



# Prediction for Risk of Recurrence and Delayed Metastases of Nasopharyngeal Carcinoma: An evaluation of CT scan

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## Abstract

**Purpose:** To analyze the imaging characteristic on CT scan of the primary nasopharyngeal carcinoma which predict the locoregional recurrence.

**Materials and Methods:** A retrospective review of 464 patients who had nasopharyngeal carcinoma at Siriraj Hospital, during 2004-2009 was performed. The treatment options were radiation therapy and concurrent chemotherapy corresponding to the staging, which were assessed by using CT. The patients who had no available initial imaging studies, incomplete treatment or had follow up less than 1 year were excluded. The imaging studies were analyzed for primary tumor size, direct tumor extension, and cervical lymph node involvement. The vascular invasion was defined as the obliteration more than half of the circumferential fat surrounding internal carotid artery. The regional nodes were evaluated for the levels of involvement and size of the largest one.

**Results:** There were 99 patients (68 male, 31 female, mean age at 50 years) with the TNM classifications as follows: T1 5.2%, T2 39.4%, T3 24.2%, T4 21.2%, N0 18.2%, N1 14.1%, N2 46.5% and metastasis 11.76%. The extensions were prevertebral space (54.5%), masticator space (30.3%), skull base destruction (18.2%), and vascular invasion (42.4%). Nodal involvement was found in 81.8%. The most frequency of the largest lymph node was at ipsilateral level V (38.4%) and II (41.4%). Recurrence was found in 40.4% with averaged at 24 months after complete treatment (95%CI). Vascular invasion and skull base invasion had significant associated to predictive the risk of recurrence ( $P=0.04$  and  $<0.001$ , respectively). The size of the tumor or lymph node showed no relation to the local regional recurrence or metastasis.

**Conclusion:** The risks of NPC recurrence have been correlated to TNM staging, skull base, and carotid space involvement. Skull base invasion has been identified to be the predictive sign for tumor recurrence. Skull base invasion and carotid space involvement have also a statistically significant prognostic factor for overall survival.

## Introduction

Nasopharyngeal carcinoma (NPC) is an aggressive cancer which is endemic in Southern China and South East Asia, which has the incidence accounting 2-10 per 100,000 person-years<sup>1-3</sup>. The gross mortality of NPC is reported about 1.34 per 100 000, comprises 1.61% of tumor caused deaths and ranks ninth in China<sup>4-5</sup>.

In Thailand, according to the statistics database of Siriraj Cancer Institute Registry in 2008, new cases of NPC were accounted for 3.28% and 1.21% which were ranking at the eighth and thirteenth common cancer in male and female patients, respectively<sup>6</sup>.

Although NPC is very radiosensitive and the treatment outcome have improved in the recent decades, but rate of local regional failure and tumor recurrence can occur in 19%-56% of patients within 2-5 years after definite radiotherapy<sup>4,5,7,8</sup>. The prognosis following local recurrence is rather poor without retreatment<sup>8,9</sup>. Moreover, after treatment, clinical examination for detection of residual or recurrence may be inconclusive; imaging studies may be equivocal due to the presence of diffuse soft tissue edema. In such cases, tumor recurrence should be confirmed by biopsy<sup>4,5</sup>.

Thus, it is essential to be able to predict the therapeutic response of the patients with NPC from the initial imaging study which CT scan is widely common used<sup>4,8-10</sup>. Those patients may be need more closely follow up for the early detection of tumor recurrence. In this regard, early retreatment may be benefit to achieve better tumor control and improve patient survival<sup>4,5,7-10</sup>.

The purpose of this paper is to analyze whether any characteristics or sign on initial CT scan which may predict the risk of tumor recurrence in the

patients with NPC after receiving complete treatment.

## Materials and Methods

### Patient characteristics

A number of 464 patients who had pathological proven of nasopharyngeal carcinoma (NPC) at Siriraj Hospital, Mahidol University, between January 2004 and April 2009 were retrospectively reviewed, under the approval of the ethic committee of our hospital.

All patients received definite standard radiation treatment with or without concurrent chemotherapy corresponding to their own primary stage. Our radiation therapy protocol for primary NPC was achieved from external-beam radiation, either conventional radiotherapy or integrated moderator radiotherapy (IMRT) at a mean dose of 70 Gy in 33 fractions (range, 65-80 Gy), which were 1.8 to 2.0 Gy per fraction for 5 fractions at a weekly interval.

After complete treatment, the patients had scheduled to follow up with evaluation of the treatment response by the joint clinics of otolaryngology, radiotherapy, and oncology for every 6-8 weeks in the first year, every 3 months in the second year, once every 4-6 months in the third year, and once every 6-9 months, thereafter. Endoscopic examination of the nasopharynx was evaluated at 6-8 weeks. The follow-up imaging was performed within 3-12 months or whenever there was clinical suspicion of tumor recurrence.

### The exclusion criterias were included

1. The patients who had unavailable initial imaging study.
2. The patients who had incomplete treatment or loss to follow up.
3. The patients who had less than 12 months

follow up after complete treatment.

4. The patients who had history of other underlying malignancy with cervical lymph node metastasis.

5. The patients who had advanced staging or distant metastasis at the presenting diagnosis which included intracranial extension, and/or metastases to mediastinal lymphnode, lung, skeleton, liver, and miscellaneous (bone marrow, skin, other viscera and soft tissue).

6. The patients who had progressive disease or distant metastasis during or immediate after complete treatment.

### **Tumor response and recurrence**

The patients who were enrolled in this study were divided into 2 groups; recurrent and non recurrent groups.

The recurrent group included those patients who had increase or newly detectable one or more of the following lesions; 1. loco-regional or primary site, 2. cervical lymph node, 3. distant metastases during the follow up period for at least one year, after initial document of tumor free-period or at least stable disease after complete treatment. The recurrent disease was diagnosed by information of physical examination, endoscopic findings, imaging feature and histopathology.

The non-recurrent group was defined as the patients who had responded to the treatment or at least stable disease after complete treatment without evidence of new lesions or recurrence over one year period.

The patients who had progressive disease after treatment, either at the primary site or cervical lymph nodes were excluded from the study.

### **CT scan analysis**

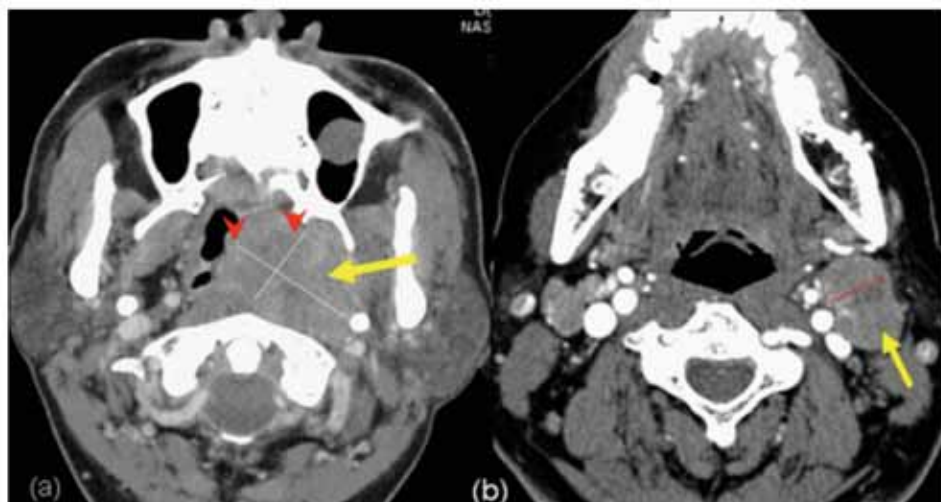
The initial CT scans were reviewed by one neuroradiologist who had more than 10 years experience and blinded from the follow up outcome of the patients. The CT images were retrieved from the picture archiving and communication system (PACS) for evaluation of the primary tumor in term of side, size (averaged diameter), extension and tumor staging using TNM staging according to AJCC 2002 guideline<sup>11</sup>. The side was observed to be one or both sides of tumor involvement. The tumor size was calculated in the averaged diameter which measured in two maximal dimensions with perpendicular axes to each other on the cross sectional CT image (figure 1) and classified as less than 5 mm, 5-10 mm, 11-15 mm and more than 15 mm. The direct extension of the primary tumors are categorized into many regions as parapharyngeal space, masticator space, parotid space, prevertebral space, skull base, internal carotid artery (ICA) or vascular invasion and presence of retropharyngeal lymph nodes.

Our criteria for ICA invasion was at least demonstration of obliteration of the circumferential fat plane between ICA and tumor more than 180 degrees.

The cervical lymph nodes were interpreted as the level system according to 1977 AJCC nodal classification<sup>12</sup>. However, the supraclavicular group was named separately. They were documented as positive if the short axis was longer than 10 mm.

### **Statistical analysis**

All the statistical analyses in this study were carried out using SPSS for Windows software version 13.0 (SPSS; statistical software version 13.0).



**Fig. 1** Demonstrated of primary tumor and lymph node measurements

- (a) The primary tumor (arrow) measurement on contrast enhanced CT image in the axial plane was obtained by the averaged measurement in two greatest dimensions in perpendicularly axes to each other (arrow head) and classified into 4 groups as less than 5 mm, 5-10 mm, 11-15 mm and more than 15 mm.
- (b) The regional nodal measurement was performed by single maximal diameter in short axis.

The univariate analysis was using the log rank test and multivariate analysis was using the Cox proportional hazards model. Survival analysis were performed using estimation method of Kaplan and Meier. Overall survival (OS) in this study was defined as the time from NPC diagnosis to death resulting from any cause or at the time of last follow-up. P values less than 0.05 was considered statistically significant.

## Results

Of 464 patients with NPC, there were 99 patients (68 men, and 31 women) who met our criteria. All patients had mean time of follow up at 24 months. Recurrent disease was found in 40/99 (40.4%) including locoregional recurrence at primary site and/or cervical lymph node in 19 cases (19.2%) and distance metastasis in 21 cases (21.2%), with

a relapse time range from 6 to 58 months (mean 12 months) after complete treatment. The comparison of the demographic data and tumor characteristics of recurrent and non recurrent groups were shown in table 1, which showed no significant statistically difference between both groups.

Concerning characteristics of primary lesion of NPC (table 2), the T stage of primary tumor according to AJCC 2002 TNM classification had statistically significant correlation to risk of tumor recurrence ( $P=0.044$ ), whereas the higher T stage had higher risk of recurrence. The lateralization and size of the primary tumor showed no statistically significant to predict risk of recurrence of NPC.

With respect to direct extension of the NPC to other neck spaces (table 3), there were significant association of tumor recurrence with the involvement of carotid space or vascular invasion

**Table 1:** Patient and tumor characteristics of recurrence and non recurrence groups

Character	Total n = 99	Number of patients	
		Recurrent n = 40	Non recurrent n = 59
Sex: Men	68	30 (44.12%)	38 (55.88%)
Women	31	10 (29.03%)	21 (70.96%)
Age range ( Mean age: years)	18–82 (50.23)	18–74 (48.61)	33–82 (50.30)
Pathological Feature (WHO)			
Type I: NK,SCC	11	4 (36.36%)	7 (63.64%)
Type II: SCC(mod-poor diff)	45	21 (46.66%)	24 (53.33%)
Type III: Undifferentiated, SCC	43	15 (34.88%)	28 (65.12%)
Treatment			
Definite Radiation Therapy	4	1 (25%)	3 (75%)
Concurrent chemoradiation	95	55 (55.56%)	44 (44.44%)
Mean radiation dose	68 ± 2 Grey	68 ± 2 Grey	68 ± 2 Grey
Mean time of follow up (months)	24 ± 2	24 ± 2	24 ± 2

**Table 2:** Comparison of feature of primary NPC between recurrence and non recurrence groups

Parameter	Total Number n = 99 (100%)	Number of patients		<i>p</i> -value
		Recurrent group n =40 (40.4%)	No recurrent group n = 59 (59.6%)	
Location <sup>a</sup> of NPC				
One side of NP	69 (70)	24 (63.13)	31 (36.87)	0.452
Both side of NP	30 (30)	16 (53.33)	14 (46.67)	
Primary tumor size <sup>b</sup>				
< 5 mm.	6 (6.06)	4 (66.67)	2 (33.33)	0.385
5 – 10 mm.	5 (5.05)	2 (40.00)	3 (60.00)	
11 – 15 mm.	13 (13.13)	7 (53.85)	6 (46.15)	
> 15 mm.	75 (75.76)	27 (36.00)	48 (64.00)	
TNM Classification <sup>c</sup>				
T stage: T1	15 (15.15)	7 (46.67)	8 (53.33)	0.044
T2	39 (39.39)	7 (17.95)	32 (82.05)	
T3	24 (24.24)	14 (58.33)	10 (41.67)	
T4	21 (21.21)	12 (57.14)	9 (42.86)	

Using Cox regression Analysis and significant p-value was less than 0.05

n: Number of cases in each group

a: Lateralization of primary nasopharyngeal cancer (NPC) which was stratified as involved one side of NP included midline lesion, or involved both side of NP

b: Primary tumor size measured from initial CT image

c: TNM tumor classification according to AJCC 2002 guideline

**Table 3:** Comparison of tumor extension between recurrence and non recurrence groups

Direction of NPC spreading	Total n = 99 (100%)	Number of patients		p-value
		Recurrent group n = 40 (40.4%)	No recurrent Group n = 59 (59.6%)	
Parapharyngeal space invasion	22/99 (22.22)	8 (36.36)	14 (63.64)	0.41
Masticator space invasion	30/99 (33.33)	13 (43.33)	17 (56.67)	0.40
Prevertebral space invasion	54/99 (54.55)	20 (37.04)	34 (62.96)	0.39
Parotid space invasion	7/99 (7.10)	4 (57.14)	3 (42.86)	0.56
Vascular invasion	42/99 (42.42)	23 (54.76)	19 (45.24)	0.04 <sup>1</sup>
Skull base invasion	18/99 (18.18)	14 (77.78)	4 (22.22)	< 0.001 <sup>2</sup>

Using Cox regression analysis and significant p-value was less than 0.05

1: The hazard risk was 2.05 with 95% Confidential Interval 1.03-4.06.

2: The hazard risk was 0.26 with 95% Confidential Interval = 0.13-0.52.

**Table 4:** Nasopharyngeal carcinoma: 6<sup>th</sup> edition TNM Classification (2002) according to AJCC staging system guideline <sup>11</sup>

T stage	
T1	Tumor confined to nasopharynx
T2	Tumor extends to soft tissue
T2a	Tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2b	Any tumor with parapharyngeal extension
T3	Tumor invades bony structures and/or paranasalsinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
N stage	
N0	No regional lymph node (LN) metastasis
N1	Unilateral metastasis in LN (s), $\leq 6$ cm in greatest dimension, above supraclavicular fossa
N2	Bilateral metastasis in LN (s), $\leq 6$ cm in greatest dimension, above supraclavicular fossa
N3	Metastasis in LN (s) >6 cm and/or to supraclavicular fossa
N3a	Metastasis in LN (s) >6 cm in dimension
N3b	Metastasis in LN (s) with extension to supraclavicular fossa
Stage group	
I	T1N0M0
IIA	T2aN0M0
IIB	T2bN0M0 or T1-T2N1M0
III	T1-T3N2M0 or T3N0-N1M0
IVA	T4N0-N2M0
IVB	Any T N3, M0
IVC	Any T, any N, M1



**Table 5:** Comparison of the feature of lymph nodes between recurrent and non recurrent groups

Parameter	Total n = 99 (100%)	Number of patients		p-value
		Recurrent group n =40 (40.4%)	No recurrent n = 59 (59.6%)	
N stage : N0	18 (18.2)	5 (27.78)	13 (72.22)	0.002
N1	14 (14.1)	10 (71.42)	4 (28.57)	
N2	46 (46.5)	13 (28.26)	33 (71.74)	
N3	21 (21.2)	12 (57.14)	9 (42.86)	
Cervical nodes involvement				
Ipsilateral side of NPC	59 (59.6)	23 (38.98)	36 (61.01)	0.690
Contralateral side NPC	40 (40.4)	17 (42.50)	23 (57.50)	
Level of nodal involvement				
Cervical LN group II	41 (41.4)	27 (65.8)	14 (34.2)	0.954
Cervical LN group III	5 (5.1)	3 (60.0)	2 (40.0)	
Cervical LN group IV	1 (1.0)	0 (0.0)	1 (100)	
Cervical LN group V	38 (38.4)	20 (52.6)	18 (47.4)	
All II - V levels	8 (8.1)	5 (62.5)	3 (37.5)	
RPLN	39 (39.4)	19 (48.7)	20 (51.3)	
SPC	6 (6.1)	4 (66.7)	2 (33.3)	
Maximal diameter of LN				
Less than 1.0 cm	17 (17.2)	4 (23.5)	13 (76.5)	0.064
1.0 -1.5 cm	25 (25.3)	6 (6.1)	19 (93.9)	
> 1.5 – 2.0 cm	20 (20.2)	11 (55.0)	9 (45.0)	
> 2.0 cm	24 (24.2)	11 (45.8)	13 (54.2)	
Matted lymph node	13 (13.1)	8 (61.5)	5 (38.5)	0.178
(Averaged diameter of LN)	-	3.6 cm	1.5 cm	

**Table 6:** Multivariate Cox regression analysis of significant factors

Predictive Factors	Recurrent	No recurrent	P-values*	HR <sup>1</sup> [95%CI]
	NPC n=40 (40.4%)	NPC n=59 (59.6%)		
Primary T stage	40/99 (40.4)	59/99 (59.6)	0.637	-
Primary N stage	40/99 (40.4)	59/99 (59.6)	0.657	-
Vascular invasion	23/99 (23.23)	19/99 (19.19)	0.285	-
Skull base invasion	14/99 (14.14)	4/99 (4.04)	< 0.001	0.259 [0.13-0.59]

\*Using Cox regression analysis and significant p-value was less than 0.05

<sup>1</sup> Harzard Risk (HR) value of Cox regression analysis

[P-value=0.04 and 95%CI; 1.03-4.06, HR=2.05] and skull base extension [P-value=<0.001 and 95%CI; 0.13-0.52, HR=0.26]. In our study, extension to other adjacent spaces such as parapharyngeal space, masticator space or parotid space had no correlation with the risk of recurrence.

All patients had cervical lymph node enlargement at presentation. The distribution of lymph nodes which were classified according to level system, the nodal stage according to AJCC 2002 TNM classification and nodal size were demonstrated in table 4 and 5. According to our data, the only lymph node feature that had statistically significant to associate with the risk of recurrent NPC was correlated with nodal stage of TNM classification ( $P=0.007$ ). Similar to T stage, the risk of recurrence was increased with the higher N stage. In our study, the mean nodal size was 3.6 cm in the short axis of recurrent group whereas it was 1.5 cm in the non recurrent group. However, there was no statistically significant to prognostic risk of recurrence between these 2 groups. ( $P=0.064$ ).

However, after using multivariate analysis by Cox proportion and hazard model of statistically significant factors (as shown in table 6), which were associated with tumor recurrence, including primary T and N stage, vascular invasion and skull base invasion. The result showed only skull base invasion that is persistent statistically significant feature ( $P < 0.001$ ), whereas another features showed no statistically significant ( $P > 0.05$ ). Thus, the skull base invasion was a predictive sign to determine risk of recurrent NPC and another feature was undetermined.

In our study, twenty-one of 40 patients with recurrent disease had distant metastases, 13 pa-

tients was found metastases to lung, 7 to liver, 3 to skeleton, and 2 had subcutaneous nodules, which the further tissues biopsy showed metastasis carcinoma. Three of them had both lung and bony metastases and one of them had progressive liver involvement after lung metastasis at the time of last follow up. The interval duration from post complete treatment to metastases was averaged at 24 months.

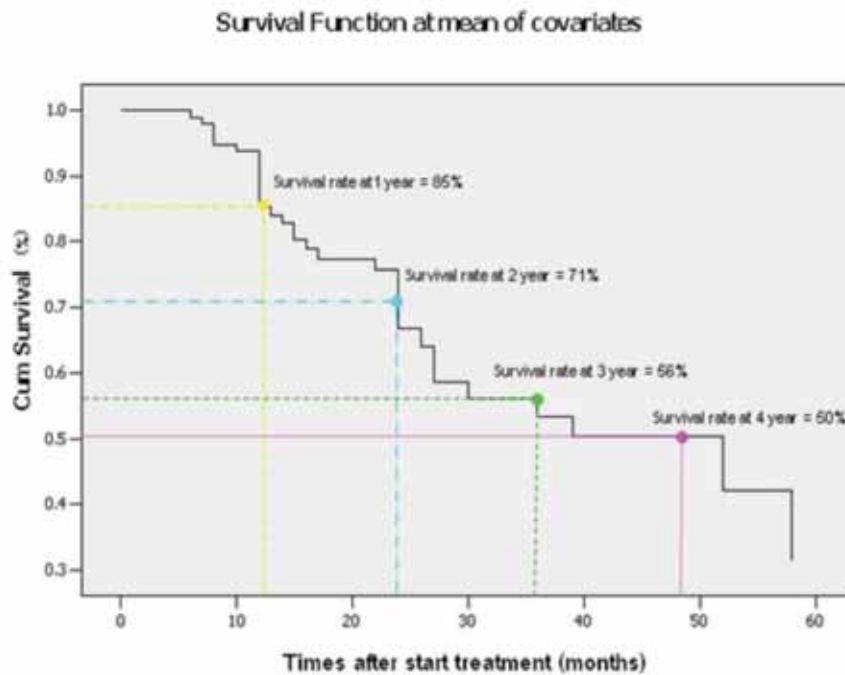
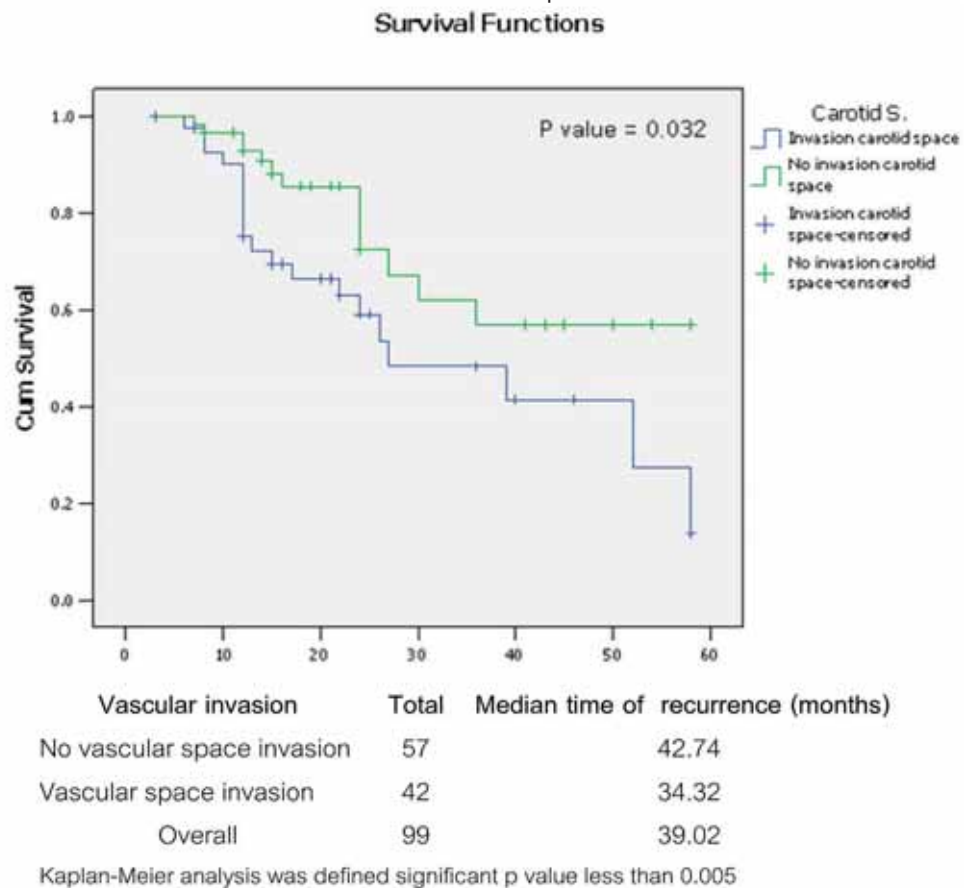
When correlation between the follow up time and evidence of recurrent NPC, overall survival rate for all 99 NPC patients were 85%, 71%, 56%, and 50% in first, second, third, and fourth-year after diagnosis, respectively (figure 2). The median overall survival rate was 39 months.

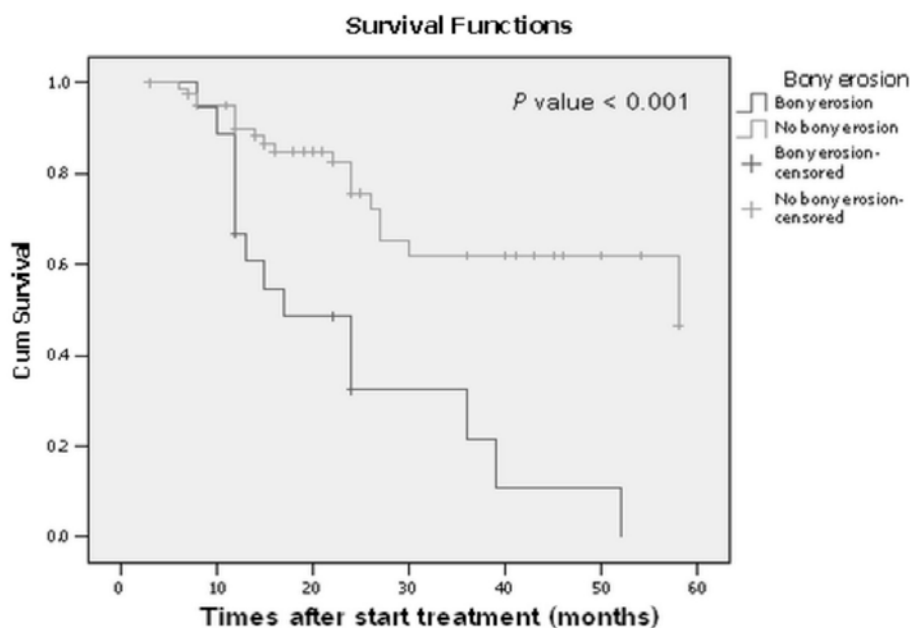
Apart of direct extension of the NPC to other neck spaces, there were two spaces of direct extension that had profound influence of the patient's survival rate. The first one was a vascular invasion (figure 3); the patient who had a vascular invasion will be the time of recurrence NPC rapidly more than the patient, who did not have the vascular invasion. Median time of recurrence was 34 months in patient with vascular invasion and 43 months in patient without this feature ( $P$  value = 0.032).

Similarly to survival time analysis of skull base invasion (figure 4); the patient who had a skull base invasion will have recurrence more rapidly than the patient who did not have the skull base invasion. Median time of recurrence were 24 and 44 months in patient with and without skull base invasion, respectively ( $P$  value = < 0.001).

In another parameter, included primary tumor size, location, the rest of primary extension, nodal size, and nodal levels, had similarly in median time of recurrence and no statistically significant difference within groups.

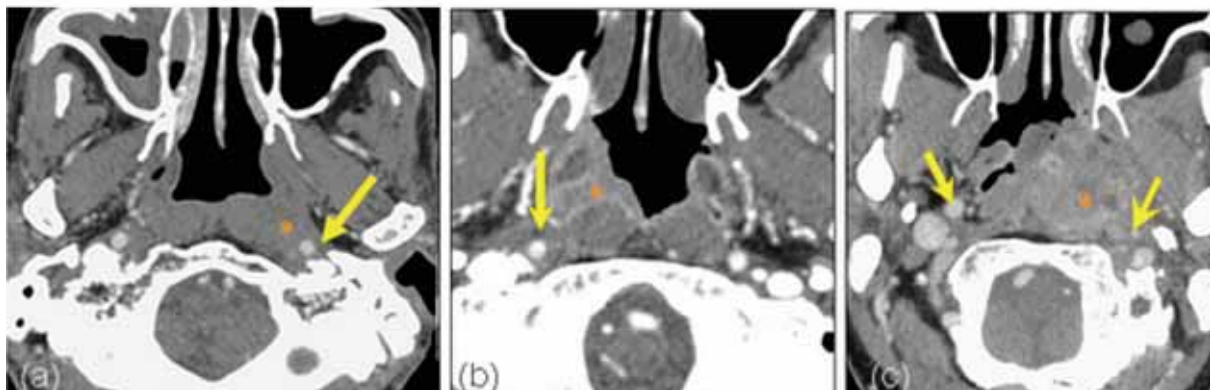


**Fig. 2** Overall survival rate of patient's entire group at mean of covariates (n= 99).**Fig. 3** Survival of patients for the different levels of vascular/carotid space invasion

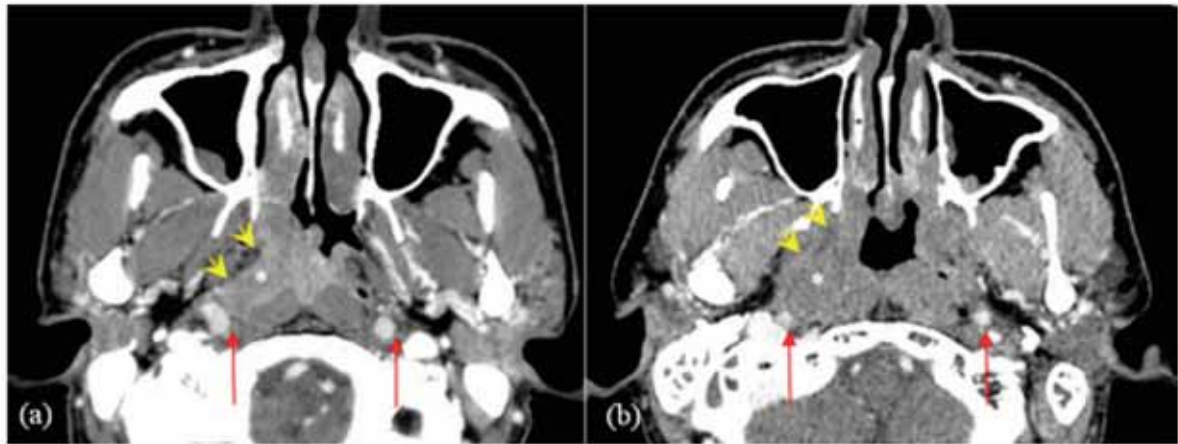
**Fig. 4** Survival of patients by skull base invasion

Bony skull invasion	Total	Median time of recurrence (months)
No bony skull invasion	81	43.564
Bony skull invasion	18	23.956
Overall	99	39.017

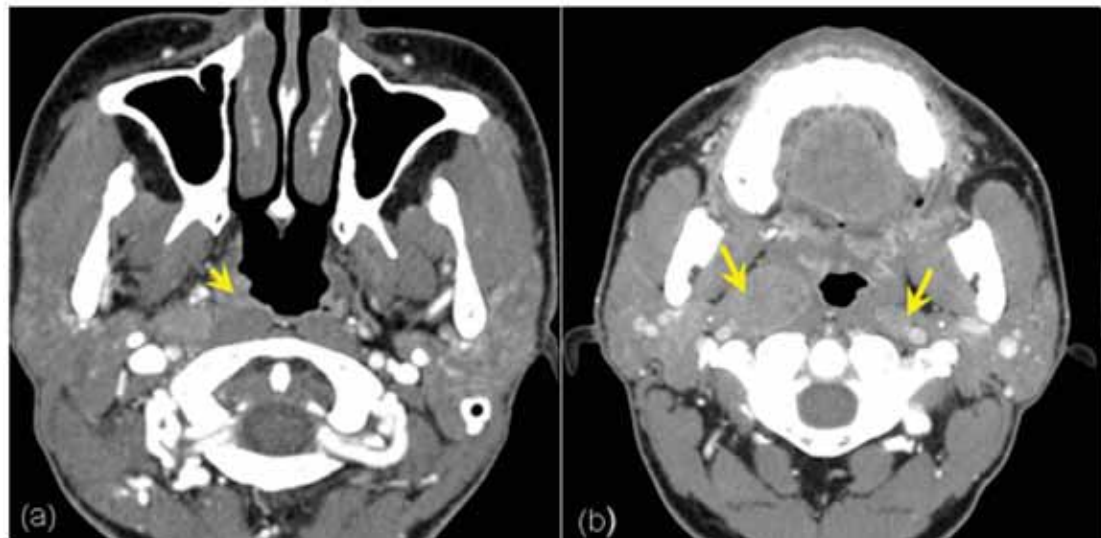
Kaplan-Meier analysis was defined significant  $p$  value less than 0.005

**Fig. 5** Vascular or Carotid space invasion

- (a) Axial contrast-enhanced CT scan of the nasopharynx in a patient with NPC. There is an enhancing tumor at left nasopharynx (\*), which extension caused obliterate the circumferential fat plane of left internal carotid artery or internal jugular vein more than half of diameter (arrow). Comparisons to the right sided, which preserves normal fat plane.
- (b) Axial contrast-enhanced CT scan of the nasopharynx in a different patient with NPC. There is an enhancing tumor at right nasopharynx (\*), which extension to across midline and caused obliterate the circumferential fat plane of right ICA more than half of diameter (arrow). Comparisons to the left sided, which preserves the normal fat plane.
- (c) Axial contrast-enhanced CT scan of the nasopharynx in a different patient with NPC. The enhancing tumor mainly occupies at left nasopharynx and across midline to the right side (\*), cause obliterate the circumferential fat plane of both ICA more than 180 degrees (arrow). Narrowing of left ICA is also noted.

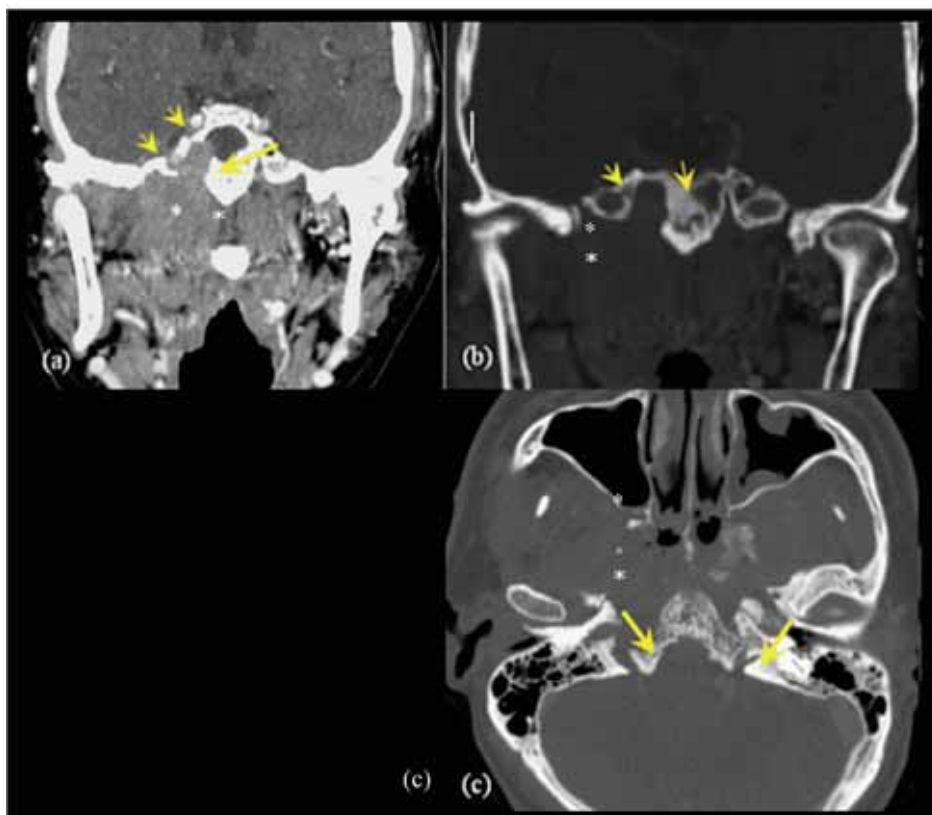
**Fig. 6** A 57 years man known case of right nasopharyngeal cancer

- (a) Axial contrast-enhanced CT scan of the nasopharynx showed enhancing NPC at right NP (\*) and extension to right parapharyngeal space; PPS (arrow head) but still preserves the normal fat plane of bilateral vascular spaces (arrow).
- (b) Axial contrast-enhanced CT scan of the other patient with right NPC (\*), revealed the NPC extends to right PPS (arrow head) and encase right carotid space nearly half of its diameter, but still preserves the normal fat plane of left vascular spaces (arrow).

**Fig. 7** A 57 years old man known case of right nasopharyngeal cancer

- (a) Axial contrast-enhanced CT scan of this patient at level of nasopharynx show enhancing tumor at right nasopharynx (arrow head).
- (b) Axial contrast-enhanced CT scan of the same patient at lower level has shown bilateral enlarged retropharyngeal lymph nodes (arrow).

**Fig. 8** A 49 years man known case nasopharyngeal cancer



- (a) Coronal view of contrast-enhanced CT scan with soft tissue window and bone window (b) shows enhancing NPC at both NP, which extended into cavernous sinus with predominate in the right sided, resulting of bony destruction at right petrous, right pterygoid plate and clivus.
- (b) Axial view of contrast-enhanced CT scan with bone window showed extensive bony destruction of petrous bones, pterygoid plates, clivus and widening of both foramen lacerum, foramen ovale and foramen spinosum.

## Discussion

Local recurrence and distant metastasis are the common mode of treatment failure of a nasopharyngeal cancer, which are determinant of survival. Locoregional control of NPC remains a significant factor of local recurrence. It has been accepted that the primary tumor, nodes and metastases (according to the TNM staging) is the most important prognostic factor. Different patterns of treatment failure had been defined across stages. T3-4 No-1 mostly has local failure; any T with N2-3 has risk of locoregional and distant failure<sup>13</sup>. In addition, some investigators suggested that tumor volume had a

close relationship with survival rates and recurrence rates. The NPC with large tumor volume was associated with more recurrence and poor survival rate<sup>14</sup>. Moreover, De-hong et al had described the relationship between post-radiation changes and recurrent diseases and suggested, that If the nasopharyngeal walls remained moderately thick (greater than 3 mm) on a CT scan beyond 6 months after radiotherapy, the risk of relapse would increase<sup>15</sup>.

In our study, which initially excluded metastases, by using univariate analyses primary tumors, nodes, skull base erosion, and carotid space invasion were independent risk factors of tumor

recurrence. According to TNM staging, the skull base involvement was corresponding to T4 stage. In term of prognostic factors, our results were in accordance with various studies, in which the higher T stage had increased risk of local failure with consequently increased risk of recurrence<sup>16</sup>. However, in our data tumor size had no statistically significant correlation with the risk of recurrence. This finding was disagreed with those reports which promoted the value of tumor volume in predicting local control. This might imply that the tumor size which was measured on the single axial image was not represented the tumor volume. Although, volumetric analysis of the primary tumor has been shown to be an important prognostic value in predicting local control, but tumor volume measurement techniques is complicated and less applicable in routine work. Furthermore, NPCs tend to be infiltrative and irregularly resulting to difficult to assessment. Accurate measurement of tumor volume requires a detailed outlining of the tumor extent from imaging, and a calculation of tumor volume from a three-dimensional perspective<sup>17</sup>.

For early detection of skull base erosion, multidetector CT scan has been the reliable and the most cost-effectiveness imaging tool for evaluation. MRI should be performed when subtle lesions adjacent to the skull base or subtle intracranial invasion is suspicious. Comparison the capacity between CT scan and MRI was not the purpose of this study.

Carotid space invasion had been recognized which showing significant correlation with tumor recurrence in our analysis. Generally speaking, carotid space is post styloid compartment of parapharyngeal space. Its involvement indicates posterolateral tumor extension in the parapharyngeal

space which is corresponding to T2b stage of TNM staging. The parapharyngeal space was the most commonly infiltrated region.

Involvement of parapharyngeal space was shown to be associated with prognostic factor and poor local control in several reports<sup>16</sup>. Kalogera-Fountzila A et al<sup>16</sup> demonstrated that the degree of the tumor extension into the parapharyngeal space was an independent prognostic factor for overall survival. Our data suggested that invasion of the carotid space which was indicated by loss of fat plane surrounding the internal carotid artery was more important sign than invasion of parapharyngeal space alone. To evaluate infiltration of perivascular fat plane, MRI is more accurate and preferred to be diagnostic method particularly if it is not extensive involvement, however, multidetector CT scan can be applied. Based on our result, skull base erosion and carotid space involvement had statistically significant, thus, posterior extension of the NPC may confer the worse prognosis.

The incidence of presence of cervical lymph node involvement in patients with NPC is quite high. About 75% of patients have enlarged cervical nodes at presentation<sup>18</sup>, 80% are bilateral. Nodal metastasis shows an orderly inferior spread and the affected nodes are larger in the upper neck<sup>19</sup>. It was found 100% in our study. There was correlation between lymph node involvement according to TNM staging and risk of tumor recurrence ( $p=0.02$ ), however, the size and the nodal levels had no significant effect.

Our data revealed metastatic retropharyngeal lymph node at 39.4%, but no difference between recurrent and non recurrent groups. It is considered to be primary station of NPC and may be seen in 65% of patients with cervical lymph node metastases, 35% of metastasis bypasses this node to reach the



cervical nodes<sup>20</sup>. Some authors had also reported that the distant failure for these lymph node metastases was similar to level II lymph node involvement. In the staging system of NPC, involvement of retropharyngeal lymph node has not been mentioned routinely. How its abnormality influence on prognosis of NPC is still not well understood. The reports of no significant influence of retropharyngeal lymph node on predicting outcome<sup>21</sup> are in agreement with our results.

Concerning the lymph node size, although we found that the averaged diameter of the largest lymph node of recurrent group was larger than the other group (3.6 cm and 1.5 cm respectively) but it was no significant difference ( $p$  value  $<0.05$ ) in relation to the risk of recurrence. However, there has been controversy over the prognostic significance of the size and various features of lymph node involvement. Lee et al<sup>22</sup> found that maximum lymph node size was independently significant in predicting survival, but in contrast, many investigators found that it was not a significant prognostic factor<sup>23,24</sup>. Furthermore, Teo et al<sup>23</sup> reported that fixed lymph nodes, and contralateral neck lymph nodes were independently significant in predicting survival, rather than maximal lymph node size.

Among the other factor that were significant, only skull base invasion had been identified to be an independent factor for prediction of NPC recurrence in multivariate analysis. However, those findings may be correlated with one another. Because of late local recurrences, even after five years are not rare, and those patients who had developed distant metastases after primary radiotherapy had a better prognosis<sup>22</sup>, thus, early detection of recurrent disease or distant metastases after complete treatment is very important. For NPC patients who have

those suggestive findings, particularly, skull base invasion should be followed up closely.

## Conclusion

The risks of NPC recurrence after complete treatment have been correlated to TNM staging, skull base invasion, and carotid space involvement. Neither tumor size, lymph node size, parapharyngeal space invasion alone nor retropharyngeal lymph nodes have been shown to be significant prognostic factors. Skull base invasion has been identified to be the predictive sign for tumor recurrence. Skull base invasion and carotid space involvement have a statistically significant prognostic factors for overall survival. Carotid space involvement is indicated by infiltration of perivascular fat plane of the internal carotid artery.

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