TECHNETIUM-99M SESTAMIBI (^{99M}TC MIBI) SINGLE-PHOTON EMISSION COMPUTERIZE TOMOGRAPHY IN THE DETECTION OF NASOPHARYNGEAL CARCINOMA

Sunanta CHIEWVIT, MD.[1] Supatra SANGRUCHI, MD.[2] Vutisiri VEERASARN, MD.[2] Nan SUNTORNPONG, MD.[2] Mongkol UIPRASERTKUL, MD.[3] Ruentip TIPPAROJ, B.sc.[1] Vacharin RATANAMART, MD.[1]

ABSTRACT

Nasopharyngeal carcinoma is a radiosensitive tumor. Recurrence after radiotherapy is a common cause of treatment failure. Early diagnosis and accurate identification of residual/ recurrent disease are essential for proper patient management. It is radiobiologically necessary to booster the irradiation dose or using combined therapy for the persistent tumor after the initial course of radiotherapy. CT and MRI cannot be used in the evaluation of response to therapy in NPC. Positron Emission Tomography (PET) have proved to be valuable as metabolic imaging tracer, however, their restricted availability and high cost are inherent limitations to their uses. We evaluated ^{99m}Tc MIBI in identifying primary tumor, neck node metastases, distance metastasis and recurrence of the diseased after therapy in NPC patients. The sensitivity and specificity in identifying primary tumor were 100% and 33% respectively. ^{99m}Tc MIBI scintigraphy can detect neck nodes metastasis 13 of 15 cases. One case of lung metastases and two cases of liver metastases can be detected by ^{99m}Tc MIBI scintigraphy in our study. The sensitivity and specificity in identifying recurrence or residual tumor in pre and post treatment group and post-treatment group were 100%, 80% and 100%, 60% respectively.

The incidence of of nasopharyngeal carcinoma (NPC) in statistical report 1997 from Tumor Registry Siriraj Cancer Center is 3.11 %[1] of all cancer. NPC is a potentially curable disease using combined modality treatment. Radiotherapy is the primary treatment modality for all locally and regionally confined stages. Systemic chemotherapy has been added to radiotherapy in locoregionally advanced and systemic metastasis diseases. Follow up after treatment of NPC are important in improving of survival rates. Early diagnosis and accurate identification of residual/ recurrent disease in patient with NPC are essential for proper patient management. Proper assessment of primary and metastatic NPC requires clinical/ fiberoptic examination followed by biopsy. Computed tomography (CT) or Magnetic resonance imaging (MRI) are the imaging to outline the anatomical planes involved by disease. CT/ MRI is the investigation of choice for accurate locoregional staging at initial presentation. CT cannot differentiate between inflammation, post-radiation fibrosis and recurrent disease. Although MRI may be useful in distinguishing between radiation fibrosis and recurrent disease, inflammatory changes and infection may simulate tumor recurrence. The presence of residual masses is 45% - 65% of

[1] Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University.
[2] Division of Radiotherapy, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University.
[3] Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University. Bangkok Thailand, 10700.

patients after therapy.[2] Incomplete eradication of locoregional disease results in further tumor growth and mutation that may lead to high metastatic propensity. It is radiobiologically necessary to retreat persistent tumors after the initial course of radiotherapy.[3] The target volume and required radiation dose will be smaller.[4,5] Thus more precise imaging modalities that could be used as a gold standard for differentiating viable tumor from post-therapy changes may detect those patients requiring additional therapy so that both unnecessary further treatment options and suboptimal therapy can be avoided. Unnecessary further treatment may cause early or late morbidity that can significantly reduce patient's quality of life. Positron emission tomography (PET) tracers such as fluorine-18-fluorodeoxy-glucose and carbon-11 methionine have proved valuable as metabolic imaging tracer, however, their restricted availability and high cost are inherent limitations to their uses.[6,7] Technetium 99m methoxyisobyltyl isonitile (^{99m}Tc MIBI) and Thallium-201 (Tl-201) single photon emission computerize tomography (SPECT) were accurated in detecting regional recurrence and distance metastasis.[8] ^{99m}Tc MIBI is taken up by cancer cells by an active transport mechanism and stored in the mitochondria and cytoplasm. Mitochondrial and plasma membrane potentials of tumor cell, and cellular mitochondrial content can play a significant role in tumor uptake of ^{99m}Tc MIBI or uptake may be caused by an indirect phenomenon such as increased tumor blood flow and capillary permeability.[9] The study evaluated ^{99m}Tc MIBI as a potential agent for the diagnosis of primary tumors, lymph node metastases, distance metastases and local recurrence in nasopharyngeal carcinoma.

MATERIALS AND METHODS

PATIENTS

Thirty-three patients with histologically proven nasopharyngeal cancer and 3 patients with histologically proven metastatic squamous cell carcinoma to neck nodes were included in the study. Six patient were studied in both pre and post treatment. There were 22 patients studied prior to radiation treatment only. Eight patients were studied after treatment. The detail statuses of the patients were presented in table 1

Table 1 The detail status of the patients in 3 groups (pre and post treatment group, pre treatment group, and post treatment group)

Group	Sex		Histologic cell type		mean age (year)
	Male (case)	Female (case)	Squamous cell carcinoma (case)	Undifferentiated carcinoma (case)	
Pre and post treatment	4	3	2	5	42.86
Pre-treatment	16	5	11	10	42.38
Post- treatment	5	3	2	6	55.50

IMAGING STUDIES

All studies were performed on a Toshiba SPECT digital gamma camera GCA-901A , equipped with a low-energy high-resolution collimator. All patients underwent dynamic blood flow, static image, whole body and SPECT of head and neck following the administration of 20 mCi of ^{99m}Tc MIBI. The SPECT was performed in a step and shoot mode at 360° for 64 frames with

an imaging time 30 sec/view.

INTERPRETATION

Physiologic uptake in the head and neck area was noted in the pituitary gland, nasal and oral cavity, parotid, submandibular and sublingual salivary glands. Any uptake other than physiologic uptake was considered positive for primary or residual/recurrent or metastatic disease depending on the location of uptake.

RESULT OF ^{99M} TC MIBI FOR NASOPHARYNGEAL CANCER

Table 2 The result of pre and post treatment group.

STUDY	SEX	AGE (YEAR)	CELL TYPE	SCAN FINDING			RESULT OF BIOPSY	T.N.M. status
				PRIMARY	NECK NODE	DISTANCE METASTASIS	-	
1-1	M	43	Undiff CA	+	+	-	+	
1-2	M	43	Undiff CA	-	-	-	-	
2-1	F	33	Squamous cell CA	+	+	-	+	T1N2aMx
2-2	F	33	Squamous cell CA	+	+(improve)	-	-	
3-1	M	43	Undiff CA	+	+	-	+	T4N3Mx CT : NPC with lymphadenopathy
3-2	M	43	Undiff CA	+	-	-	+	Squamous cell CA (post Px)
4-1	F	48	Undiff CA	+	-	Lung	+	T4N1M1 CXR positive
4-2	F	48	Undiff CA	+	-	Lung	+	CT +
5-1	M	36	Squamous cell CA	+	+	-	+	T1N2bMx bone scan: multiple bone metastasis
5-2	M	36	Squamous cell CA	-	-	-	-	
6-1	M	49	Undiff CA	-	-	-	+	
6-2	M	49	Undiff CA	-	-	-	-	
7-1	F	48	Undiff CA	+	+	-	+	T2N1M0
7-2	F	48	Undiff CA	-	-	-	-	

Table 3 The result of pre-treatment group.

STUDY	SEX	AGE (YEAR)	CELL TYPE	SCAN FINDING			RESULT OF BIOPSY	T.N.M.status
				PRIMARY	NECK NODE	DISTANCE METASTASIS		
1	M	79	Squamous cell CA	+	-	Liver	+	CT: suggested multiple liver metastasis T2N2 Mx
2	F	47	Undiff CA	+	-	-	+	
3	F	33	Squamous cell CA	+	+	-	+	CT: NPC with intracranial extension, lymph node negative.
4	F	31	Squamous cell CA	+	+	-	+	Bilat. Lymphadenopathy rt. 1.5 lt. 4cm.
5	M	23	Undiff CA	+	+	-	+	loss radiation treatment
6	M	61	Undiff CA	+	+	-	+	T1N3M1 loss radiation treatment
7	M	30	Meta. Undiff CA	-	+	-	-	CT: no mass at nasopharynx, multiple lymphadenopathy jugular chain.
8	M	51	Meta.squamous cell CA	+	-	-	-	study post cervical LN biopsy, scalp : squamous cell CA
9	M	23	Undiff CA	+	+	-	+	T3N1M0
10	F	35	Undiff CA	+	+	-	+	
11	M	49	Undiff CA	+	+	-	+	
12	F	47	Undiff CA	+	-	-	+	
13	M	66	Meta. Squamous cell CA	+	+	-	-	biopsy at nasopharynx is negative CT: bilat. NPC, enlarge left cervical node.
14	M	41	Undiff CA	+	+	-	+	T3N3Mx
15	M	15	Squamous cell CA	+	+	-	+	T2N2Mx
16	M	46	Undiff CA	+	+	Liver	+	T4N2M1 U/S multiple liver meta, Bone scan multiple bone meta
17	M	36		+	+	-	+	
18	M	48	Squamous cell CA	+	+	-	+	T4N2bMx
19	M	24	Squamous cell CA	+	+	-	+	
20	M	56	Squamous cell CA	+	+	-	+	
21	M	49	Squamous cell CA	+	-	-	+	

Table 4 The result of post-treatment group.

STUDY	SEX	AGE (YEAR)	CELL TYPE	SCAN FINDING			RESULT OF BIOPSY	T.N.M.status
				PRIMARY	NECK NODE	DISTANCE METASTASIS		
1	M	63	Undiff CA	+	-	-	-	MRI: positive tumor mass at base of skull
2	M	61	Undiff CA	+	+	-	-	Lt. LN 3Cm.
3	M	60	Undiff CA	+	-	-	+	
4	F	43	Undiff CA	-	-	-	-	
5	M	72	Undiff CA	+	+	-	+	biopsy at neck node and primary :recurrent NPC
6	F	58	Squamous cell CA	+	+	-	+	
7	F	38	Squamous cell CA	-	-	-	-	
8	M	49	Undiff CA	-	-	-	-	

Table 5 The Statistical analysis in the pre-post treatment group, pre-treatment group and post treatment group

Group of patients	True positive (case)	True negative (case)	False positive (case)	False negative *(case)	Total (case)
Pre and post treatment group	2	4	1	-	7
Pre treatment group	18	1	2	-	21
Post treatment group	3	3	2	-	8

*There were no false negative studies for primary disease

Table 6 The Sensitivity and specificity of pre and post treatment group, pre-treatment group and post treatment group.

Study	Cases	Sensitivity %	Specificity %
Pre and post treatment group	7	100	80
Pre treatment group	21	100	33
Post treatment group	8	100	60

Table 7 The comparative sensitivity and specificity of our study and Lale et al. study.

		No of patients	Sensitivity %	Specificity %
Lale Kostakoglu[11]	3 month F/U	5	100	85
	6 month F/U	3	100	93
Sunanta	3-9 month F/U	6	100	80
Lale Kostakoglu[10]	Pre-treatment	22	100	67
	Post-treatment	16	100	67
Sunanta	Pre-treatment	22	100	33
	Post-treatment	8	100	60

Fig. 1,2 Case of undifferentiated nasopharyngeal carcinoma,

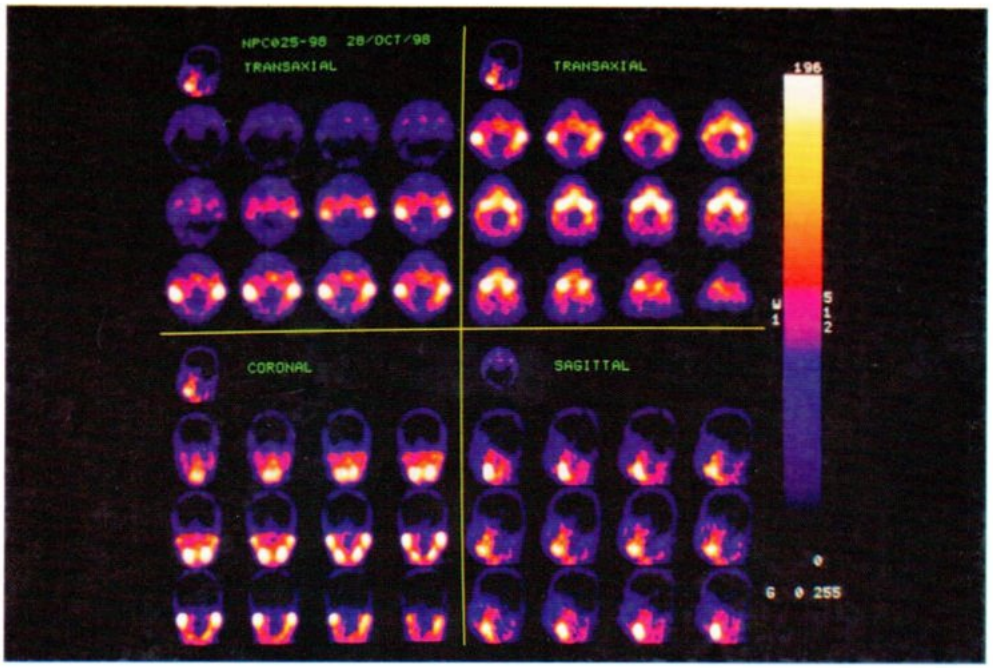

Fig. 1 (pre-treatment) reveals increased uptake of the radioactivity at left nasopharynx.

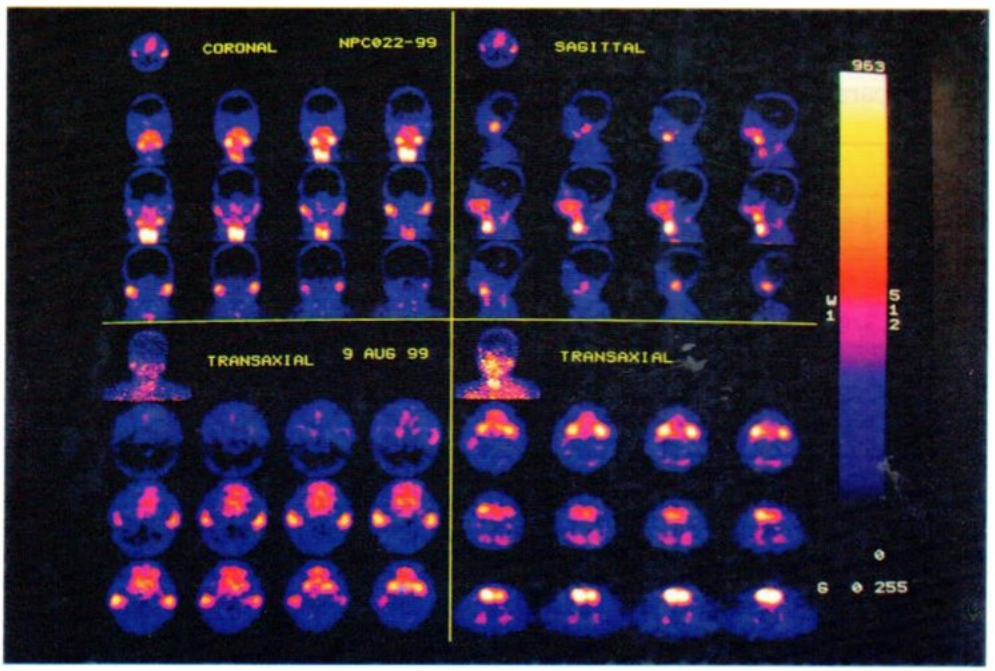

Fig. 2 (post-treatment) shows no abnormal increased uptake at nasopharynx.

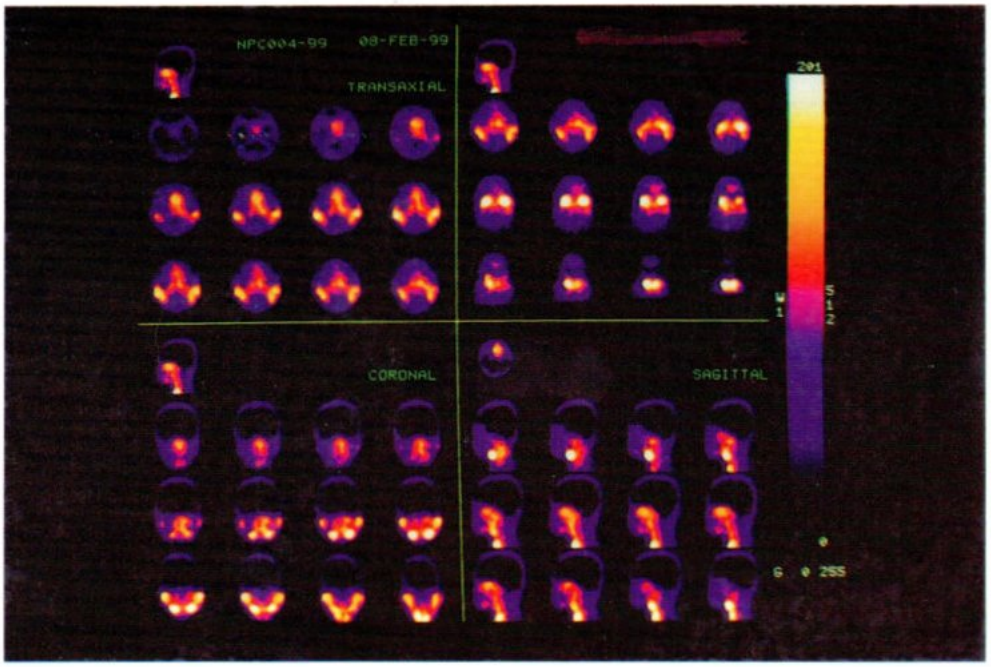

Fig. 3 Case of squamous cell nasopharyngeal carcinoma reveals increased uptake of the radioactivity at nasopharynx. There are multiple areas of increased uptake of the radioactivity at both upper cervical nodes.

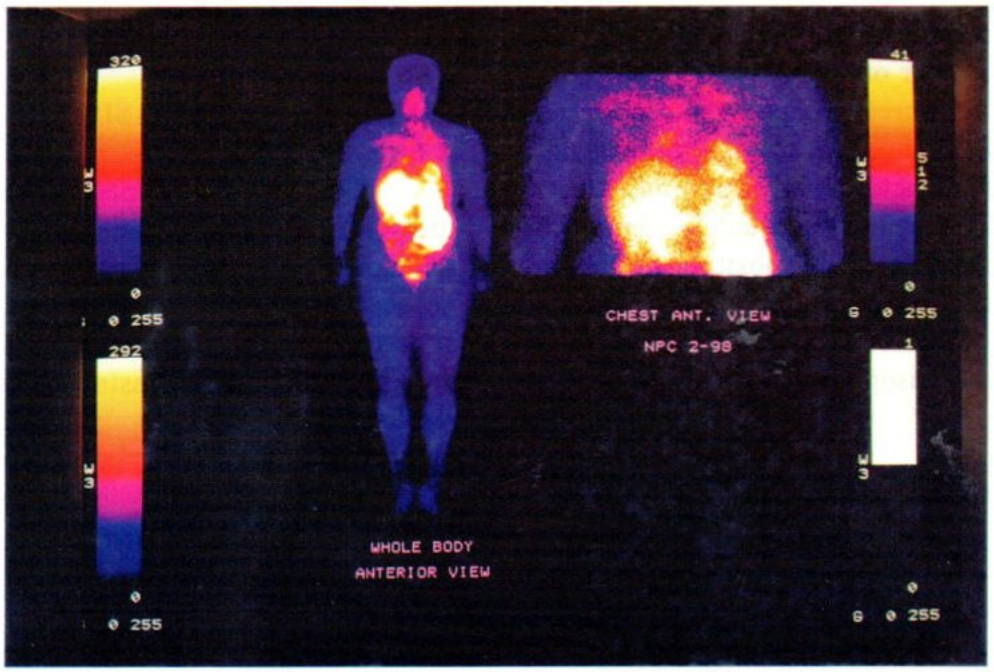

Fig. 4 Whole body image shows increased uptake of ^{99m}Tc MIBI at right chest. CA Nasopharynx with lung metastasis is suggested.

Fig. 5 Multiple areas of decreased uptake of the tracer in the liver compatible with liver metastases

The result of the study is based on histological confirmation. There were no false-negative studies for primary cancer in pre and post treatment group, pre-treatment group, and post-treatment group. Four of five cases of false positive finding in the three groups of our study were chronic inflammation in histological diagnosis. Chronic inflammation could be postulated that the high blood flow might account for the positive finding. One case of the positive finding was squamous cell carcinoma of scalp with neck node metastasis. Two of five cases with negative histology had nasopharyngeal mass by CT and MRI.

NECK NODES METASTASIS

We evaluated 15 cases of known cases of Nasopharyngeal Carcinoma with neck node metastases. ^{99m}Tc MIBI scintigraphy detected 13/15 cases of the metastatic lymph nodes, missing two cases which were possibly obscured by the physiologic uptake in the adjacent salivary glands. Lale et al.[11] studied in 18 cases of nasopharyngeal cancer with neck nodes metastasis and found a sensitivity of 94.7%. There was no true negative study to determine specificity.

DISTANCE METASTASIS

One case of lung metastasis and two cases of liver metastasis can be detected by ^{99m}Tc MIBI scintigraphy. Two cases of positive bone scan were not seen by ^{99m}Tc MIBI scintigraphy. Bone scan is superior than ^{99m}Tc MIBI scintigraphy in the detection of bone metastasis. False-negative results obtained for bone metastases may be due to the lower extraction fraction of radiotracer by the skeletal or obscured by the physiologic uptake in the adjacent organ such as liver, bowel and urinary bladder.

DISCUSSION

Nasopharyngeal carcinoma is a radiosensitive tumor. Recurrence after radiotherapy is a

common cause of treatment failure.[5] Incomplete eradication of loco-regional disease results in further tumor growth and mutation that may lead to high metastasis propensity. It is radiobiologically necessary to booster the radiation doses or combined therapy for the persistent tumor after the initial course of radiotherapy. Histological confirmation is the currently approved gold standard for the present of residual tumor, however biopsy may be misleading due to sampling errors. Therefore a specific functional imaging (Tl-201, ^{99m}Tc MIBI) modality is important to differentiate physiologic from pathologic uptake in NPC. The limitation of ^{99m}Tc MIBI scintigraphy is physiologic uptake at salivary glands, nasal and oral cavity and false positive study in chronic inflammation ^{99m}Tc MIBI could detect metastasis in the lymph node and distance metastasis. ^{99m}Tc MIBI scintigraphy is useful in the detection of distance metastases such as lung and liver metastases. Cold nodules were seen in case of liver metastases. Bone scan is superior than ^{99m}Tc MIBI scintigraphy in the detection of bone metastasis. MIBI is recognised as a transport substrate of P-glycoprotein, which is encoded by multidrug-resistance gene. Lale et al[10] reported no influence of P-glycoprotein pump on MIBI accumulation. There was no patient whose disease had progressed over the duration of 12-15 month when MIBI was negative.

CONCLUSION

^{99m}Tc MIBI scintigraphy was found to be sensitive in detecting residual/ recurrent tumor, lymph nodes and distance metastases. Therefore, ^{99m}Tc MIBI scintigraphy may be incorporated after therapy to evaluate the persistent masses or confirmation of diagnosis in case of false negative biopsy caused by sampling error.

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REFERENCE

1. Tumor registry Siriraj cancer center. Statistical report 1997. Faculty of Medicine, Siriraj Hospital Mahidol University: page 3
2. International Nasopharynx Cancer Study Group VUMCA I Trial preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy versus radiotherapy alone in Stage IV (≥N2, M0) undifferentiated nasopharyngeal carcinoma a positive effect on progression free survival. Am J Radiat Oncol Biol Phys 1996;35:463-469.
3. Taifu L. Trend in the clinical management of NPC. Int J Radiat Oncol Biol Phys 1992; 23:469-471.
4. Wither HR, Peter s LJ. Basic principles of radiotherapy: biological aspects of radiation therapy. In: Fletcher GH, ed. Textbook of radiotherapy, 3rd edn. Philadelphia: Lea and Febiger.1980:103-108.
5. Sham JST, Wei WI, Kwan WH, Chan CW, Kwong WK, Choy D. Nasopharyngeal carcinoma: pattern of tumor regression after radiotherapy. Cancer 1990;65:216-220.
6. Rege S, Maas A, Chaiken L. et al. Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers. Cancer 1994;73: 3047-3058.

7. Lindholm P, Leskinen-Kallio, Grenman R. et al. Evaluation of response to radiotherapy in head and neck cancer by positron emission tomography and (^{11}C) methionine. Int J Radiat Oncol Phys 1995; 32:787-794.
8. Abdel-Dayem H, Scott AM. Macapinlac HA, El- Gazzar AH, Larson SM. Role of Tl-201 chloride and Tc-99m-sestamibi in tumor imaging. In: Freeman LM, ed. Nuclear medicine annual. New York: raven press; 1994:181-234.
9. Cumali Aktolun, Hikmet Bayhan, and Metin Kir. Clinical Experience with Tc-99m MIBI imaging in patients with malignant tumors preliminary results and comparison with Tl 201. Clin Nucl Med 1992;17:171-176.
10. Lale Kostakoglu, Ugur Uysal, Enis Ozyar et al. A comparative study of technetium-99m sestamibi and technetium-99m tetrofosmin single-photon tomography in the detection of nasopharyngeal carcinoma. Eur J Nucl Med 1997;24:621-628.
11. Lale Kostakoglu, Ugar Uysal, Enis Ozyar et al. Monitoring response to therapy with Thallium-201 and Technetium-99m-sestamibi SPECT in nasopharynxgeal carcinoma. J Nucl Med 1997; 38: 1009-1014.