EVALUATING THE ROLE OF FDG PET-CT SCAN AS A SOLE IMAGING MODALITY IN THE MANAGEMENT OF MUO NECK

Oncology

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ABSTRACT

Aim: to study the role of PET-CT SCAN as a single imaging modality in the diagnosis of MUO neck. **Methodology:** retrospective study analysis of 51 cases of clinical unknown primary with cervical metastasis. **RESULTS:** FDG PET CT tracer uptake was detected in 24/51. true positive in 18 cases out of 24, false positive in 6 cases, false negative in 2 cases with sensitivity of 90%, specificity of 82%, positive predictive value of 75%, negative predictive value of 93% and accuracy of 84.91%. **Conclusion:** FDG PET CT can be used as a sole imaging modality in the diagnosis of MUO neck. it is complimentary to endoscopy.

KEYWORDS

fluorodeoxyglucose positron emission tomography, cervical metastasis with unknown primary, panendoscopy.

INTRODUCTION:

Head and neck cancers in India accounts for 30% of all cancers in male and 11-16% of cancers in female (1)

Majority of them present in the locally advanced stage. In 3 to 9 % of cases primary may not be evident after clinicoradiological examination and considered as carcinoma of unknown primary (2).

A carcinoma of unknown primary (CUP) is defined as a biopsy-proven malignancy from an unidentified origin following clinical and diagnostic evaluation (3)

The most frequently involved neck nodal areas are level II and level III. levels I, IV and V are rarely involved (4). bilateral lymph nodal involvement may be there upto 10% of cases (5)

As we all now, lymphatics drain in a predictable fashion from the each particular primary site unless it is disturbed by previous surgery or radiation to that particular site. Depending on the lymph nodal station involved we can predict the possible primary sites in a retrograde manner. so the knowledge of 1st echelon nodes from each site is must for the management of MUO.

Lymph nodes and their possible primary sites or in other word's various primary sites and their first echelon nodes.

Level I drains from oral cavity and oropharynx. level II most commonly involved nodal station in our study as well as in other studies because it drains from wide range areas like oral cavity, oropharynx, larynx, hypopharynx, nose, nasopharynx, parotid. level III also drains from multiple areas like oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, thyroid. level IV lymph nodes drains from Larynx, hypopharynx, thyroid, oesophagus. level V drains from nasopharynx, hypopharynx, thyroid and oropharynx. level VI drains from thyroid, larynx, hypopharynx, cervical esophagus. (6), (5)

True MUO definition:

no evidence of primary tumor is found after adequate clinical examination, fiberoptic endoscopy, imaging investigations which includes PET-CT and biopsy of putative mucosal sites. It is a diagnosis of exclusion. (7)

Clinical MUO: no obvious or highly suspicious lesion on out patient assessment, then the patient should be regarded as "clinical" unknown primary, should be evaluated further (5)

Possible Hypothesis for MUO NECK

1. primary acquires metastatic transformation soon after transformation and remains small, either due to inborn error leading to involution or due to extreme slow growth rate 2. inhibiting the growth of primary by metastasis. (8)

-tonsils, BOT, pyriform sinus, post nasal space/nasopharynx contribute to maximum number of cases other sites like scalp, parotid and thyroid must not be forgotten.

we need to diagnose primary in order to give specific treatment, so that OS and DFS can be improved (9). As per Haas et al the 3-year survival rate in patients diagnosed with head and neck primary tumours in workup was 100% after treatment, compared to 58% in whom primary could not be identified/true MUO (10).

- reduce treatment related toxicity like pan mucosal irradiation
- FNAC is really useful if the histology is other than squamous cell carcinoma like papillary carcinoma, mucoepidermoid or poorly differentiated variants. EBV is useful marker whenever suspecting the nasopharyngeal primary similarly HPV in oropharyngeal cancers.
- pet is the functional imaging technique
- many studies found that FDG PET CT IS better than CT in evaluating of MUO cases (11), (12)

The rationale for using the FDG as a Radiotracer is many cancer cells express increased GLUT1 receptors (13) and increased glucose uptake (Warburg effect)

- FDG PET CT IS considered as the imaging investigation of choice for MUO which gives both functional and anatomical orientation. Problems with PET scan is false positives-especially in oropharynx/walddelayers ring due to physiological uptake and cannot detect tumors below 4mm and false negatives. **Our approach to clinical muo:**

Detailed and relevant history of all patients were taken, followed by thorough clinical examination of all head and neck sites were done. FNAC of involved nodes were done. later proceeded with imaging. our institute doesn't have PET CT facility so we depend on outside diagnostics. only in affordable patient PET-CT was done other cases CECT or MRI was preferred as there were available in our institution free of cost.

Any clue regarding primary if found were further evaluated with biopsy and correlated. If imaging failed to localize the primary then triple endoscopy and biopsies from suspected sites were done.

RESULTS:

IN our study total 51 patients data were considered. 46 were male (90.1%) and 5 cases (9.9%) were female. age range varies from 43 years to 80 years. Majority of them falling between 60-70 yrs followed by 51-60 yrs, 40-50 yrs and above 70 yrs.

most common lymph nodal level involved is level 2 in 36/51 cases, followed by level 3 in 26/51 cases, level 4 in 15/51 cases, level 5 in 8/51

cases and level 1 in 5/51 cases. bilateral lymph nodal metastasis noted in 3/51 cases. In addition mediastinal lymphadenopathy was noticed in 3 cases and axillary lymphadenopathy was noticed in 1 case.

Out of 51 cases 46 were squamous cell carcinomas, 3 were adenocarcinomas, 1 was poorly differentiated/lymphoma carcinoma, 1 was mucoepidermoid ca.

In FDG PET CT evaluation 24 cases shown tracer upatake, were as no evidence of any uptake in 27 cases. out of 24 cases 5 cases are from tonsil, 4 each from pyriform sinus and lung. 3 cases from each primary sites from parotid and base of tongue. two cases of vallecular site. one case each from nasopharynx, maxillary sinus mucosa.

Out of 24 cases 18 cases histologically were proven to be malignant and 6 were false positive. 4 cases from tonsil, 3 cases from pyriform sinus and lung, 2 cases from base of tongue. 2 cases from parotid, 2 cases from vallecular, 1 case each from nasopharynx were malignant. one case from base of tongue, tonsil, parotid, pyriform sinus, maxillary sinus, lung were found to be false positive.

2 cases had not shown any tracer uptake in FDG PET CT but biopsies from suspected sites based on endoscopy confirmed the diagnosed, both of them were from tonsil.

Despite of all the diagnostic efforts primary could not be localized in 31 cases out of 51 cases (60.7%).

STATISTICS :

In this study 95% confidence interval were considered, Sensitivity of 90% (CI 68.3 -98.7%), specificity of 81.2% (CI 64.54-93.02), positive predictive value of 75% (CI 58.91-86.26), negative predictive value of 93.10 (CI 78.21-98.07), positive likelihood ratio of 4.95 (CI 2.72-1036), negative likelihood ratio of 0.12 (CI 0.03-0.46) and accuracy of the test was 84.91 (CI 72.41-93.25) were obtained.

35.2% of cases were diagnosed with PET CT scan were as 4% of cases without PET CT scan using only triple endoscopy. Z test for 2 independent proportions were used and P Value is less than 0.01 (0.0006)

In our study lesion is positive in FDG PET CT and confirmed in pan endoscopy directed biopsies considered as True positive. Positive in FDG PET CT but negative in panendoscopy directed biopsy are considered as false positive. negative in FDG PETCT as well as in pan endoscopy are true negative, those negative in FDG PET CT but positive in pan endoscopy directed biopsies are considered as false negatives.

AGE OF PATIENTS

Age range	Number of cases	percentage
40-50	11	21.5%
51-60	14	27.4%
61-70	19	37.2%
ABOVE 70	7	13.7%

SEX OF THE PATIENTS

MALE	FEMALE
46	5

VARIOUS LEVELS OF LYMPH NODES INVOLVED

Level of lymph nodes	no of cases	percentage of cases
1A	1	1.9%
1B	4	7.8%
II	36	70.5%
III	26	50.9%
IV	15	29.4%
V	8	15.6%
Level II and III	23	45%
II, III and IV	5	9.8%
II, III, IV and V	4	7.8%
BILATERAL	3	5.8 %

51 cases of MUO PET SCAN FINDINGS

PET SCAN FINDINGS

NO EVIDENCE OF PRIMARY	PRIMARY ?-LOCALISED TRACER UPTAKE
27 CASES (53%)	24 CASES (47%)

SUBSITES OF TRACER UPTAKE

S.NO	PRIMARY SUB SITE	NO OF CASES/51	PERCENTAGE
1	BOT	3	5.8%
2	TONSILS	5	7.8%
3	NASOPHARYNX	1	1.9%
4	Preepiglottic space	1	1.9%
5	PYRIFORM SINUS	4	7.8%
6	PAROTID	3	5.8%
7	VALLECULA, PRE EPIGLOTTIC SPACE	2	3.9%
8	PNS	1 (MAXILLARY)	1.9%
9	LUNG	4	7.8%

HPR REPORTS FROM THE CONCERNED FDG UPTAKE POSITIVE SITES

S.NO	SUBSITES POSITIVE IN HP	FDG UPTAKE	HPR PROVEN
1.	BOT	3	2scc
2.	TONSILS	5	4 SSC
3	VALLECULA	2	2 SCC
4	PREPIGLOTTIC SPACE	1	1scc
5	PYRIFORM SINUS	4	3 SCC
6	NASOPHARYNX	1	1scc
7	PAROTID	3	1 MUOCOEPIDERMOID, 1 LYMPHOMA
9	PNS	1	NEGATIVE FOR MALIGNENCY
10	LUNG	4	3 Adeno carcinoma

HPR AND FDG PET CORRELATION

FDG PET POSITIVE CASES	HPR POSITIVE CASE	percentage
24	18	75%
FDG NEGATIVE CASES	HPR POSITIVE FROM panendoscopy and BIOPSIES	
27	2 tonsil-surface irregularities	

Metastasis: distant metastasis were noted in 4 cases. mediastinal lymphadenopathy noted in 3 cases. one case axillary lymph nodal involvement.

DISCUSSION:

in our study mean age of patient was 55 years. In the studies conducted by BRUNA et al 59 years, wartski et al 57 years, nassenstein et al were 60 years

male to female ration in our study was 46:05. similarly, male predominance were noted in other studies as well, karapolat et al overall Primary detection rate in our study was 39.2% (20/51). in the meta analysis conducted by kwee et al primary detection rate was between 22-73%. PET scan alone was able to detect primary in 35.2% of our cases (18/51). in the meta analysis of kwee et al detection was 37%. rusthoven et al reported as 24.5%

Most common site of primary in our study was oropharynx 8/20 (40%). similarly oropharynx was most common site in the studies conducted by mendelhall et al and wartski et al Most common false positive sites in our study was oropharynx (2/6) 33%. In the metaanalysis conducted by kwee et al reported oropharynx and lung were the most common sites for false positives results.

Sensitivity in our study was 90%. in the meta analysis conducted by Thomas kwee et al was 55%-100%. chnet al reported sensitivity in 91.7%. similar results were reported by hans et al 91.5%, yoon et al 87.5%, Dandekar et al 92.8%

Specificity in our study was 81.8%. in the meta analysis conducted by Thomas kwee is 73%-100%. Chen et al reported specificity of 86.7%. similarly han A et al 85.2%. were as Dandekar et al reported towards lower side of 71.4%

Negative predictive value in our study was 93.1%. similar results were seen karapolat et al 90% and hassan et al 86.7%. in contrast miller et al results were towards lower side of 76.5%

Positive predictive value in our study was 75%. similar results were reported in miller et al 88.8%. according to karapolat et al study it is 77% and hassan et al 74.5%.

LIMITATION OF OUR STUDY:

1. instead of routine tonsillectomies and blind biopsies we followed pan endoscopy and PET/CT directed biopsies from suspected sites due to time constrain and patient overload. 2. Molecular markers like HPV and EBV were not used. PET/CT reports from machines of different standard were considered due to lack of inhouse PETCT facility.

CONCLUSION:

3-9 % OF Head And Neck Malignancies Present As MUO Neck. diagnosis of MUO Is Challenging. PET CT as an single imaging modality can Detect significant number of cases in complimentary to endoscopy in the diagnosis of MUO neck.

REFERENCES

1. <https://www.researchgate.net/publication/269656774> Head and Neck Cancer Burden in India. kulkarni, manik rao.
2. Management of lymph node metastases from an unknown primary site to the head and neck (Review). *Molecular and Clinical Oncology*, 2, 917-922. <https://doi.org/10.3892/mco.2014.361>. Zhuang.
3. Cervical Lymph Node Metastases of Unknown Origin: Primary Tumor Detection with Whole-Body Positron Emission Tomography/Computed Tomography. *Acta Radiologica*, 48:10, 1101-1108, DOI: 10.1080/02841850701581768. nassenstein.
4. Diagnosis and management of neck metastases from an unknown primary. Calabrese, L.
5. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. Mackenzie, K.
6. <https://www.researchgate.net/publication/20802488> The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. shah, jatin p.
7. Approach to Metastatic Carcinoma of Unknown Primary in the Head and Neck: Squamous Cell Carcinoma and Beyond. D, Rebecca.
8. Arosio, A. D., Pignataro, L., Gaini, R. M., & Garavello, W. (2017). Neck lymph node metastases from unknown primary. *Cancer Treatment Reviews*, 53, 1–9. doi:10.1016/j.ctrv.2016.11.014. Arosio.
9. In search of an unknown primary tumour presenting with cervical metastases: performance of hybrid FDG-PET-CT. *Nucl Med Commun.* 2007 May;28(5):365-71. doi: 10.1097/MNM.0b013e3280708edf. PMID: 17414886. Wartski, Myriam.
10. Diagnostic strategies in cervical carcinoma of an unknown primary (CUP). *Eur ArchOtorhinolaryngol* 2002;59:325-333. Haas I, Hoffmann TK, Engers R, Ganzer U.
11. Detection of Occult Primary Tumors in Patients with Cervical Metastases of Unknown Primary Tumors: Comparison of 18F FDG PET/CT with Contrast-enhanced CT or CT/MR Imaging—Prospective Study. Jae Ryung Lee.
12. Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. *Arch Otolaryngol Head Neck Surg.* 2009 Oct;135(10):1024-9. doi: 10.1001/archoto.2009.145. PMID: 19841343. waltonen.
13. Utility of PET in unknown primary with cervical metastasis. Dandekar MR.
14. Added Value of PET-CT in Patients with Metastases of Unknown Primary. Bruna C, Journo A, Netter F et al.
15. Wartski M, Le Stanc E, Gontier E et al.
16. PET/CT for the Detection of Unknown Primary Tumours in Patients with Cervical Lymph Node Metastases. *Mol Imaging Radionucl Ther.* 2012 Aug;21(2):63-8. doi: 10.4274/Mirt.344. Epub 2012 Aug 1. PMID: 23487242; PMCID: PMC3590973. KARAPOLAT.
17. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. c.kwee, thomas.
18. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. Rusthoven, Kyle E.
19. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Head Neck* . Mendenhall.
20. Chen, Yue-Hong. Value of Fused Positron Emission Tomography CT in Detecting Primaries in Patients With Primary Unknown Cervical Lymph Node Metastasis.
21. Clinical value of 18F-FDG PET-CT in detecting primary tumor for patients with carcinoma of unknown primary. *Cancer Epidemiol.* 2012 Oct; 22504050., 36(5):470-5. doi: 10.1016/j.canep.2012.03.002. Epub 2012 Apr 14. PMID: . Han A, Xue J, Hu M, Zheng J, Wang X.
22. Utility of Combined (18)F-fluorodeoxyglucose-positron Emission Tomography and Computed Tomography in Patients With Cervical Metastases From Unknown Primary Tumors. Yoon, Jong-LyelRohJae SeungKimbJeong HyunLeeKyung-JaChodSeung-HoChoiSoon YuhlNamaSang.
23. The role of FDG PET in the diagnosis of occult primary with cervical lymph node metastases: A meta-analysis study. Hassan, Ossama. METAANALYSIS.
24. Positron Emission Tomography in the Management of Unknown Primary Head and Neck Carcinoma. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):626–629. doi:10.1001/archoto.131.7.626. millerFR.
25. Utility of Panendoscopy for the Detection of Unknown Primary Head and Neck Cancer in Patients with a Negative PET/CT Scan. *Ear, Nose & Throat Journal.* 2011;90(8):E16-E20. doi:10.1177/014556131109000818. pattani, KAVITHA M.