation 4
- Radiotherapy alone is the main treatment in Stage I nasopharyngeal carcinoma (NPC).
- Concurrent chemoradiotherapy should be offered in Stage II, III, IVA and IVB NPC.
- Intensity modulated radiotherapy is the preferred radiation technique in NPC.

6.2 Recurrent Cancer

NPC can recur at local, locoregional or distant metastatic sites. These conditions can be difficult to manage. Treatment for primary site recurrence depends on the T staging. Treatment for rT1 and rT2 can be endoscopic nasopharyngectomy or brachytherapy. For rT3, selected rT4 and nodal recurrence, conventional nasopharyngectomy, radical neck dissection or re-irradiation is the treatment option.[42-43, level II-3; 44, level II-2]

Five-years overall survival rate post-nasopharyngectomy ranges from 42.1% to 52%.[42-43, level II-3; 44, level II-2] The survival rate is higher in rT1 (49.1% to 73%) and rT2 (24.7% to 40%) compared with higher T staging.[42, level II-3; 44, level II-2]

Transient complications of nasopharyngectomy such as palatal fistula and submandibular necrosis may resolve spontaneously or require further intervention.[42, level II-3; 44, level II-2] Uncommon complications are:
- permanent morbidities due to nerve injury (paralysis causing dysphagia) and severe trismus[42, level II-3; 44, level II-2]
- mortality caused by massive bleeding due to injury to carotid artery[43, level II-3; 44, level II-2]

Significant poor prognostic factors on survival of post-nasopharyngectomy are: [42, level II-3]
- advanced T stage of disease at treatment
- lymph node metastasis
- invasion of skull base
- invasion of parapharyngeal space
- positive surgical margin

With a carefully selected subset of patients, the potential for durable local control and respectable survival rates with re-irradiation can be achieved. Re-irradiation poses a therapeutic challenge as the radiation dose that can be given is limited by previous radiation treatment dose and normal organs tolerance.

3D-CRT, IMRT and brachytherapy are the different RT approaches that can be offered. A cohort study showed that these three approaches were beneficial and feasible for rT1-T2 NPC in terms of local control, disease-free survival and overall survival.[45, level II-2] Long term toxicity for re-irradiation are of concern. Severe adverse effects for re-irradiation include nasopharyngeal necrosis, cranial nerve palsy, trismus, hearing deficit and temporal lobe necrosis.[45, level II-2; 46, level III]

The choice of therapeutic approach depends upon local expertise and facilities, and the extend of recurrent disease.

Recommendation 5
- In recurrent nasopharyngeal carcinoma, nasopharyngectomy or re-irradiation may be offered.

6.3 Advanced Disease

In advanced disease with distant metastasis (M1) of NPC, options of treatment include chemotherapy, radiotherapy and palliative care. NPC patients with distant metastasis (Stage IVC) receiving either chemotherapy or radiotherapy have better 1-year overall survival rate compared with those without treatment (p=0.0015). The radiation dose that might be given is 70.2-75.6 Gy.[47, level III]

Multimodality treatment which include chemotherapy, radiotherapy with or without surgery increase survival rate significantly compared with best supportive care or chemotherapy alone in metastatic NPC.[48, level III]

Palliative care is very important in order to provide comfort and support to patients and families who are living with or dying from advanced NPC. These patients will have complex physical and psychosocial problems. A comprehensive approach of treatment such as surgery, radiotherapy, chemotherapy, psychological and social supports, pain control, nutritional and spiritual supports may alleviate some of the discomfort for a better quality of life.[49] Palliative chemotherapy may be considered in patients with good Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 as outlined in **Appendix 7.**

For pain management in cancer patients, refer to CPG Management of Cancer Pain.[50]

Recommendation 6
- Multimodality treatment including palliative care should be considered in advanced nasopharyngeal carcinoma.

7. SUPPORTIVE CARE

7.1 Dental Care

Refer to **Subchapter 8.1** on **Oral Complications.**

7.2 Treatment of Otitis Media with Effusion

Otitis media with effusion (OME) is common in NPC patients. The treatment options for post-irradiation OME are:[51, level I]

- Myringotomy plus grommet insertion
- Simple aspiration (auripuncture)
- Tympanic membrane fenestration with cauterization

Myringotomy and grommet insertion has higher cure rate at the end of 2-year follow-up compared with simple auripuncture plus aspiration (51% vs 38%, p=0.011) despite higher incidence of complications (28.9% vs 15.6%).[51, level I]

7.3 Contraception

Ideally, highly effective reversible contraceptives, such as intrauterine or implantable contraceptives, are recommended for women treated for cancer including NPC. However, combined hormonal contraceptive methods (containing oestrogen and progestin) should be avoided by women with active cancer or who have been treated for cancer in the last six months due to the increased risk of venous thromboembolism (VTE). For women who are cancer-free for at least six months and have no history of hormone-mediated cancers, chest wall irradiation, anaemia, osteoporosis or VTE, the use of any method of contraception can be recommended.[52, level III]

7.4 Nutritional Support

NPC patients are at risk for malnutrition due to disease process or complications of the treatment. Adequate nutrition is important for supportive or palliative care to ease the treatment process and improve quality of life. Nutritional intake for NPC patients can be in the form of oral, enteral and parenteral feed depending on patients' ability to tolerate the food and their requirements. Nutritional supplements may be used to maintain adequate calorie and nutrient intake which includes:[49]

- Nutritionally complete supplements
- Energy and protein supplements
- Carbohydrate supplements
- Protein supplements
- Fat supplements

8. MANAGEMENT OF COMPLICATIONS

Post-radiotherapy complications such as oral and aural complications, and cranial nerve palsies are common in the treatment of NPC. Other late toxicities post-radiotherapy are listed in **Appendix 8**.

8.1 Oral Complications

The common oral complications post-radiotherapy are:
- xerostomia (80% to 100%)[53-55, level II-3]
- mucositis (60% from third to fourth week after the beginning of radiotherapy)[53, level II-3]
- candidiasis (16% to 67%)[53-55, level II-3]

It is essential that NPC patients receive dental assessment prior to radiotherapy to minimise post-treatment oral complications. The oral complications among NPC survivors causes significant negative impact in functional, physical, social and handicap in oral health-related quality of life (Oral Health Impact Profile-subscale).[56, level II-3]

At present, there is no retrievable evidence on specific dental management in NPC patients. However, some of the techniques used in dental care are:
- fluoride therapy[57, level I]
- chlorhexidine rinse[57, level I]
- dental extraction[55, level II-3]

Treatment for xerostomia is limited. Locally, symptomatic relief such as frequent sipping of plain water and moisturising mouth gel or gargle has been offered to the affected patients. Pilocarpine, another option of treatment, is efficacious and safe. Its most common complication is sweating.[58-59, level I]

8.2 Osteoradionecrosis

Dental diseases increase the risk of osteoradionecrosis (ORN). Therefore, dental assessment prior to radiotherapy is essential to reduce the risks of ORN.

Osteoradionecrosis of the skull base post-radiotherapy can be controlled by sequestrectomy combined with hyperbaric oxygen in majority of NPC patients. In extensive cases, radical sequestrectomy with microvascular free flap reconstruction are justified.[62, level III] Long-term antibiotics can be used but may not be sufficient to treat an extensive disease.

Recommendation 7
- All nasopharyngeal carcinoma (NPC) patients should have dental assessment prior to radiotherapy and treated accordingly.
- Pilocarpine should be offered for treatment of post-radiotherapy xerostomia in NPC patients, if it is available.

8.3 Cranial Nerve Palsy

There is no definite treatment for cranial nerve palsy post-radiotherapy in NPC patients. Symptomatic treatments such as nasogastric tube or gastrostomy tube feeding for dysphagia or aspiration may be offered. In intractable aspiration secondary to radiation encephalopathy or radiation damage of cranial nerve, closure of laryngotracheal cavity and tracheostomy is an option.[60, level III] Strabismus as a result of sixth cranial nerve palsy can be treated temporarily by Botulinum Toxin A injection.[61, level III]

8.4 Otitis Media with Effusion

Refer to **Subchapter 7.2** under **Supportive Care**.

9. PROGNOSIS AND FOLLOW-UP

9.1 Prognosis

Different prognostic categories (based on the difference in failure patterns) can be defined across different stages, as shown in **Table 2**.[63, level II-3; 64, level III] These prognostic groupings have important implications for the selection of appropriate treatment strategies.

Table 2 : Prognosis of Different NPC Stages

Stage	Prognosis
T1-2 N0-1	Relatively good treatment outcome
T3-4 N0-1	Mainly local failure
T1-2 N2-3	Mainly regional and distant failure
T3-4 N2-3	Local, regional and distant failure

Males ($p<0.05$) and tumour with lymph nodes involvement ($p<0.05$) have poorer prognosis as compared with females and tumour confined to the primary site in 5-year LRFS. The 5-year LRFS for male is 33.3% and for N1 patients is 35.0%.[63, level II-3]

Distant metastasis is the most common mode of failure in NPC, followed by local recurrence. While a small percentage of locally recurrent NPC can be salvaged, the vast majority of distant metastasis succumbs to the disease. However, patients with non-disseminated NPC (6.88%) survive two years or more after distant metastasis is diagnosed.[65, level II-3]

9.2 Follow-up

Radiotherapy acute toxicities usually take about one to two months to resolve and tumour will regress maximally within two to three months. Hence, the patients need to be reviewed post-radiotherapy to assess acute toxicities and manage accordingly.

The aims of following-up patients after NPC treatment are:

- to assess the response to treatments
- to manage side effects and complications which may arise due to the disease process or from the treatment[64, level III] (refer to **Chapter 8** on **Management of Complications**)
- to provide surveillance and early detection of locoregional relapses, which are amenable to radical salvage treatment[64, level III] to detect occurrence of second primary cancer
    - There is a 24% increased risk in the development of a second cancer after NPC as compared with the general population (standardised incidence rate=1.24, 95% CI 1.15 to 1.33).[66, level III] The average interval between the occurrence of the first and the second cancers is 5.33 years. The second primary cancers are oral/pharyngeal cancer, head and neck sarcoma, skin cancer and salivary gland cancer.[67, level III]

The CPG DG and RC suggest the following procedures to be conducted on NPC patients during follow-up.

The follow-up procedures in NPC are:
- clinical examination of the nasopharynx including an endoscopic examination to detect superficial tumours
- examination of the neck and other systems (thorax and abdomen)
- if post-radiotherapy cross sectional imaging is required, it should be offered no earlier than 3 months
- cross-sectional imaging, as needed, to detect deep infiltrating tumours not associated with mucosal lesion during the initial 3 - 5 years post-treatment

There is no standard local follow-up schedule for NPC patients. However, the CPG DG and RC suggest the following schedule on NPC.

Table 3 : Follow-up Schedule of NPC Without Recurrence

Year after completion of treatment	Frequency of follow-up
First year	Every 1 to 2 months
Second year	Every 2 to 3 months
Third year	Every 3 to 5 months
Fourth to fifth year	Every 6 months
After fifth year	Every 6 to 12 months

*interval of follow-up may be adjusted based on clinical judgement

10. IMPLEMENTING THE GUIDELINES

Implementation of CPG is important as it helps in providing quality healthcare services based on best available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

10.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

- availability of CPG to healthcare providers (hardcopies and softcopies)
- conferences and updates on management of NPC

Limiting factors in the CPG implementation include:

- limited awareness in managing and referrals of NPC among healthcare providers
- inadequate NPC training at all levels of healthcare providers
- variation in NPC treatment at different levels of care due to administrative and financial constraints

10.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

- ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
- reinforce training of healthcare providers via regular seminars and workshops
- involve multidisciplinary team at all levels
- improve the diagnostic and therapeutic facilities, and trained experts
- strengthen the head and neck cancer registry

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

$$\text{Percentage of NPC patients treated with IMRT} = \frac{\text{Number of NPC patients treated with IMRT}}{\text{Total number of NPC patients treated with radiotherapy}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

REFERENCES

1. Al-Sarraf M, LeBlanc, M., Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol 1998; 16: 1310-1317.
2. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; Year. Available at: http://globocan.iarc.fr. 2010 (accessed on 28 September 2016)
3. Zainal Ariffin O, Nor Saleha IT. National cancer registry report 2007. Malaysia: Ministry of Health. 2011.
4. Pua KC, Khoo AS, Yap YY, et al. Nasopharyngeal carcinoma database. Med J Malaysia. 2008 Sep;63 (Suppl C):59-62.
5. Suzina SA, Hamzah M. Clinical presentation of patients with nasopharyngeal carcinoma. Med J Malaysia. 2003 Oct;58(4):539-45.
6. Prasad U, Pua KC. Nasopharyngeal carcinoma: a delay in diagnosis. The Medical journal of Malaysia. 2000 Jun;55(2):230-5.
7. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015 Mar 1;65(2):87-108.
8. Tiong TS, Selva KS. Clinical presentation of nasopharyngeal carcinoma in Sarawak Malaysia. Med J Malaysia. 2005 Dec;60(5):624-8.
9. Chien YC, Chen JY, Liu MY, et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. N Engl J Med. 2001 Dec 27;345(26):1877-82.
10. Guo X, Johnson RC, Deng H, et al. Evaluation of nonviral risk factors for nasopharyngeal carcinoma in a high-risk population of Southern China. Int J Cancer. 2009 Jun 15;124(12):2942-7.
11. Friborg J, Wohlfahrt J, Koch A, et al. Cancer susceptibility in nasopharyngeal carcinoma families--a population-based cohort study. Cancer Res. 2005 Sep 15;65(18):8567-72.
12. Ekburanawat W, Ekpanyaskul C, Brennan P, et al. Evaluation of non-viral risk factors for nasopharyngeal carcinoma in Thailand: results from a case-control study. Asian Pac J Cancer Prev. 2010;11(4):929-32.
13. Xue WQ, Qin HD, Ruan HL, et al. Quantitative association of tobacco smoking with the risk of nasopharyngeal carcinoma: a comprehensive meta-analysis of studies conducted between 1979 and 2011. Am J Epidemiol. 2013 Aug 1;178(3):325-38.
14. Jia WH, Huang QH, Liao J, et al. Trends in incidence and mortality of nasopharyngeal carcinoma over a 20-25 year period (1978/1983-2002) in Sihui and Cangwu counties in southern China. BMC Cancer. 2006 Jul 6;6:178.
15. Health Technology Assessment Section (MaHTAS) MDD, Ministry of Health Malaysia. Nasopharyngeal Carcinoma Screening. 2010. MOH/P/PAK/211.10(TR).
16. Yang S, Wu S, Zhou J, et al. Screening for nasopharyngeal cancer. The Cochrane Library. 2015 Jan 1.
17. Barnes L, Eveson JW, Reichart P, et al. Word Health Organization Classification of Tumours: Pathology and genetics of head and neck tumors. 2005.
18. Wei KR, Xu Y, Liu J, et al. Histopathological classification of nasopharyngeal carcinoma. Asian Pac J Cancer Prev. 2011;12(5):1141-7.
19. Marks JE, Phillips JL, Menck HR. The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer. 1998 Aug 1;83(3):582-8.
20. Edge SB, Byrd DR, Compton CC. American Joint Committee on Cancer, American Cancer Society: AJCC Cancer Staging Manual (7th edition). Springer, New York. 2009.

21. Liao XB, Mao YP, Liu LZ, et al. How does magnetic resonance imaging influence staging according to AJCC staging system for nasopharyngeal carcinoma compared with computed tomography? Int J Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1368-77.
22. King AD, Vlantis AC, Bhatia KS, et al. Primary nasopharyngeal carcinoma: diagnostic accuracy of MR imaging versus that of endoscopy and endoscopic biopsy. Radiology. 2011 Feb;258(2):531-7.
23. Vellayappan BA, Soon YY, Earnest A, et al. Accuracy of (18)F-flurodeoxyglucose-positron emission tomography/computed tomography in the staging of newly diagnosed nasopharyngeal carcinoma: a systematic review and meta-analysis. Radiol Oncol. 2014 Nov 5;48(4):331-8.
24. Chang MC, Chen JH, Liang JA, et al. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. Eur J Radiol. 2013 Feb;82(2):366-73.
25. Xu G, Li J, Zuo X, et al. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope. 2012 Sep;122(9):1974-8.
26. Chua ML, Ong SC, Wee JT, et al. Comparison of 4 modalities for distant metastasis staging in endemic nasopharyngeal carcinoma. Head Neck. 2009 Mar;31(3):346-54.
27. Liu T, Xu W, Yan WL, et al. FDG-PET, CT, MRI for diagnosis of local residual or recurrent nasopharyngeal carcinoma, which one is the best? A systematic review. Radiother Oncol. 2007 Dec;85(3):327-35.
28. Comoretto M, Balestreri L, Borsatti E, et al. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. Radiology. 2008 Oct;249(1):203-11.
29. Zhang MX, Li J, Shen GP, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up. Eur J Cancer. 2015 Nov;51(17):2587-95.
30. Marta GN, Silva V, de Andrade Carvalho H, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 2014 Jan;110(1):9-15.
31. Xiao WW, Han F, Lu TX, et al. Treatment outcomes after radiotherapy alone for patients with early-stage nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2009 Jul 15;74(4):1070-6.
32. Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst. 2011 Dec 7;103(23):1761-70.
33. Pfister DG, Ang KK, Brizel DM, et al. Head and neck cancers, version 2.2013. Journal of the National Comprehensive Cancer Network. 2013 Aug 1;11(8):917-23. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed on 28 September 2016)
34. Chan AT, Grégoire V, Lefebvre JL, et al: EHNS–ESMO–ESTRO Guidelines Working Group. Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2012 Oct 1;23(suppl 7):vii83-5.
35. Huncharek M, Kupelnick B. Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. Am J Clin Oncol. 2002 Jun;25(3):219-23.
36. Baujat B, Audry H, Bourhis J, et al; MAC-NPC Collaborative Group. Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004329.
37. Blanchard P, Lee A, Marguet S, et al; MAC-NPC Collaborative Group. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol. 2015 Jun;16(6):645-55.

38. Chen YP, Wang ZX, Chen L, et al. A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. Ann Oncol. 2015 Jan;26(1):205-11.

39. He X, Xu K, Guo J, et al. A meta-analysis of neoadjuvant chemotherapy plus radiation in the treatment of locally advanced nasopharyngeal carcinoma. J Cancer Res Ther. 2015 Oct;11 Suppl 2:C205-8.

40. OuYang PY, Xie C, Mao YP, et al. Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials. Ann Oncol. 2013 Aug;24(8):2136-46.

41. Liang ZG, Zhu XD, Zhou ZR, et al. Comparison of concurrent chemoradiotherapy followed by adjuvant chemotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a meta-analysis of 793 patients from 5 randomized controlled trials. Asian Pac J Cancer Prev. 2012;13(11):5747-52.

42. Bian X, Chen H, Liao L. A retrospective study of salvage surgery for recurrent nasopharyngeal carcinoma. Int J Clin Oncol. 2012 Jun;17(3):212-7.

43. Hao SP, Tsang NM, Chang KP, et al. Nasopharyngectomy for recurrent nasopharyngeal carcinoma: a review of 53 patients and prognostic factors. Acta Otolaryngol. 2008 Apr;128(4):473-81.

44. Fee WE Jr, Moir MS, Choi EC, et al. Nasopharyngectomy for recurrent nasopharyngeal cancer: a 2- to 17-year follow-up. Arch Otolaryngol Head Neck Surg. 2002 Mar;128(3):280-4.

45. Qiu S, Lu J, Zheng W, et al. Advantages of intensity modulated radiotherapy in recurrent T1-2 nasopharyngeal carcinoma: a retrospective study. BMC cancer. 2014 Nov 3;14(1):1.

46. Cheah SK, Lau FN, Yusof MM, et al. Treatment outcome with brachytherapy for recurrent nasopharyngeal carcinoma. Asian Pac J Cancer Prev. 2013 Jan 1;14(11):6513-8.

47. Yeh SA, Tang Y, Lui CC, et al. Treatment outcomes of patients with AJCC stage IVC nasopharyngeal carcinoma: benefits of primary radiotherapy. Jpn J Clin Oncol. 2006 Mar;36(3):132-6.

48. Zheng W, Zong J, Huang C, et al. Multimodality Treatment May Improve the Survival Rate of Patients with Metastatic Nasopharyngeal Carcinoma with Good Performance Status. PLoS One. 2016 Jan 12;11(1):e0146771.

49. Booth DS, Davies A, editors. Palliative care consultations in head and neck cancer. Oxford University Press; 2006.

50. Ministry of Health Malaysia. Management of Cancer Pain. Putrajaya: MOH; 2010.

51. Xu YD, Ou YK, Zheng YQ, et al. The treatment for postirradiation otitis media with effusion: a study of three methods. Laryngoscope. 2008 Nov;118(11):2040-3.

52. Patel A, Schwarz EB; Society of Family Planning. Cancer and contraception. Release date May 2012. SFP Guideline #20121. Contraception. 2012 Sep;86(3):191-8.

53. Wang WC, Chen YK, Lin LM. Oral care experiences with 181 nasopharyngeal carcinoma patients receiving radiotherapy in a Taiwanese hospital. Auris Nasus Larynx. 2008 Jun;35(2):230-4.

54. Schwarz E, Chiu GK, Leung WK. Oral health status of southern Chinese following head and neck irradiation therapy for nasopharyngeal carcinoma. J Dent. 1999 Jan;27(1):21-8.

55. Epstein JB, Emerton S, Lunn R, et al. Pretreatment assessment and dental management of patients with nasopharyngeal carcinoma. Oral Oncol. 1999 Jan;35(1):33-9.

56. McMillan AS, Pow EH, Leung WK, et al. Oral health-related quality of life in southern Chinese following radiotherapy for nasopharyngeal carcinoma. J Oral Rehabil. 2004 Jun;31(6):600-8.

57. Hong CH, Napeñas JJ, Hodgson BD, et al; Dental Disease Section, Oral Care Study Group, Multi-national Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer. 2010 Aug;18(8):1007-21.

58. Rieke JW, Hafermann MD, Johnson JT, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two prospective randomized clinical trials. Int J Radiat Oncol Biol Phys. 1995 Feb 1;31(3):661-9.

59. LeVeque FG, Montgomery M, Potter D, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. J Clin Oncol. 1993 Jun;11(6):1124-31.

60. Qu S, Su Z, He X, et al. Closure of laryngotracheal cavity and tracheostomy for intractable aspiration secondary to radiation encephalopathy or radiation damage of cranial nerve after radiotherapy of nasopharyngeal carcinoma. Acta Otolaryngol. 2006 Sep;126(9):962-6.

61. Quah BL, Ling YL, Cheong PY, et al. A review of 5 years' experience in the use of botulinium toxin A in the treatment of sixth cranial nerve palsy at the Singapore National Eye Centre. Singapore Med J. 1999 Jun;40(6):405-9.

62. Hao SP, Chen HC, Wei FC, et al. Systematic management of osteoradionecrosis in the head and neck. Laryngoscope. 1999 Aug;109(8): 1324-7;discussion 1327-8.

63. El-Sherbieny E, Rashwan H, Lubis SH, et al. Prognostic factors in patientswith nasopharyngeal carcinoma treated in Hospital Kuala Lumpur. Asian Pac J Cancer Prev. 2011;12(7):1739-43.

64. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet. 2005 Jun 11-17; 365(9476):2041-54.

65. Teo PM, Leung SF, Yu P, et al. A comparison of Ho's, International Union Against Cancer, and American Joint Committee stage classifications for nasopharyngeal carcinoma. Cancer. 1991 Jan 15;67(2):434-9.

66. Wang CC, Chen ML, Hsu KH, et al. Second malignant tumors in patients with nasopharyngeal carcinoma and their association with Epstein-Barr virus. International Journal of Cancer. 2000 Jul 15;87(2):228-31.

67. Chen MC, Feng IJ, Lu CH, et al. The incidence and risk of second primary cancers in patients with nasopharyngeal carcinoma: a population-based study in Taiwan over a 25-year period (1979–2003). Annals of oncology. 2008 Jun 1;19(6):1180-6.

Appendix 1

EXAMPLE OF SEARCH STRATEGY

1. Nasopharyngeal Neoplasms/
2. ((neoplasm* or cancer* or carcinoma*) adj1 (nasopharynx or nasopharyngeal)).tw.
3. 1 or 2
4. RADIOTHERAPY/
5. (radiotherap* adj1 targeted).tw.
6. radiotherap*.tw.
7. Chemoradiotherapy/
8. ((concomitant or concurrent or synchronous) adj1 (chemoradiotherap* or radiochemotherap*)).tw.
9. chemoradiotherap*.tw.
10. radiochemotherap*.tw.
11. CHEMORADIOTHERAPY, ADJUVANT/
12. (adjuvant adj1 (radiochemotherap* or chemoradiotherap*)).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13
15. limit 14 to (english language and humans and last 20 years)

Appendix 2

CLINICAL QUESTIONS

1. What is the epidemiology of nasopharyngeal carcinoma?
2. What are the risk factors of nasopharyngeal carcinoma?
3. What are the clinical presentations of patient with nasopharyngeal carcinoma?
4. What are the investigations for nasopharyngeal carcinoma?
5. What are the staging modalities in nasopharyngeal carcinoma?
6. What are the effective and safe treatments for various stages of nasopharyngeal carcinoma?
7. What are the effective and safe supportive cares for patients with nasopharyngeal carcinoma?
8. What are the effective and safe management of complications following treatment of nasopharyngeal carcinoma?
9. What are the effective follow-up plans for patients with nasopharyngeal carcinoma?
10. What are the effective and safe management of advanced disease (distant metastases) of nasopharyngeal carcinoma?

Appendix 3

CLINICAL PRESENTATIONS

Figure 1 : Painless neck lumps

Figure 2 : Recurrent NPC with lymph node metastasis

Figure 3 : NPC with neck lump and trismus

Appendix 3

CLINICAL PRESENTATIONS

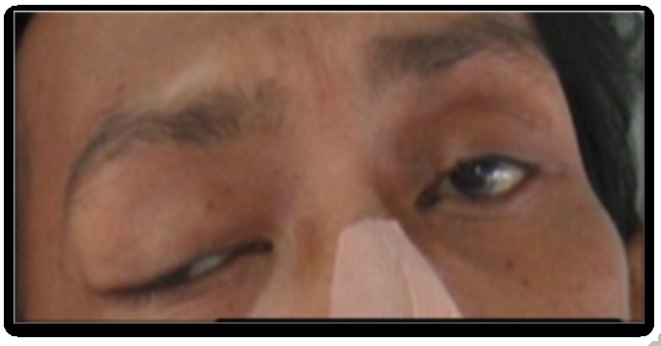


Figure 4 : NPC with neck lump and ptosis

Figure 5 : NPC with ophthalmoplegia

Figure 6 : NPC with neck lump and cranial nerve 12 palsy (tongue deviation)

Appendix 3

CLINICAL PRESENTATIONS

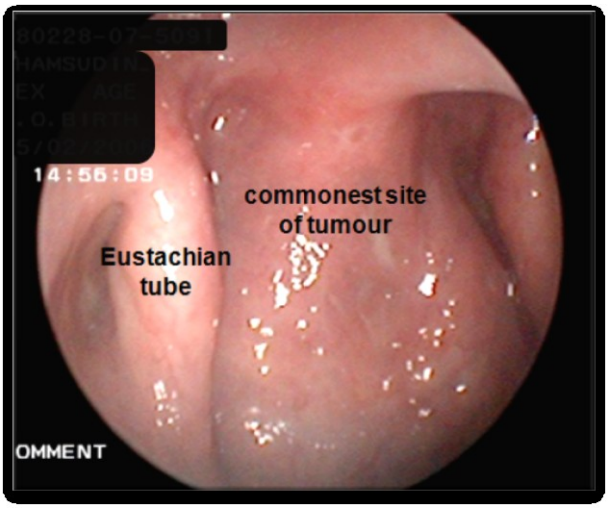


Figure 7 : Normal nasopharynx on endoscopy

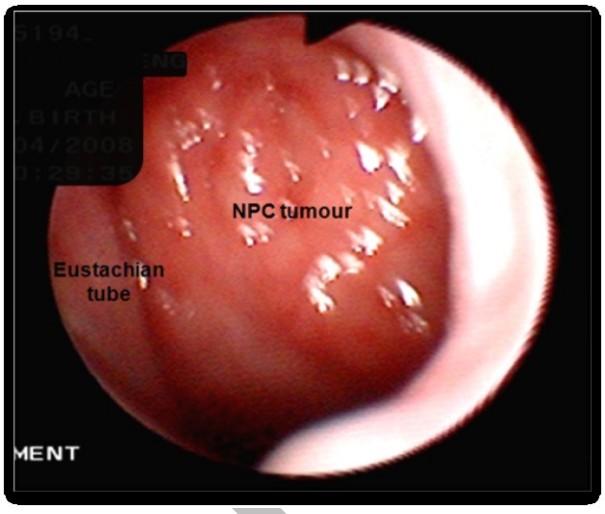


Figure 8 : Nasopharyngeal carcinoma on endoscopy

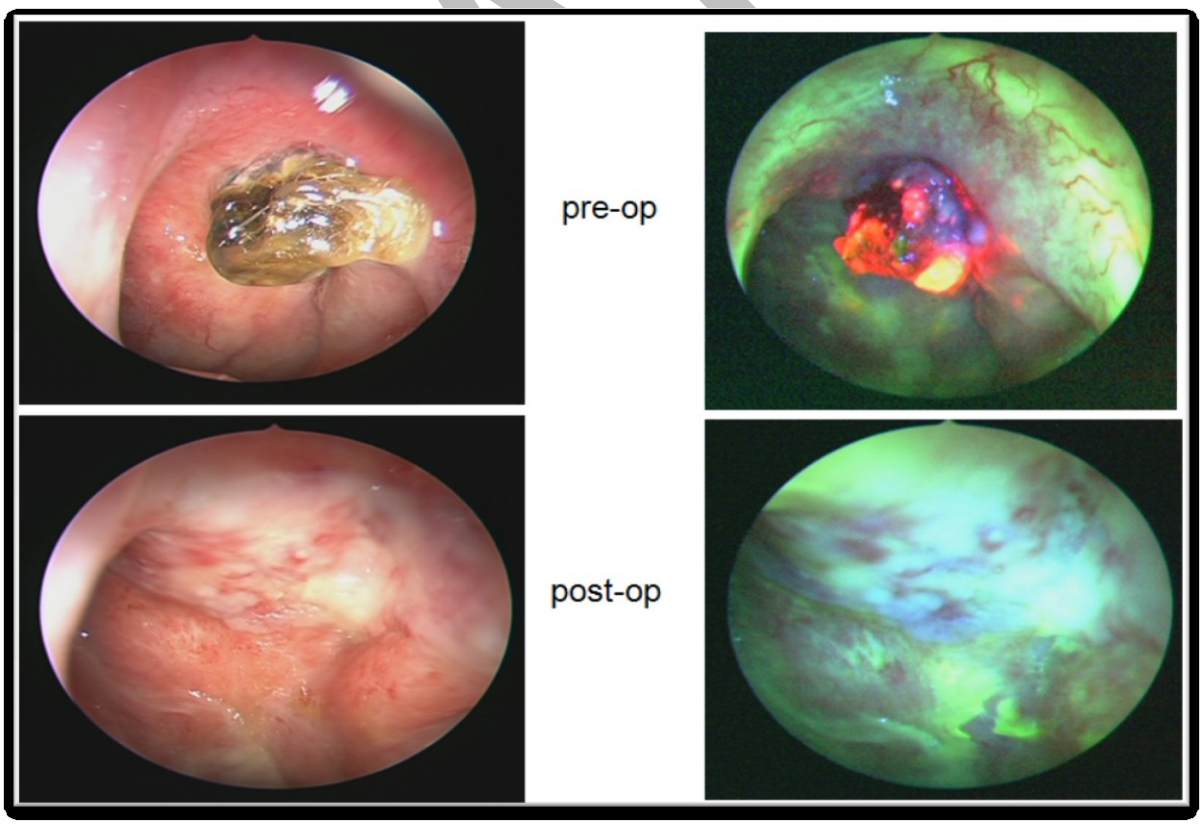


Figure 9 : Recurrent NPC pre- and post-endoscopic nasopharyngectomy. Endoscopic pictures in white light as compared with auto-flourescence pictures in green.

Appendix 4

TNM STAGING DIAGRAM

NASOPHARYNX STAGING FORM			
CLINICAL *Extent of disease before any treatment*	**STAGE CATEGORY DEFINITIONS**		**PATHOLOGIC** *Extent of disease during and from surgery*
y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	**Tumor size**:_____	**Laterality** ☐ left ☐ right ☐ bilateral	y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
PRIMARY TUMOR (T)			
☐ TX	Primary tumor cannot be assessed		☐ TX
☐ T0	No evidence of primary tumor		☐ T0
☐ Tis	Carcinoma		☐ Tis
☐ T1	Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension*		☐ T1
☐ T2	Tumor with parapharyngeal extension*		☐ T2
☐ T3	Tumor involves bony structures of skull base and/or paranasal sinuses		☐ T3
☐ T4	Tumor with intracranial extension and/or involvement of involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/ masticator space * Parapharyngeal extension denotes posterolateral infiltration of tumor.		☐ T4
REGIONAL LYMPH NODES (N)			
Nasopharynx The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.			
☐ NX	Regional lymph nodes cannot be assessed		☐ NX
☐ N0	No regional lymph node metastasis		☐ N0
☐ N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension		☐ N1

☐	N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*	☐ N2
☐	N3	Metastasis in a lymph node(s)* >6 cm and/or extension to supraclavicular fossa	☐ N3
☐	N3a	Greater than 6 cm in dimension	☐ N3a
☐	N3b	Extension to the supraclavicular fossa**	☐ N3b
		* Midline nodes are considered ipsilateral nodes. **Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder (see Fig. 4.2). Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.	

DISTANT METASTASIS (M)

☐	M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐	M1	Distant metastasis	☐ M1

ANATOMIC STAGE • PROGNOSTIC GROUPS-NASOPHARYNX

CLINICAL

GROUP	T	N	M
☐ 0	Tis	N0	M0
☐ I	T1	N0	M0
☐ II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
☐ III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
☐ IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
☐ IVB	Any T	N3	M0
☐ IVC	Any T	Any N	M1
☐	Unknown Stage		

PATHOLOGIC

GROUP	T	N	M
☐ 0	Tis	N0	M0
☐ I	T1	N0	M0
☐ II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
☐ III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
☐ IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
☐ IVB	Any T	N3	M0
☐ IVC	Any T	Any N	M1
☐	Unknown Stage		

NASOPHARYNX STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
REQUIRED FOR STAGING: None
CLINICALLY SIGNIFICANT:
Size of Lymph Nodes: _____
Extracapsular Extension from Lymph Nodes for Head & Neck: _____
Head & Neck Lymph Nodes Levels I-III: _____
Head & Neck Lymph Nodes Levels IV-V: _____
Head & Neck Lymph Nodes Levels VI-VII: _____
Other Lymph Node Group: _____
Clinical Location of cervical nodes: _____
Extracapsular spread (ECS) Clinical: _____
Extracapsular spread (ECS) Pathologic: _____
Human Papillomavirus (HPV) Status: _____
Tumor Thickness: _____

Histologic Grade (G) (also known as overall grade)

Grading system	**Grade**
☐ 2 grade system	☐ Grade I or 1
☐ 3 grade system	☐ Grade II or 2
☐ 4 grade system	☐ Grade III or 3
☐ No 2, 3, or 4 grade system is available	☐ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

☐ Lymph-Vascular Invasion Not Present (absent)/Not Identified
☐ Lymph-Vascular Invasion Present/Identified
☐ Not Applicable
☐ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

☐ RX Presence of residual tumor cannot be assessed
☐ R0 No residual tumor
☐ R1 Microscopic residual tumor
☐ R2 Macroscopic residual tumor

General Notes: For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

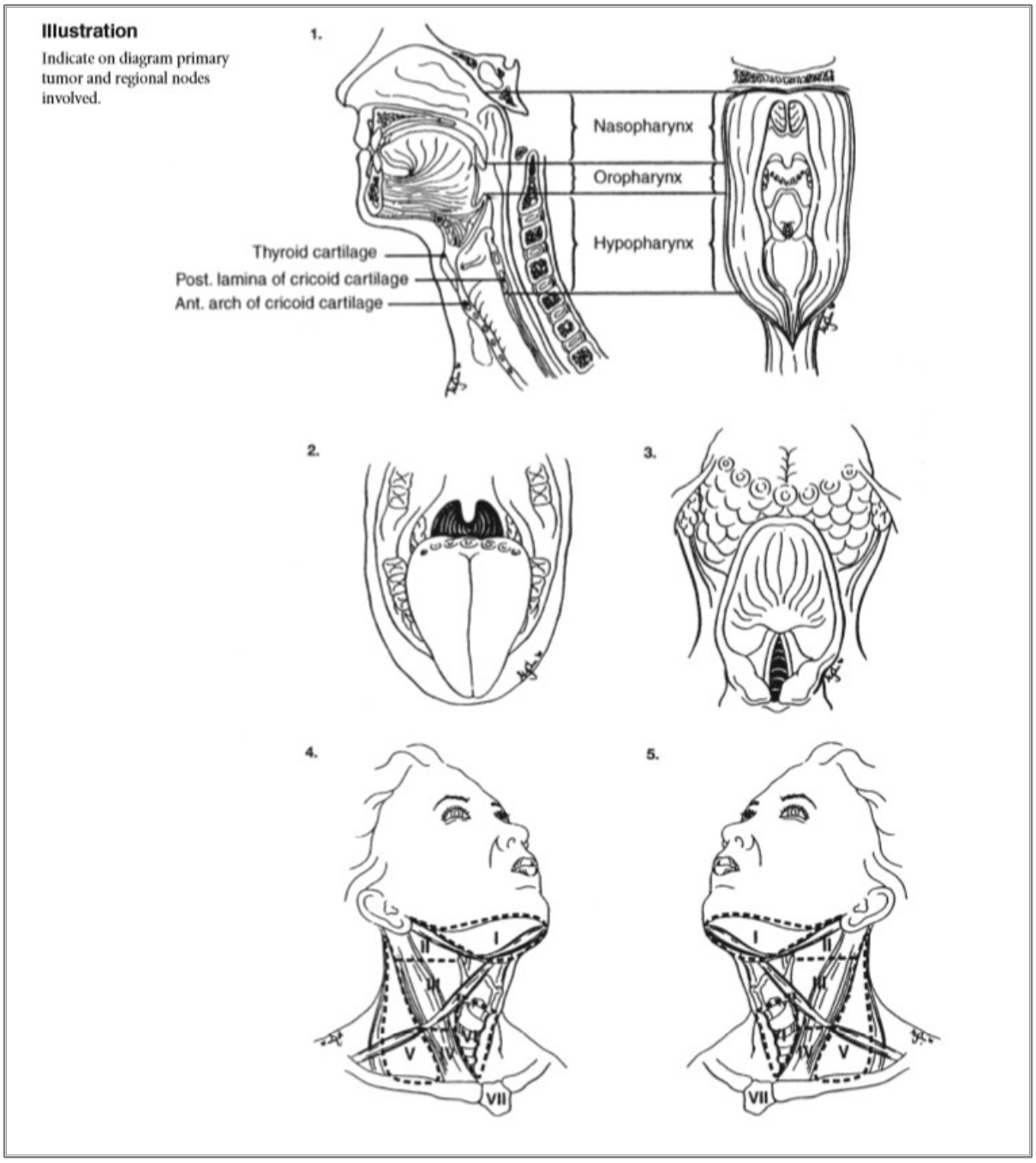
neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

HOSPITAL NAME/ADDRESS	**PATIENT NAME /INFORMATION**

Source : Edge SB, Byrd DR, Compton CC. American Joint Committee on Cancer, American Cancer Society: AJCC Cancer Staging Manual (7th edition). Springer, New York. 2009.

Appendix 4

NASOPHARYNX STAGING FORM



Source : Edge SB, Byrd DR, Compton CC. American Joint Committee on Cancer, American Cancer Society: AJCC Cancer Staging Manual (7th edition). Springer, New York. 2009.

Appendix 5

RADIOLOGICAL STAGING

Primary Tumour (T staging)

Figure 1 : ***T1*** - Left nasopharyngeal mass confined within the nasopharyngeal mucosal space.

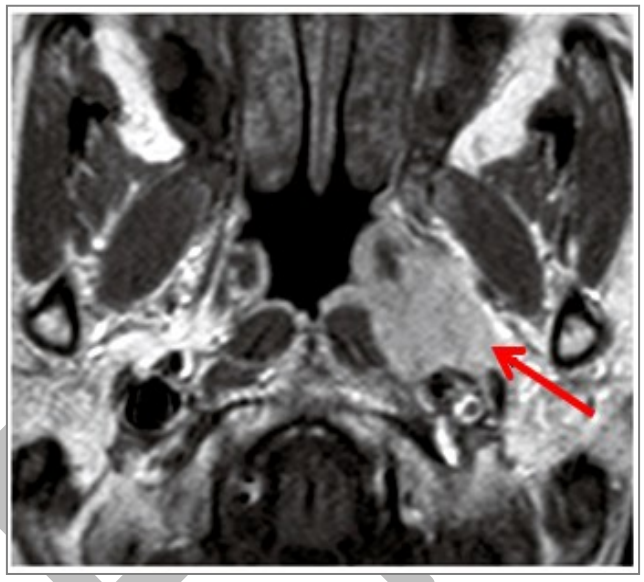


Figure 2 : ***T2*** - Extension of the left nasopharyngeal mass into the parapharyngeal space. *(Source : King AD, Bhatia KS. Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. World J Radiol. 2010 May 28;2(5):159-65.)*

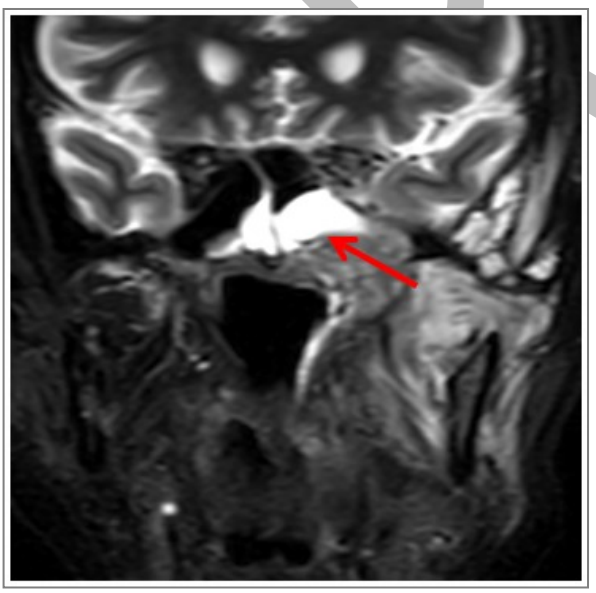


Figure 3 : ***T3*** - Extension of the mass into the floor of the left sphenoid sinus

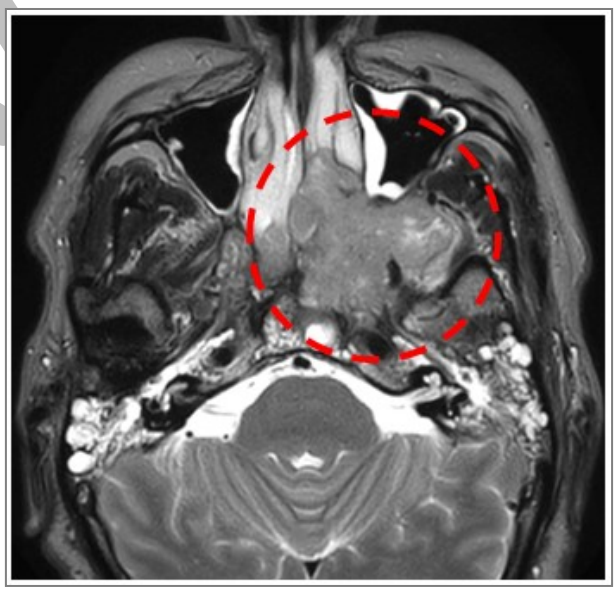


Figure 4 : ***T4*** - Left masticator space involvement

Appendix 5

RADIOLOGICAL STAGING

Nodal staging (N staging)

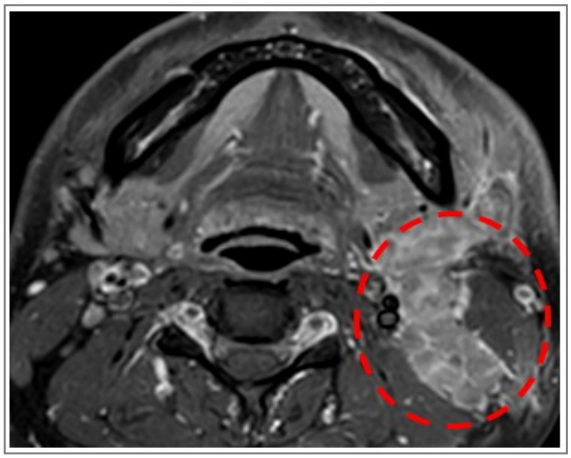


Figure 5 : *N1* - Unilateral left cervical lymph nodes involvement.

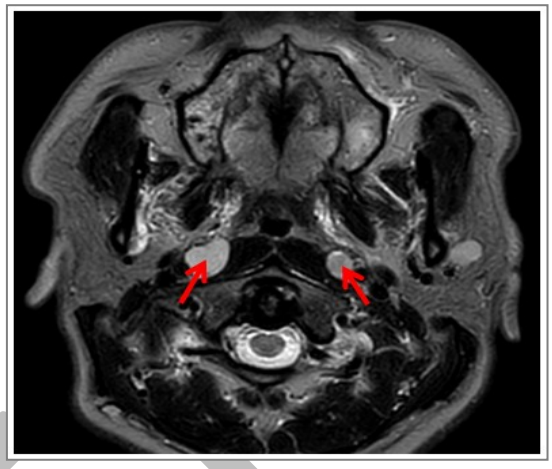


Figure 6 : ***N1*** - Bilateral retropharyngeal lymph nodes involvement.

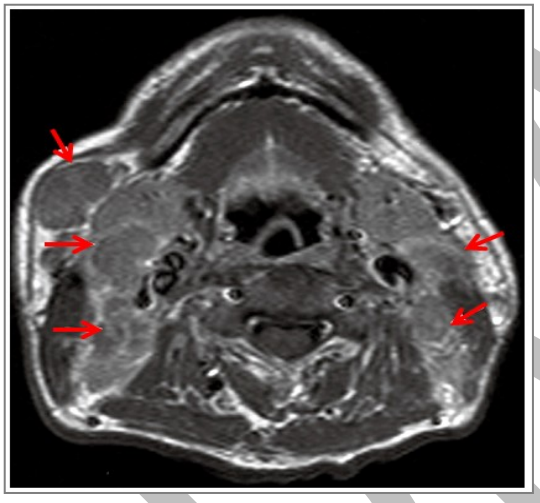


Figure 7 : ***N2*** - Bilateral enlarged cervical and right submandibular lymph nodes *(Source : King AD, Bhatia KS. Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. World J Radiol. 2010 May 28;2(5):159-65.)*

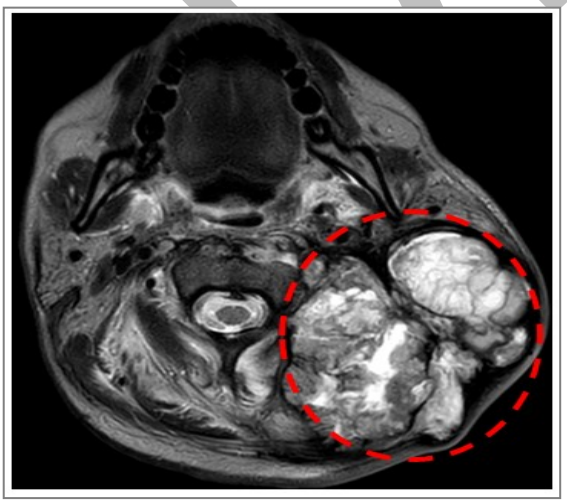


Figure 8 : *N3a* - Left cervical lymph nodes measuring more than 6 cm.

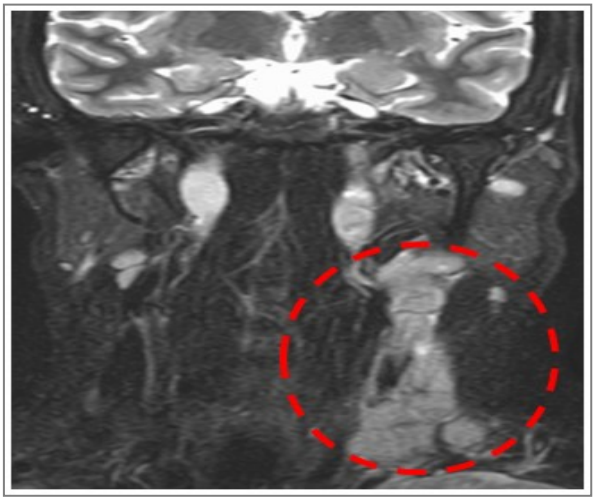


Figure 9 : *N3b* - Left supraclavicular lymph nodes involvement

Appendix 6

CHEMOTHERAPY DRUGS AND SIDE EFFECTS

CHEMOTHERAPY DRUGS	SIDE EFFECTS	REMARKS
Cisplatin	• Gastrointestinal (nausea and vomiting). • Blood (anaemia, thrombocytopaenia). • Renal toxicity. • Electrolyte imbalance (hypomagnesaemia, hypocalcaemia, hypokalaemia). • Auditory (tinnitus; with or without hearing loss). • Neurology (peripheral neuropathy, paraesthesia, seizure). • Hypersensitivity reaction (shortness of breath, hypotension, facial oedema, flushing).	• Observe for cumulative renal toxicity. It may be minimised by adequate hydration and urinary output at least 24 hours after administration. • Prophylactic anti-emetics and corticosteroids should be given. • Observe for anaphylactic-like reactions during infusion.
Carboplatin	• Blood (anaemia, thrombocytopaenia, neutropaenia). • Gastrointestinal (nausea and vomiting). • Hypersensitivity reaction (rash, facial oedema). • Electrolyte imbalance (hypomagnesaemia, hyponatraemia, hypokalaemia). • Hepatotoxicity (elevated ALP, AST).	• Obtain baseline renal function, then monitor renal function at every cycle. • Prophylactic anti-emetics and corticosteroids should be given. • Observe for anaphylactic-like reactions during infusion; increased risk with prior platinum therapy.
Fluorouracil	• Gastrointestinal (diarrhoea, stomatitis, oesophagitis, heart burn). • Blood (anaemia, leucopenia, thrombocytopaenia). • **Cardiovascular** (angina, myocardial infarction, pulmonary oedema). • Dermatological (alopecia, dermatitis, hand-foot syndrome).	• Prophylactic anti-emetics and corticosteroids should be given. • Use with caution in patients who are receiving radiation or received high-dose pelvic radiation or previously treated with alkylating agents. These patients may have increased risk of toxicity. • Use cautiously in patients with history of heart disease. • Monitor for hand-foot syndrome.
Docetaxel	• Blood (neutropaenia, anaemia, thrombocytopaenia). • Cardiovascular (fluid retention). • Dermatological (alopecia, cutaneous reaction, nail changes). • Gastrointestinal (stomatitis, diarrhoea, nausea and vomiting). • Hypersensitivity reaction (hypotension, bronchospasm, rash).	• Pre- and post-treatment with corticosteroid is recommended to decrease fluid retention and hypersensitivity reaction. • Prophylactic anti-emetics should be given. • Observe for anaphylactic-like reactions and extravasationduring infusion.

*To monitor FBC, LFT, RP and serum electrolytes prior to every cycle of chemotherapy.

Source:

1. Ministry of Health & Ministry of Higher Education Malaysia. Systemic Therapy of Cancer 3rd Edition. Putrajaya: MoH & MoHE; 2011
2. Micromedex Solutions, Truven Health Analytics Inc. MIMS Gateway Service Portal. Available at: http://www.mimsgateway.com/Malaysia/Online.aspx

Appendix 7

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS	
Grade	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light house work and office work
2	• Ambulatory and capable of all self-care but unable to carry out any work activities • Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	• Completely disabled • Cannot carry on any self-care • Totally confined to bed or chair
5	Dead

Source : Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55

Appendix 8

TOXICITIES OF RADIOTHERAPY ON HEAD AND NECK

<table>
<tr><th colspan="2">ACUTE TOXICITIES</th></tr>
<tr><td>Lethargy
Radiation dermatitis
Mucositis
Dysphagia</td><td>Taste changes
Nausea and vomiting
Haematological toxicities (neutropaenia)</td></tr>
<tr><th colspan="2">LATE TOXICITIES</th></tr>
<tr><td colspan="2">Neurological Complications</td></tr>
<tr><td colspan="2">Temporal lobe injuries
Cranial nerve palsies
Lhermitte’s syndrome</td></tr>
<tr><td colspan="2">Non-neurological Complications</td></tr>
<tr><td>Tinnitus
Hearing loss
Otorrhea
Trismus
Dysphagia
Subcutaneous fibrosis</td><td>Endocrinopathy
- primary hypothyroidism
- hypopituitarism
Xerostomia
Second cancer within radiotherapy fields</td></tr>
</table>

Source : 1. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2000 Apr 1;47(1):13-47.

2. Zeng L, Tian YM, Sun XM, et al. Late toxicities after intensity-modulated radiotherapy for nasopharyngeal carcinoma: patient and treatment-related risk factors. Br J Cancer. 2014 Jan 7;110(1):49-54.

LIST OF ABBREVIATIONS

AC	Adjuvant chemotherapy
CCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CPG	Clinical practice guidelines
CT	Computed tomography
DG	Development Group
EBV	Ebstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
FNAC	Fine needle aspiration cytology
HR	Hazards ratio
IMRT	Intensity modulated radiotherapy
LRFS	Locoregional failure survival
MRI	Magnetic resonance imaging
MoH	Ministry of Health
NACT	Neoadjuvant chemotherapy
NPC	Nasopharyngeal carcinoma
OME	Otitis media with effusion
OR	Odds ratio
OS	Overall survival
PET	Positron emission tomography
PFS	Progression free survival
RC	Review committee
RCT	Randomised controlled trial
RR	Relative risk / risk ratio
RT	Radiotherapy
SCC	Squamuous cell carcinoma
SR	Systematic review
TFT	Thyroid function test
WHO	World Health Organization

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- Technical Advisory Committee for CPG for their valuable input and feedback
- All those who have contributed directly or indirectly to the development of the CPG

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