InaJCC The Indonesian Journal of Cancer Control

Case Report

Diagnosis and post chemoradiation treatment: A case report on recurrent nasopharyngeal carcinoma

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e-ISSN 2797-457X
DOI: 10.52830/inajcc.v3i1.66

Received: April 4th, 2023
Accepted: March 9th, 2024

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is a common malignant disease in Southeast Asia and radiotherapy is the preferred treatment. Approximately 10% of patients show local recurrence after radiotherapy. Following radiotherapy, fibrous hyperplasia of the nasopharynx and poor local circulation due to local vascular occlusion often occur, leading to low treatment efficacy and many side effects from re-irradiation. Residual tumor after the first treatment may mutate and other mechanisms can cause the tumor to be resistant to the same treatment. Surgical treatment of residual and recurrent NPC has been advocated. Thus, early detection and accurate residual/recurrent NPC staging are essential for treatment and prognosis. Fluorodeoxyglucose-positron emission tomography-computed tomography (FDG PET-CT) is the most accurate imaging modality for assessing local residual or recurrent NPC but has several limitations. Diffusion weighted imaging-magnetic resonance imaging (DWI-MRI) is an imaging technique that can detect distant metastases of NPC and post-radiotherapy biological changes and has a lower cost than FDG PET-CT.
Objective: To determine the right choice in the diagnosis and management of patients with residual/recurrence NPC.
Methods: Literature searching was done in Pubmed and Cochrane for managing residual/ recurrent NPC with seven literature results and one relevant literature.
Conclusion: The combination treatment preceded by surgery is superior to conventional conformal radiotherapy (CRT) alone. For diagnosis, DWI-MRI can provide qualitative and quantitative information about tumor cell levels and identify residues, local fibrosis, and post-radiotherapy recurrence in NPC.

Keywords: chemoradiation, DWI-MRI, FDG PET-CT, nasopharingectomy, recurrent or residual nasopharyngeal carcinoma
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Abstrak

Latar Belakang: Karsinoma nasofaring merupakan keganasan yang umum terjadi di Asia Tenggara dan radioterapi merupakan pilihan pengobatan yang lebih disukai. Sekitar 10% pasien menunjukkan kekambuhan lokal setelah radioterapi. Selain itu, hiperplasia fibrosa pada nasofaring dan sirkulasi lokal yang buruk akibat oklusi vaskular lokal sering terjadi, menyebabkan efikasi terapi yang rendah dan banyak efek samping radiasi ulang. Residu tumor setelah terapi yang pertama dapat bermutasi dan mekanisme lain dapat menyebabkan tumor menjadi resisten terhadap terapi yang sama. Terapi pembedahan disarankan dilakukan pada kanker nasofaring, baik residu, kekambuhan pada residu, atau kekambuhan kanker nasofaring. Oleh karena itu, deteksi dini dan penentuan stadium yang akurat pada kanker nasofaring sangat penting untuk terapi dan prognosis. *Fluorodeoxyglucose-positron emission tomography-computed tomography* (FDG PET-CT) merupakan modalitas pencitraan yang paling akurat untuk menilai residu lokal atau kanker nasofaring yang berulang, namun terdapat beberapa keterbatasan. *Diffusion weighted imaging-magnetic resonance imaging* (DWI-MRI) merupakan teknik pencitraan yang dapat mendeteksi metastasis jauh pada kanker nasofaring dan perubahan biologis pasca-radioterapi dengan biaya yang lebih murah dibandingkan FDG PET-CT.
Tujuan: Untuk menentukan pilihan yang tepat dalam diagnosis dan tatalaksana pasien dengan kanker nasofaring berulang atau residu.
Metode: Pencarian literatur di PubMed dan Cochrane mengenai tatalaksana kanker nasofaring berulang atau residu memperoleh tujuh literatur dan satu literatur yang relevan.
Kesimpulan: Kombinasi terapi didahului oleh pembedahan lebih unggul dibandingkan CRT konvensional saja. Untuk diagnosis, pemeriksaan DWI-MRI dapat memberikan informasi kualitatif dan kuantitatif mengenai tingkat sel tumor dan mengidentifikasi residu kanker, fibrosis lokal, kekambuhan pasca-radioterapi pada kanker nasofaring

Kata kunci: DWI-MRI, FDG PET-CT, karsinoma nasofaring berulang atau residu, kemoradioterapi, nasofaringektomi

Introductions

Nasopharyngeal carcinoma (NPC) is a disease rarely found in Western countries, such as Europe and the United States, while the frequency reaches 20 cases per 100,000 people in Eastern countries, such as China, Japan, and Singapore. In Indonesia, NPC is the 4th most common malignancy after breast, cervical, and lung cancer.[1] Based on the 2021 GLOBOCAN survey, the number of new cases of nasopharyngeal cancer in 2020 was 133,354 (with 96,371 new cases occurring in men and 36,983 new cases in women), 80,0008 deaths from NPC (58,094 in men, and 21,914 in women). NPC is mainly found in men of childbearing age (the ratio of male and female patients is 2.18:1), and 60% of patients are between 25 and 60 years of age.[2] The local recurrence rate can reach up to 20% of cases with a 5-year survival rate of 18%.[3] 4-10% of NPC patients also have synchronous metastases (smNPC, metastases at initial diagnosis), and 20-30% have metachronous metastases (mmNPC, metastases after radical chemo-radiotherapy) 3 years after definitive therapy was performed.[4]

Nasopharyngeal carcinoma is sensitive to radiation during initial treatment; therefore, radiotherapy is the preferred therapy. However, about 10% of patients show local recurrence after radiotherapy. After radiotherapy, patients often develop nasopharyngeal fibrotic hyperplasia and poor local circulation due to local vascular occlusion. This condition can lead to low treatment effectiveness and high side effects from re-radiation. Remaining tumors after the first treatment may have mutations or other mechanisms that persist, rendering the tumor resistant to the same treatment. Therefore, surgical management of persistent and recurrent NPC is recommended.[5]

In cases of residual or recurrent NPC, which still has the potential to be cured, the main issue that must be considered is the most appropriate treatment option, which includes nasopharyngectomy, brachytherapy, radiosurgery, stereotactic RT, IMRT, or a combination of surgery and RT, with or without concurrent chemotherapy. Treatment decisions are tailored to the specific situation of each case, taking into account volume, location, and extent of recurrent tumors. Regional recurrences can be treated with radical neck dissection if resectable.[6]

Compared with the maxillary swing approach for resectioning recurrent tumors, endoscopic nasopharyngectomy is less invasive and produces no facial scars. Therefore, several institutions have started performing endoscopic nasopharyngectomy for resection of persistent and recurrent NPC.[7]

Anatomical Changes After Chemoradiation

Radiation damage can be acute (occurring during radiotherapy), early-delayed (occurring within three months after initial exposure), and late-delayed radionecrosis, within six months to 10 years after exposure). The theory of vascular occlusion, demyelination, injury due to free radicals, direct damage to cell DNA, and damage to the blood-brain barrier is suspected as the pathophysiology of post-chemoradiation organ damage. The effects of radiotherapy include inhibition of osteoblasts and osteoclasts, damage to blood vessels, and loss of cellular balance and metabolism, leading to osteoradionecrosis. Osteoradionecrosis is a slow process of ischemic bone necrosis with soft tissue necrosis in the absence of malignancy. Chemotherapy and radiation therapy slow or stop the growth of new cells. This cancer treatment slows or stops normal cell growth. Radiation therapy can damage and destroy oral tissues, salivary glands, and bones. Radiation therapy also has the effect of causing fibrosis (growth of fibrous tissue) in the mucosa of the oropharynx, tooth decay and gum disease, tissue/ bone damage, and muscle fibrosis in the area receiving radiation.[8]

Detection for Residual and Recurrent NPC

Careful history, physical examination, endoscopic follow-up, evaluation by magnetic resonance imaging (MRI), and examination of plasma Epstein-Barr virus (EBV DNA) levels are recommended in all post-treated NPC patients. Early detection's importance is related to a higher chance of survival and better therapeutic options with lower toxicity.[9]

Nasoendoscopy with narrow band imaging

Narrow band imaging (NBI) is the latest optical examination technique that can improve endoscopic diagnostic capabilities in determining network characteristics by using narrow bandwidth filters in video endoscopy systems. Early diagnosis of residual or recurrent NPC after therapy should be made immediately. One obstacle that arises is when the tumor is not visible or doubtful. Therefore, an examination technique is needed to help establish the diagnosis of recurrence.[10,11]

Narrow band imaging is the latest endoscopic examination technique used for the early detection of superficial mucosal lesions, which are generally difficult to detect compared to conventional endoscopic examination of post-chemoradiation NPC. One of the effects of radiation on malignancy is the occurrence of a diffuse inflammatory reaction in the radiation area

and its surroundings. This gives an uncertain picture of the residual mass. Several studies have shown that the macroscopic appearance of the nasopharyngeal wall does not reflect the presence of residues, especially in post-irradiation patients, because the nasopharyngeal mucosa becomes fibrosis, nasopharyngitis, and osteoradionecrosis. However, it turns out that 30% of cases of recurrent NPC are without a tumor visible on endoscopy, but histopathological examination reveals malignancy.[12]

There was a difference in the appearance of NBI in post-therapy NPC due to lysis and death of cancer cells after exposure to chemoradiotherapy. The emergence of recurrent NPC appears as brown spots that are clear and inhomogeneous in size. The results of the image display from the NBI technique show an image of brown mucosal micro vascularization and an image of cyan (blue-green) submucosal blood vessels.

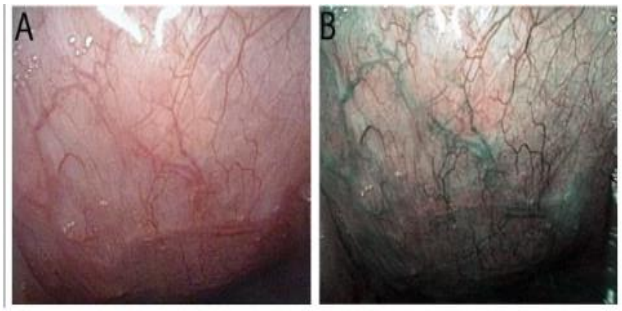

Figure 1. View of the nasopharyngeal mucosa with white light (A) and by NBI, mucosal microvascularization in brown and submucosal blood vessels in cyan (B)

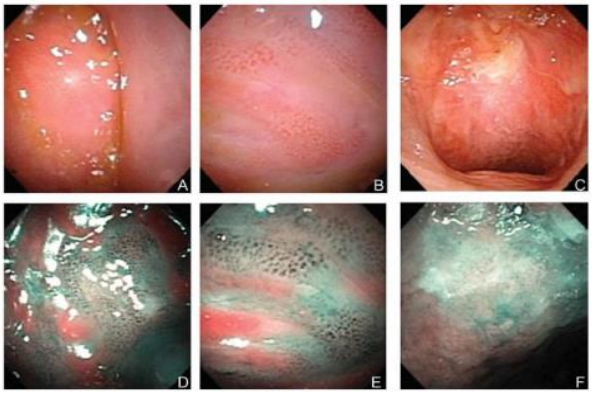

Figure 2. (A) and (B): Post-therapy nasopharyngeal mucosa appears smooth and asymmetrical on conventional endoscopic examination, (D) and (E): Well-defined brownish spots appear on the nasopharyngeal mucosa with NBI technique, (C) and (F): Mucosa The nasopharynx 6 months after nasopharyngectomy looks smooth and symmetrical with conventional endoscopy and does not show brown spots on the NBI technique.

In post-therapy NPC patients, the NBI technique can be used to view the appearance of brown spots with irregular blood vessels in the nasopharyngeal mucosa so that a biopsy is carried out precisely in the area suspected of recurrence. Although NBI has limitations, this examination is expected to guide clinicians to perform a biopsy correctly in terms of time and to increase patient comfort.[13]

Imaging examination after therapy

Magnetic resonance imaging (MRI) is superior to a CT scan in soft tissue differentiation to assess both normal and pathological tissue. It is also more sensitive in evaluating retropharyngeal metastases and deep cervical nodules. It can detect bone marrow infiltration by tumor, while CT can only detect infiltration if there is bone erosion. However, MRI cannot evaluate the presence of bone erosion in detail.

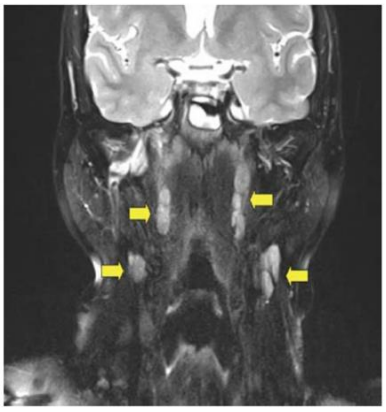

Figure 3. MRI shows bilateral multiple lymph node enlargement (arrows), depicting regional metastases of NPC.

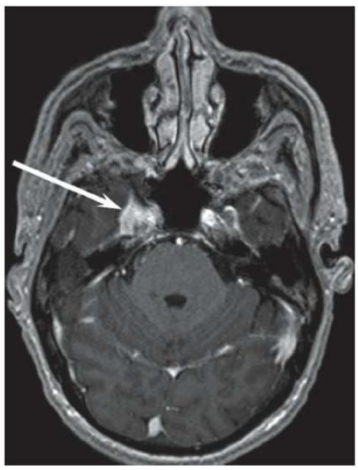

Figure 4. Axial MRI shows a stinging mass (arrows) in the cavernous sinus and right medial cranial fossa, depicting direct spread of the NPC mass.

Magnetic resonance imaging was previously considered the gold standard of local therapeutic efficacy in NPC. However, inflammatory changes after radiotherapy affected image interpretation and increased specificity (ranging from 44% to 83%). In contrast, PET-CT showed good diagnostic ability in evaluating therapeutic efficacy and discriminating lesions (specificity 93.4%). Several studies have compared PET-CT and MRI in differentiating residual/recurrent NPC.

With the wide clinical application, MRI is becoming an important method for pre-treatment examination and post-radiation efficacy assessment in NPC. MRI can efficiently differentiate tumor lesions from normal tissue and identify fibrosis and tumor recurrence after local radiotherapy. Tissue-specific signals from MRI clearly describe the scope, size, and depth of tumor invasion and localize nasopharyngeal masses, areas involved (especially the parapharyngeal space), peri-neural infiltration, skull base damage, and intracranial extension.

Different from MRI, FDG PET-CT is a metabolic imaging technique that provides information about the nature of the lesion based on differences in glucose metabolism. Malignant lesions have a higher glucose metabolism. These metabolic changes are known to precede morphological changes; therefore, the specificity of FDG PET-CT is higher than MRI in detecting small malignant lesions.[14]

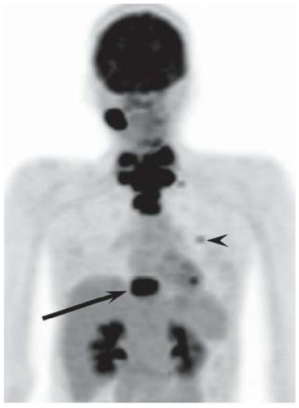

Figure 5. PET scan shows extensive NPC metastases in the neck and upper mediastinum, as well as metastases in the lower mediastinum (arrows) and lungs (arrows).

However, the clinical application of FDG PET-CT is limited by cost, scarce resources, radioactivity, and false positive and false negative findings. DWI MRI is an imaging technique that can detect distant metastases of NPC and biologic changes after radiotherapy and requires a lower cost than FDG PET-CT.

DWI is a non-invasive imaging method that can detect the microscopic movement of water molecules in vivo, determining the initial morphological and physiological changes related to water content in tissues. This technique is very sensitive and specific in the diagnosis or differential diagnosis of tumor-like lesions and tumor stages. This may be because tumor size shrinks in the early stages of effective anti-tumor therapy, and cell membrane integrity is destroyed. The tumor cells then undergo necrosis and dissolution, and the extracellular space enlarges, increasing water molecules' diffusion. When the radiation is finished, if the tumor is completely regressed, the tumor cells disappear, and the necrosis and dissolution gradually stop. Smaller tumors will completely disappear, and the pharyngosal cavity will heal. As for larger tumors, when the tumor cells are damaged by radiation, the blood vessels that supply blood are simultaneously damaged, and the tissue will gradually turn into fibrous tissue hyperplasia or scar tissue.[15]

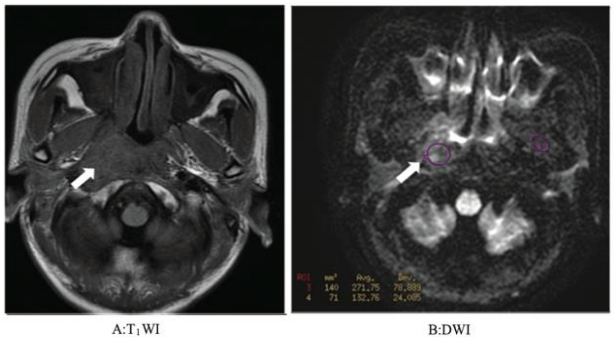

Figure 6. MRI and DWI images of a 22-year-old woman with residual tumor after NPC radiotherapy. A) Mass with the same T1 signal on T1WI (white arrow). B) The lesion is characterized by an uneven and slightly elevated signal on DWI. The ADC value is 1.21 × 10−3 mm2/s. Local tumor residue confirmed by biopsy (white arrow)

Pathology anatomy examination

Definitive diagnosis if there is suspicion from endoscopic examination and imaging results is established by biopsy of the suspected residual or recurrence. A biopsy can be performed under local anesthesia or exploration of the nasopharynx with general anesthesia if the biopsy with local anesthesia does not produce a positive result while the symptoms and signs found indicate residual or recurrent NPC.

The World Health Organization (WHO) divides NPC into two types based on histologic classification: keratinizing squamous cell carcinoma (KSCC, WHO

type I) and non-keratinizing carcinoma (NKC). The NKC subtypes are further classified as 'differentiated' (DNKC) and 'undifferentiated' (UNKC).

Environmental, genetic, and ethnic factors are associated with this histological category. KSCC is the dominant type of NPC among Caucasians, while in the Asian population, KSCC is only found in 0.4-1% of the population. The DNKC subtype has a worse prognosis than the UNKC subtype. Local recurrence is common in the KSCC type, whereas metastases are much more common in the NKC subtype.[16]

Staging and Classification of Residual or Recurrent NPC

The clinical staging system of NPC is very important for planning, managing, and evaluating therapeutic outcomes.

The clinical stage of NPC is based on the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) systems. Routine staging procedures include history taking, physical examination of cranial nerves, complete blood cell count, serum biochemistry (including liver function tests), chest X-ray, nasopharyngoscopy, CT-Scan or MRI of the nasopharynx, skull base, and neck. Imaging for distant metastases, including isotope bone scans and CT scans of the chest and upper abdomen, may be considered, especially in stage N3 and for patients with detectable clinical or biochemical abnormalities. Pre-treatment and post-treatment plasma/serum levels of Epstein-Barr viral DNA have been shown to have prognostic value.[17]

Table 1. Classification Based on Time (before therapy, post therapy, or post recurrence)

✓	*Classification*	*Definition*
	cTNM or TNM	Clinical Classification: Used for all patients with cancer identified before treatment. It is composed of diagnostic workup information, until first treatment, including clinical history and symptoms, physical examination, imaging, endoscopy, biopsy of the primary site, biopsy or excision of a single regional node or sentinel nodes, or sampling of regional nodes, with clinical T, biopsy of distant metastatic site, surgical exploration without resection, and other relevant examinations
	pTNM	Pathological Classification: Used for patients if surgery is the first definitive therapy. Composed of information from diagnostic workup from clinical staging combined with operative findings, and pathology review of resected surgical specimens
	ycTNM	Posttherapy Clinical Classification: after primary systemic and/or radiation therapy, or after neoadjuvant therapy and before planned surgery. **Criteria:** First therapy is systemic and/or radiation therapy
	ypTNM	Posttherapy Pathological Classification: Used for staging after neoadjuvant therapy and planned post neoadjuvant therapy surgery. **Criteria:** First therapy is systemic and/or radiation therapy and is followed by surgery.
	rTNM	Recurrence or Retreatment Classification: Used for assigning stage at time of recurrence or progression until treatment is initiated.
	aTNM	Autopsy Classification: Used for cancers not previously recognized that are found as an incidental finding at autopsy, and not suspected before death (i.e., this classification does not apply if an autopsy is performed in a patient with a previously diagnosed cancer).

Table 2. Primary Tumor (T)

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed
	T0	No tumor identified, but EBV-positive cervical node(s) involvement
	Tis	Tumor *in situ*
	T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
	T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
	T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
	T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Table 3. Lymph Node (N)

✓	*N Category*	*N Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
	N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
	N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Table 4. Metastasis (M)

✓	*M Category*	*M Criteria*
	cM0	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

Management of Residual NPC, Recurrent and Metastasis

In cases of metastatic NPC, palliative chemotherapy should be based on the patient's overall health status. Platinum combination regimens are generally used as first-line therapy because cisplatin is the most effective drug. Other active agents include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, and oxaliplatin, which can be used alone or in combination. Polychemotherapy is more effective than monotherapy. In this context, the treatment choice should be based on previous treatments and the expected toxicity.

Management of recurrent NPC is generally divided into surgical approaches and re-irradiation. Surgical management can include open surgery (open surgery) and endoscopic resection. Meanwhile, in the re-irradiation approach, the use of IMRT, stereotactic RT (SRT), or intensity-modulated proton therapy (IMPT) has surpassed the role of brachytherapy, 3D conformal RT, and other old techniques.[18]

After the initial radical dose of radiation, residual or recurrent NPC in the nasopharynx can still be managed with a second external RT with a larger radiation dose. Complications arising from the second dose of external RT significantly affected the patient's quality of life. However, with the development of precision RT, such as IMRT, external administration of a second RT is quite effective with tolerable side effects. Alternative measures such as stereotactic RT, brachytherapy, and surgical resection have been introduced to reduce the complications of re-radiation. This treatment option applies to small, localized residual, or recurrent tumors in the nasopharynx.[19]

Stereotactic radiotherapy

The rate of local tumor control achieved by stereotactic RT for treating residual or recurrent tumors are 72% in the first two years and 86% in the first three years. A recent study with 90 patients treated using this approach in local and recurrent residual cases reported a 3-year local control rate of 83%. Using stereotactic RT with single fraction treatment achieves excellent results for cases with small tumor volumes.[20]

Brachytherapy

Intracavitary brachytherapy has been used for NPC as an adjunct to primary treatment and persistent or recurrent disease. With brachytherapy, a radiation source is placed directly into the tumor. Thus, the radiation dose is highest at the tumor source, but the dose may decrease with increasing distance from the tumor to the radiation source. This allows the delivery of high radiation doses to both residual and recurrent tumors in the nasopharynx while the radiation dose to surrounding tissues is much smaller. Brachytherapy radiation sources also provide radiation continuously, providing an advantage over fractionated external radiation.

The radiation source is either placed in the tube or inserted into the nasopharynx. Good local control has been reported with intracavitary brachytherapy.

However, given the irregular contours of the primary tumor in the nasopharynx, it is difficult to apply the radiation source accurately to any part of the tumor to produce a tumoricidal effect. To avoid this problem, radioactive interstitial implants have been used to treat small, localized, persistent tumors or recurrent tumors of the nasopharynx.[21]

Nasopharyngectomy

The next treatment option is surgery for residual or recurrent tumors in the nasopharynx that have expanded into the paranasopharyngeal space or are too large for brachytherapy. Nasopharyngectomy is effective for localized tumor eradication. Adequate resection of a small and thick tumor located on the posterior wall of the nasopharynx can be achieved using an endoscope inserted through the nasal cavity.

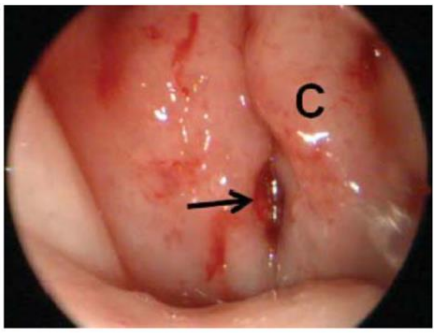

Figure 7. Endoscopic view shows a small recurrent tumor (arrow) located medial to the left eustachian tube (C).

Microwave coagulation therapy has also been reported to be successful when applied transnasally. Rigid endoscopic instruments are limited, unable to remove tumors superior to the nasopharynx's lateral wall. For tumors that are more extensive in the nasopharynx, resection with an open approach is required. Successful treatment depends on adequate tumor removal with tumor-free resection margins and extensive exposure to the tumor and its surroundings. Since all patients had previously undergone radical RT, wound healing may take some time, and approximately 25% of patients develop trismus. The prognosis is satisfactory as long as residual or recurrent tumors can be resected with clear margins.[22]

Principles of selecting surgical therapy

1. Relapse Management

Resectable primary tumors should be resected if possible. Tumor recurrence in the neck that has not been treated previously should be treated by dissection or modification of neck dissection, depending on the clinical situation. Non-surgical therapy can also be used as per clinical need.

2. Resectability Assessment

Tumor involvement of the following organs is associated with poor prognosis or function (cannot be resected based on technical ability to obtain clear margins). None of the following organ involvement is an absolute contraindication to resection in a particular patient in which total removal of the cancer is possible:

- Involvement of the pterygoid muscles, especially when associated with involvement of the trismus or pterygopalatine fossa with cranial neuropathy
- Tumor spread to the skull base (eg erosion of the pterygoid plate or sphenoid bone, widening of the foramen ovale)
- Direct extension to the superior nasopharynx or extension to the Eustachian tube and lateral nasopharyngeal wall
- Invasion into the internal carotid artery or the main carotid artery (encasement) is usually assessed radiographically and defined as a tumor surrounding the carotid artery of 2700 or more
- Direct extension of the tumor to involve the outer skin
- Direct extension to mediastinal structures, pre-vertebral fascia, or cervical vertebrae
- Presence of subdermal metastases.

Case Report

A male patient aged 48 years with a history of T4N2M0 nasopharyngeal carcinoma came to the clinic after chemoradiation. The patient had previously received chemoradiation in 2018. The patient had received chemotherapy for four cycles and radiation 33 times. Patient routinely came for control once every three months during the first year after chemoradiation, evaluated per nasoendoscopy, and said there were no abnormalities from the results of the nasopharyngeal examination. Patient also routinely checked up on radiation oncology every three months for the first year after chemoradiation. The patient underwent a contrast MRI DWI Nasopharyngeal examination at the RSCM every three months for the first year after chemo-radiation. Results of MRI DWI nasopharyngeal contrast three months after chemoradiation There was no contrast-enhancing mass in the nasopharynx. T1 isointense area, T2 hyperintense in right lateral pterygoid muscle, DD/inflammation. Colli lympha-denopathy was not seen. Hyperintense T1 and T2 in the os clivus, DD/ fatty changes after radiation. Then three months after the control patient returned to the

radiation oncology department, a contrast MRI DWI Nasopharyngeal evaluation was carried out, repeated with the results: Post chemoradiation T4N2M0 NPC status, compared with previous contrast MRI, currently Edema m. right lateral pterygoid stqa. No mass was seen in the nasopharynx. Colli lymphadenopathy was not seen.

Six months later, a contrast MRI of the nasopharynx was evaluated, with the results of T4N2M0 NPC follow-up status after chemoradiation, compared with contrasting nasopharyngeal DWI MRI, there was Edema m. right lateral pterygoid, stqa. No visible mass in the nasopharynx.

Six months after the last control, the patient began to complain of numbness in the right cheek, the complaint was felt to be getting worse, and two months after that, the patient began to develop double vision. Contrast Nasopharyngeal MRI examination: T4N2M0 NPC status after chemoradiation, Parapharyngeal edema, slightly reduced right masticator space. There was an enhancement in the right nasopharynx and right sphenoid bone DD/residual inflammation. Colli lymphadenopathy was not seen. A nasoendoscopy was performed and found a thickening of the right nasopharyngeal wall. Histological nasopharyngeal biopsy results were consistent with non-keratinizing squamous cell carcinoma, an undifferentiated subtype of the nasopharynx, and no lymphovascular invasion was found. Nasopharyngeal MRI examination results with contrast: Nasopharyngeal asymmetry. The patient was diagnosed with Residive rT4N2Mx Nasopharyngeal Carcinoma and planned DWI T2 for operative consideration and recent re-evaluation of distant metastases.

Literature Analysis

Clinical Questions I

Patients with residual or recurrent nasopharyngeal carcinoma who underwent endoscopic nasopharyngectomy plus chemoradiotherapy or with chemoradiotherapy alone had a better clinical outcome or outcome.

Q : Residual or recurrent NPC
I : Endoscopic nasopharyngectomy plus chemoradiotherapy
C : Chemoradiotherapy
O : survival rate

Search Method

The literature search was conducted through the PubMed/Medline and Cochrane databases. The keywords used in the literature search were Recurrent or Residual nasopharyngeal carcinoma, nasopharyngectomy chemoradiation, and survival rate. The initial search results gave rise to 7 literature. Screened for the same article (duplication), according to clinical questions, searched for the last five years, and the full text found three selected articles. A review of the three articles with full text was carried out, and only 1 article met the eligibility criteria for the author's article selection. Eligibility criteria for article selection that have been set include:

1. Study in English
2. Study design: cohort, case control
3. Adult patients with residual or recurrent NPC undergoing endoscopic nasopharyngectomy plus chemoradiotherapy. And those who only undergo chemoradiotherapy
4. The clinical outcome assessed is survival rate

Exclusion criteria:

1. Journals that are not in English
2. The text is incomplete and full text is not available
3. Not in accordance with the clinical question

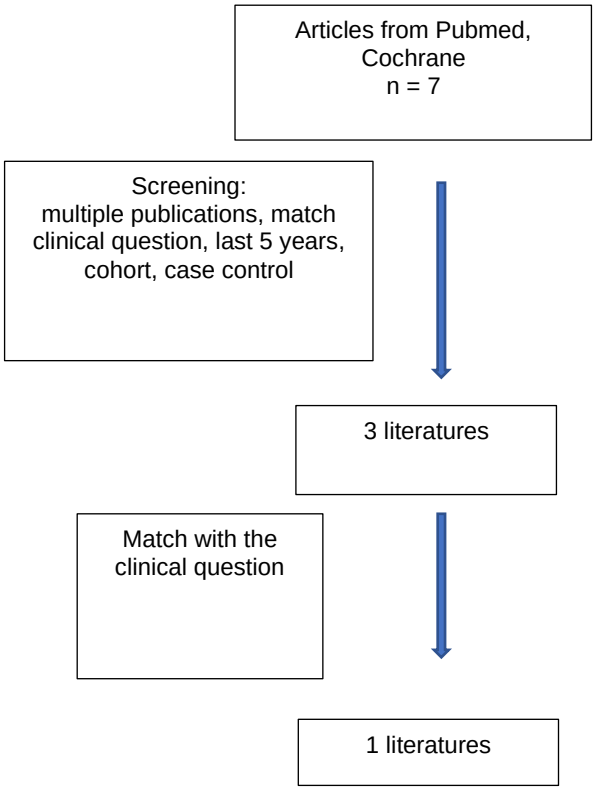

Figure 8. Search method I

Critical review results

Jingjin Weng et al. described in his study, A total of 62 patients with localized residual or recurrent NPC were studied retrospectively: 36 patients received endoscopic nasopharyngectomy combined with CRT, while 26 patients who refused surgery or had surgical contraindications underwent CRT alone. Serum Epstein-Barr DNA (EBV) levels were measured before and after treatment. Differences in prognosis between the two treatment regimens and changes in EBV-DNA levels before and after treatment were analyzed. The results showed the results.

The median follow-up time was 31 months, with a 3-year overall survival of 51.40% and 3-year disease-free survival of 46.86%. The operation + CRT group had a better OS than the CRT alone group (χ 2 = 4.054, P = 0.044). EBV-DNA pre-treatment levels showed a positive correlation with the clinical stage of recurrent NPC (χ 2 = 11.674, P = 0.009). Patients with negative pre-treatment serum EBV-DNA showed superior OS than patients who tested positive for EBV-DNA (χ 2 = 9.833, P = 0.002). Post-treatment EBV-DNA levels, compared with pre-treatment levels, decreased significantly in the surgery + CRT group (Z= 43,484, P = 0.000). In contrast, EBV-DNA levels after CRT alone did not decrease significantly (Z= 91,956, P = 0.051). Multivariate analysis showed that local staging, pre-treatment EBV-DNA load, and treatment method were independent risk factors for OS. Subgroup analysis showed that patients who tested negative for EBV-DNA before treatment and those who received surgery + CRT showed better OS than those who received CRT alone.

Clinical Question II

What modality is used to evaluate patients with residual or recurrent NPC.

Q : Patients with residual and recurrent
I : DW MRI
C : MRI
O : sensitivity and specificity

Search Method

The literature search was conducted through the PubMed/Medline and Cochrane databases. Keywords used in the literature search were Recurrent or Residual nasopharyngeal carcinoma, magnetic resonance imaging, diffusion-weighted imaging, sensitivity and specificity. The initial search results gave rise to 7 literatures. Screening for the same article (duplication), according to clinical questions, searching for the last 10 years, and full text found 1 literature that met the author's article selection eligibility criteria.

1. Study in English
2. Study design: cross sectional, systematic review of cross sectional
3. Adult patients with residual or recurrent NPC who were evaluated with DWI MRI. And those evaluated by MRI
4. The clinical outcomes assessed were sensitivity and specificity

Exclusion criteria:

1. Journals that are not in English
2. The text is incomplete and full text is not available
3. Not in accordance with the clinical question

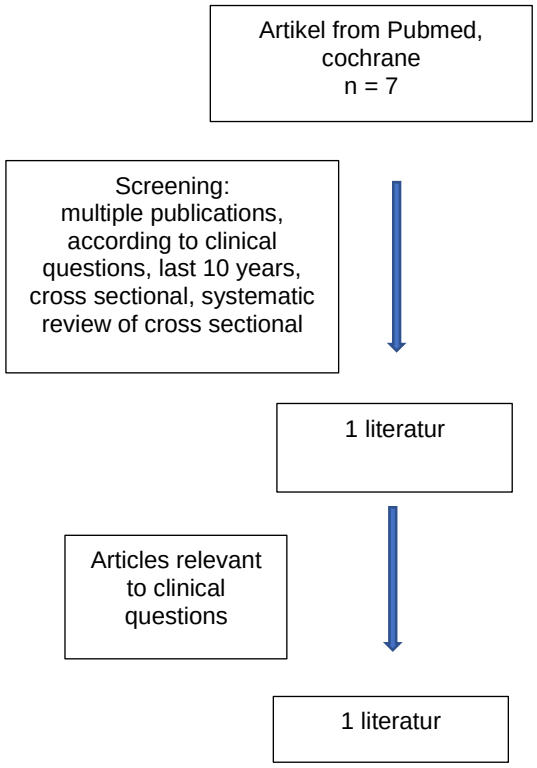

Figure 9. Search method II

Critical review results

Ji-Fei Xu et al. explained in his study, from 83 NPC patients, 33 cases were in the non-residual group, 4 cases were in the residual group, 41 cases were in

the non-recurrent group and 5 cases were in the recurrence group. Of the 33 patients in the non-residual group, the morphology of the nasopharynx was normal in 4 cases, a residual lump in the nasopharynx was observed in 17 cases, thickening of the nasopharyngeal wall was observed in 12 cases, residual damage of the skull base was observed in six cases and damage to the lamina of the sphenoid bone was observed in two cases. case. It is represented as soft tissue irregularity in the nasopharynx with moderate or low signal on T1WI, and normal or moderately high signal on DWI. Of the four cases in the residual group, residual tumors in the nasopharynx were observed in two cases, which were shown as irregular soft tissue tumors with indistinct margins and uneven signalling, mainly the same T1 and T2, on T1WI and T2WI. One case of damage to the clivus and corpus ossis sphenoid was observed on T1WI and T2WI, with slightly higher and slightly higher lesion signal on DWI. Comparison of ADC values in local residual group, non-local residue group and lateral pterygoid muscle group after radiotherapy in NPC (x ± s, × 10−3 mm2/s). there was a statistically significant value between the ADC values of the lateral pterygoid muscle group and the residual group ($P < 0.05$). Comparison of ADC values in recurrent group, non-recurrent group and lateral pterygoid muscle group after radiotherapy in NPC (x ± s, × 10−3 mm2/s). there was a statistically significant value between the ADC values of the lateral and recurrent pterygoid muscle groups, ($P < 0.05$).

Discussion

The clinical outcome of post-therapy NPC patients has improved over the last few years with chemotherapy and IMRT. However, failure in the form of residual or recurrent disease still occurs in 10-30% of cases. Assessment of treatment response and clinical evaluation after definitive therapy is important to detect treatment failure and further initiation of therapy. Patients are assessed clinically by cranial nerve examination, neck palpation, and endoscopic inspection, in combination with imaging techniques such as CT, MRI, or PET-CT. A biopsy was then performed to obtain histologic confirmation.[23]

In this case report, patient monitoring was carried out once every three months in the first year after chemoradiation. This is in accordance with the NCCN Guidelines Version 1.2018 follow-up recommendations. Patients are evaluated in the first 1-2 months post-therapy. The evaluation includes history taking and physical examination (including head and neck examination and nasoendoscopy). Evaluation of therapy response was carried out by CT-Scan of the nasopharynx and neck or MRI of the nasopharynx and neck for contrast at 2-3 months after therapy. However, the patient underwent a re-contrast MRI Nasopharyngeal examination at the control time six months after therapy. This is not in accordance with the NCCN guidelines, where MRI is not routinely performed for every control patient for three months unless signs of residual or recurrence are found during history taking, physical examination, and nasoendoscopy examination. At six months post-therapy, the patient was not tested for TSH levels. This TSH examination is recommended based on the NCCN guidelines. In NPC patients undergoing radiation to the neck, it is recommended to check TSH levels 6-12 months after therapy. Because the dose given during radiation therapy to the neck can induce hypothyroidism, screening to rule out the occurrence of these effects is important.

In the second-year post-therapy, the patient underwent routine follow-up every six months. At the next follow-up, he began feeling numb in the right cheek, had double vision and slightly crossed eyes. Nasopharyngeal contrast MRI results showed recurrent NPC. This is in accordance with the literature, which shows that metachronous metastases often occur within three years of definitive therapy.[5] In determining cases of recurrent NPC, the recommended imaging examination is FDG-PET/CT examination to confirm the diagnosis which is a more specific examination to distinguish between inflammation with malignant lesions that recur after therapy or for evaluation of distant metastases. This examination is rarely carried out because it is expensive and is not covered by the government's health insurance. In addition, the MRI examination carried out accompanied by DWI is sufficient to provide complete information in distinguishing post-radiation fibrosis tissue, normal tissue or cancerous lesions.[15]

The patient was then consulted to ENT Oncology on 19/12/2019. A nasoendoscopy was performed and found thickening of the nasopharyngeal wall, especially on the right side, and a suggestion for a nasopharyngeal biopsy under local anesthesia. This is in accordance with the path of determining the diagnosis of recurrent cases that to confirm the diagnosis if residue or recurrence is suspected at the time of endoscopic and imaging examinations, to confirm these suspicions is to carry out an anatomical, pathological examination of nasopharyngeal mucosal biopsies suspected of having residue or recurrence. 2 months after that the patient agreed to do a biopsy. The biopsy showed histologic results in non-keratinizing squamous cell carcinoma (NKC) and

undifferentiated subtype (UNKC), and no lympho-vascular invasion was found. Based on the literature, local recurrence is rare in NPC type NKC, and distant metastases are more common. The patient was then advised to re-contrast Nasopharyngeal MRI at Mitra Keluarga Hospital with the result of asymmetry in the nasopharynx. Then the ENT Oncology Meeting was repeated, and the patient was diagnosed with Residive rT4N2Mx Nasopharyngeal Carcinoma. It was advised for a repeat DWI T2 for operative consideration and a recent re-evaluation of distant metastases. Based on the NCCN Guidelines, post-chemoradiation recommendations, if the patient is confirmed positive for a locoregional recurrence or a second primary with a previous history of radiation, it must be determined beforehand whether resectable or unresectable. To determine this, it must refer to the results of contrast nasopharyngeal MRI, how large the tumor is, and its expansion to surrounding organs. The patient has been advised to do a T2 DWI to see the expansion of the tumor, but so far, this examination has not been carried out. Because at the same time, the patient underwent full dose chemotherapy, and consideration of surgery after the results of the T2 DWI is currently delayed due to restrictions on surgery due to the pandemic. Currently, the patient is undergoing chemotherapy by TS IPD HOM and has already undergone the second cycle of chemotherapy.

Unlike the initial diagnosis of NPC, in recurrence, the treatment of choice is surgery. In resectable lesions, surgery aims to achieve complete resection of the tumor. In principle, the treatment for rT1–2 tumors is surgery, brachytherapy, or stereotactic radiosurgery, while for rT3–4 NPC tumors, the treatment of choice is an external beam, preferably IMRT.[24] Surgery cannot be performed in all cases of recurrent NPC. Patients with endoscopic nasopharyngectomy contra-indications include internal carotid artery encasement, massive intracranial involvement, and orbital invasion.[24]

Despite the lack of high-level evidence, chemotherapy is often given with re-irradiation. Induction chemo-therapy is considered especially in rT3-4 because it can reduce tumor size and eradicate micro-metastasis. However, the potential for post-chemotherapy toxicity should be considered.[17]

Research by Weng et al. (2017) showed that surgical treatment patients had better disease-free survival among NPC patients with late-stage local recurrence than those receiving only CRT (P = 0.032). These findings suggest that surgery on end-stage local NPC can achieve better therapeutic efficacy than non-surgical treatment.[24]

The prognosis for patients with recurrent NPC is generally poor, with a median survival (OS) of about 20 months. Other poor prognostic factors are age 50 years, rT3–4, tumor volume greater than 30 cm^3, and nodal recurrence.25,30 In these patients, factors contributing to poor prognosis include disease staging and recurrence.[5]

Conclusion

NPC is a malignant tumor that is one of the leading causes of death in several countries. Despite aggressive treatment, local or regional failure and/or distant metastases may still occur in some patients. Recurrent NPC is tumor recurrence after achieving complete remission with radical radiotherapy. Recurrent NPC can be further subdivided into local and regional recurrences. Local-alone and regional-alone failures account for 70% and 25% of recurrent NPC cases, respectively, and 8%-28% of patients have locoregional failure.

The median interval between initial treatment and recurrence ranged from 1 month to 10 years. According to Sun Yat-sen University Cancer Center data, most patients had a recurrence within three years of initial treatment: 5.9% in 6 months, 23.7% in less than one year, and 48.7% in less than one year or two years. 16.9% after five years, and 3.3% after ten years. A study from Hong Kong by Lee et al. reported that 52% of patients had recurrent NPC within two years and 39%, within 2-5 years.

Accurate timing of evaluation of treatment response is very important to determine the prognosis of patients with recurrent NPC. The recommended imaging examination during follow-up is a DWI MRI of the nasopharynx and neck performed three months after radiotherapy or six months after therapy because the tumor will regress within three months after chemoradiation. Three months later, it must be confirmed by imaging whether there is residue or recurrence. Then imaging examinations are carried out periodically yearly according to clinical indications. Thoracic X-ray examination, CT-Scan thorax/ abdomen, ultrasound abdomen, Bone scan, and PET-CT are performed on high-risk NPC patients periodically if there are clinical indications. According to clinical indications, smoking and alcohol counselling and dental care are also recommended three months after radiotherapy.

In cases of recurrent/residual NPC, Treatment decisions according to the specific situation of each case, taking into account the volume, location, and extent of recurrent/residual tumors. Regional

recurrences can be treated with modified radical neck dissection. Multidisciplinary evaluation and care must be prospectively coordinated and integrated by all disciplines involved in patient care prior to initiation of treatment. Regarding the choice of modality in cases of residual/recurrent NPC, FDG-PET CT examination to confirm the diagnosis is a more specific examination in differentiating post-therapy inflammation from malignant lesions that reappear after treatment. However, it has some limitations, such as high medical costs, high false positives, availability, and radiation. MRI examination with DWI is sufficient to provide complete information in differentiating post-radiation fibrotic tissue, normal tissue, or cancerous lesions.

References

1. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, et al. Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 2012;31(4).
2. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006 Oktober;15(10).
3. Toumi N, Ennouri S, Charfeddine I, Daoud J, Khanfir A. Local and lymph node relapse of nasopharyngeal carcinoma: A Single-Center Experience. Ear, Nose Throat J. 2020;0–5.
4. Liao W, Tian M, Chen N. Characteristic and novel therapeutic strategies of nasopharyngeal carcinoma with synchronous metastasis. Cancer Manag Res. 2019;11:8431–42.
5. You R, Zou X, Hua YJ, Han F, Li L, Zhao C, et al. Salvage endoscopic nasopharyngectomy is superior to intensity-modulated radiation therapy for local recurrence of selected T1-T3 nasopharyngeal carcinoma. A case-matched comparison. Radiother Oncol. 2015;115:399–406.
6. Lee AW, Law SC, Foo W, Poon YF, Cheung FK, Chan DK, et al. Retrospective analysis of patients with nasopharyngeal carcinoma treated during 1976-1985: Survival after local recurrence. Int J Radiat Oncol Bio Phys 1993;26:773-82.
7. Chen MY, Wen WP, Guo X, Yang AK, Qian CN, Hua YJ, et al. Endoscopic nasopharyngectomy for locally recurrent nasopharyngeal carcinoma. Laryngoscope. 2009;119:516–22.
8. Lok B, Setto J, Ho F, Rias N. Nasopharynx. In: Halperin E, Wazer D, Perez C, Brady L, editors. Perez and Brady's Principles and Practice of Radiation Oncology. 6th ed. Philadelphia: Lippincot Williams & Wilkins; 2013. p. 730–60.
9. Lu J, Kong L, Lee N. Nasopharyngeal Carcinoma. In: Lu J, Brady L, editors. Decision Making in Radiation Oncol- ogy Volume 1. New York: Springer-Verlag Heidelberg Dodrecht; 2011. p. 45–74.
10. Carioli G, Negri E, Kawakita D, Garavello W, La Vecchia C, Malvezzi M. Global trends in nasopharyngeal cancer mortality since 1970 and predictions for 2020: Focus on low-risk areas. Int J Cancer. 2017;140(10):2256 –64.
11. Ho KY, Lee KW, Chai CY, Kuo WR, Wang HM, Chien CY. Early recognition of nasopharyngeal cancer in adults with only otitis media with effusion. J Otolaryngol Head Neck Surg. 2008;37(3):362-5.
12. Lin YC, Wang WH. Narrow-band imaging for detecting early recurrent nasopharyngeal carcinoma. Head and Neck. 2009; 591-4.
13. Lee AW, Foo W, Law SC, Poon YF, Sze WM, O SK, et al. Nasopharyngeal carcinoma: Presenting symptoms and duration before diagnosis. Hong Kong Med J. 1997;3:355-61.
14. Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt. 2004;9(3):568-77.
15. Xu JF, Wu XW, Wang WQ, Kong LL, Wu LM, Wang F. Value of diffusion-weighted magnetic resonance imaging on the follow-up of nasopharyngeal carcinoma after radiotherapy. J X-Ray Sci Technol. 2014;22:605–12.
16. Wu SG, Lian CL, Wang J, Zhang WW, Sun JY, Lin Q, et al. The effect of histological subtypes on survival outcome in nasopharyngeal carcinoma after extensive follow up. Ann Transl Med. 2019;7(23):768.
17. Edge SB, Byrd DR. Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging hand book. 7th edition. New York, NY: Springer, 2010.
18. Lee AWM, Ng WT, Chan JYW, Corry J, Mäkitie A, Mendenhall WM, et al. Management of locally recurrent nasopharyngeal carcinoma. Cancer Treat Rev. 2019;79.
19. Zhang L, Zhao C, Peng PJ, Lu LX, Huang PY, Han F, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: Preliminary results. J Clin Oncol. 2005;23:8461-8.
20. Law SCK, Lam WK, Ng MF, Au SK, Mak WT, Lau WH, et al. Reirradiation of nasopharyngeal carcinoma with intracavitary mold brachytherapy: An effective means of local salvage. Int J Radiat Oncol Bioi Phys. 2002;54:1095-113.
21. Danesi G, Zanoletti E. Mazzoni A. Salvage surgery for recurrent nasopharyngeal carcinoma. Skull Base. 2007;17:173-80.
22. Meng K, Tey J, Ho FCH, Asim H, Cheo T. Utility of magnetic resonance imaging in determining treatment response and local recurrence in nasopharyngeal carcinoma treated curatively. BMC Cancer.2020;20(1):1–7.
23. Chua DTT, Wu SX, Lee V, Tsang J. Comparison of single versus fractionated dose of stereotactic radiotherapy for salvaging local failures of nasopharyngeal carcinoma: A matched-cohort analysis. Head Neck Oncol. 2009;1:13.
24. Weng J, Wei J, Si J, Qin Y, Li M, Liu F, et al. Clinical outcomes of residual or recurrent nasopharyngeal carcinoma treated with endoscopic nasopharyngectomy plus chemoradiotherapy or with chemoradiotherapy alone: A retrospective study. Peer J. 2017;5:e3912.