

Original Article

Differences of Methods of Searching Primary Site of Carcinoma Unknown Primary between Traditional and Standard Guideline

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Abstract:

Background: Trends of searching primary has been changed as etiological backup are changing. PET- CT and other viral molecular markers has been included in most recent protocols for searching primary of carcinoma unknown primary (CUP). Despite of the exhaustive effort with traditional tool many unknown primaries are not known. Patients with CUP without localizing primary, are subjected to radical surgery, wide-field radiation and chemotherapy during treatment.

Objectives: To determine the effectiveness of localization of the primary tumor by using conventional technique and to compare the outcome of it to the standard guideline.

Methods: This was a prospective study. In conventional search, after thorough clinical examination and diagnostic workup, Panendoscopy with bilateral Tonsillectomy and excision of tongue base mucosa in selective cases is done. Biopsy from nasopharynx, Larynx and hypopharynx is done only when clinically suspected. PET-CT and other viral/molecular markers has been done for recent standard protocol group.

Results: In conventional method, Out of 29 patient, 6 primaries found. 5 in tonsil and 1 in base of the tongue base.

In standard protocol method, out of 34 cases with PET-CT and viral marker 8 primaries detected, 5 in tonsil and 2 in tongue base and 1 in nasopharynx.

Conclusion: Unknown head and neck primaries present a diagnostic challenge that outcome in the search of primary for CUP may be improved by digital examination and appropriate tissue examination in traditional detection protocols.

Key words: Carcinoma unknown primary (CUP), Traditional guideline, Standard guideline,

Introduction:

Carcinoma of Unknown Primary (CUP) is a heterogeneous disease entity. It is metastatic

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lymphadenopathy without obvious primary by clinical development of a primary lesion within a subsequent 5-year period.¹

5-10% patients of Head-Neck Cancer present as a Carcinoma Unknown Primary (CUP).²

The oropharynx is the most common primary site of unknown primary sites in the head-neck. Identification of a primary cancer site after a comprehensive battery of diagnostic investigations is reported to a little over 50%.^{3,4}

The emergence rate of primary for head-neck CUP is about 3% per year, which is equivalent to the development of second primary in head-neck.⁵

Concept of searching for primary has been changing.

PET- CT and other viral/molecular markers has been included in recent standard protocols for searching primary of CUP.

According to meta-analysis, PET-CT identification rate is 44%, sensitivity 99% and specificity 68%. It has been established as an investigation of choice for Head-Neck CUP.⁶

Incorporation of viral markers in diagnostic investigations increases the rate of detection of primary sites. Identification of Epstein - Barr virus (EBV) suggests nasopharyngeal origin and Human Papilloma Virus (HPV) suggests oropharyngeal origin.⁷

Transoral surgical approaches (Laser/ Robotics) also find more primary in the head-neck CUP. But, these resources are not easily available in Bangladesh.

Objectives:

To observe the effectiveness of localization of the primary tumor site by using conventional technique and comparison of it with that of standard guideline. This is not to challenge the existing standard protocol, but to see the efficacy of methods practicing in limited resource area of Bangladesh.

Rationality: To predict searching efficacy of various groups for Primary in Head-Neck CUP in centers of various level of recourse availability.

Method:

Design:

Prospective, Quasi-Randomized study.

All Patients with neck node cytologically proved Squamous Cell Carcinoma and without primary (negative biopsy) in the period of diagnosis or follow-up.

Place of study was in Bangabandhu Sheikh Mujib Medical University, from 2012 to 2019. Patients were divided into 2 groups: Traditional/Conventional search group and Standard protocol group depending on availability/capability of patients doing relevant investigations (Viral Markers, PET-CT etc.)

In conventional search after thorough Clinical examination and Diagnostic workup, Panendoscopy with Bilateral Tonsillectomy was done in all cases and excision of tongue base mucosa in selective cases. Biopsy from nasopharynx, Larynx and hypopharynx only when clinically suspected.

In addition, thorough clinical examination, Tonsil, Tongue base and Nasopharynx were gently palpated by gloved finger with Surface anaesthesia. Specimen for histopathological examination was collected from those different sites.

PET-CT, Viral/Molecular markers (Markers against Human Papilloma Virus and Epstein Barr Virus) etc has been included in standard protocol (NCCN Guideline etc.) group. Mostly these investigations are unavailable, costly, time consuming which delays the treatment in many tertiary centers of Bangladesh.

Participants who have already investigated with Viral Markers and/or PET-CT elsewhere and comply with inclusion criteria have been included for standard Protocol Group. Others included for Conventional group.

Results:**Table-I :**
Group set up

Group	PET-CT & Viral Marker	PET-CT only	Viral Marker only	No PET-CT and Viral Marker	Total
Standard Protocol Group	28	4	2	-	34
Conventional Group	-	-	-	29	29

In conventional Group, 29 participants were studied. No PET-CT and Viral Markers was done in this group. Out of other assessments with palpation by gloved finger after spraying of surface anaesthesia and HRCT of Neck extending from base of the skull to clavicle was done. 6 primaries were found. 5 in tonsil and 1 in base of the tongue base.

Out of 32 cases with PET-CT and viral markers 8 primaries were detected, 5 in tonsil and 2 in tongue base and 1 in nasopharynx.

Table II:
Detected Primary Sites:

Group	Tonsil	Tongue base	Nasopharynx	Total
Standard	5	2	1	8
Conventional	5	1	—	6

Outcome of conventional method almost similar to standard protocol in this setup.

Discussion:

2-5% of Head- Neck Squamous Cancer present as Neck nodal metastasis and diagnosed as Carcinoma of unknown primary (CUP). Primary site should be detected for precise and accurate management of disease. Hence, Primary site detection will increase the survival rate and reduce the morbidity. Treatment protocol varies according to known primary with

metastasis. Surgical planning can be better determined. Radiation field will be focused. Adjoining healthy tissues/areas can be spared and morbidity can be minimized.^{2, 8,9}

According to UK National multidisciplinary Guidelines-PET-CT imaging, in conjunction with panendoscopy, directed biopsy as appropriate and bilateral tonsillectomy offer the greatest chance of identifying the occult primary tumour in the routine clinical setting. The role of tongue base mucosectomy by transoral laser or robotic approach, with or without PET-CT or HPV positivity needs prospective evaluation.^{10,11}

Total 29 participants out of 63 were in the conventional group study. Again 6 primary detected out of 29 participants. It is about 20.68 %. Total of 34 participants out of 63 were in standard protocol group. In this group 8 primary detected out of 34 participants and it is about 23.53%.

In this study, standard protocol group detection rate is superior to conventional/traditional group. Statistical significance test is not performed as this study is ongoing and small cohort.

Most primaries were detected in palatine tonsil.

Some study claims that, In Traditional or conventional group, by meticulous physical examination and Radiological imaging about 30% primaries detected. With addition of

EUA along with physical examination and Radiological imaging detection rate increases up to 50%. In addition of PET-CT, it increases up to 68%, which should be done before EUA. With the addition of viral markers it increases up to about 90%.¹²⁻¹⁵

In this study, detection rates are lower than many standard publications. This is probably due to efficacy of battery of tests and etiological backup.

Determination of primary sites in Head-Neck unknown primary is now a days easier by detecting HPV after the onset of HPV epidemic era.¹⁶ In Bangladesh, probably prevalence of HPV in Oropharyngeal carcinoma (OPC) is very few. In literature, not much information available in this regard. In this institution, in another ongoing study on the presence of HPV in OPC, no HPV was detected at all in 24 participants. In this search, Real Time PCR was done to detect HPV.

According to some other articles, detection rate was much higher by the use of transoral approach-Robotics, Laser etc. Outcome by robotics is higher than that of Laser.¹⁷⁻¹⁹ Transoral robotic surgery not yet started in this institution. Laser has not been much practiced for tongue base mucosectomy in this centre.

Conclusion:

Outcome of the search of primary for Head-Neck CUP can be improved by digital examination of suspected sites and appropriate tissue examination in traditional detection methods.

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