

CARCINOMA OF UNKNOWN PRIMARY WITH SECONDARY METASTASIS TO NECK- ANALYSIS OF PATIENT AND DISEASE RELATED FACTORS PREDICTING SUPERIOR PATIENT OUTCOMES IN CUPS NECK

Preeti Singh¹, Vishal Pathania², Mohanlal Khatri³

¹Assistant Professor, Department of ENT, SGT Hospital.

²Associate Professor, Department of ENT, SGT Hospital.

³Professor, Department of Anaesthesia, SGT Hospital.

ABSTRACT

BACKGROUND

Carcinoma of unknown primary with secondary metastasis to neck (CUPS Neck) is involvement of cervical nodes with squamous cell carcinoma without identifiable primary lesion in oral cavity, oropharynx and upper aerodigestive tract. Most commonly affects older male with history of tobacco and alcohol abuse. Commonly involved neck nodes are level II and III. Metastasis to these nodes usually comes from head and neck tumours.

The aims of this study are to evaluate the factors (relating to patient and disease) associated with improved outcomes following treatment in patients with metastatic squamous cell carcinoma of neck with unknown primary site.

MATERIALS AND METHODS

Study was done in ENT and Head Neck Centre, Base Hospital, Delhi Cantt. The investigation and treatment of such cases aim to detect a primary lesion, if possible in the upper aerodigestive tract (UADT) and in any case to institute the optimal management protocol. Many factors impact the outcomes of treatment in terms of survival and quality of life.

RESULTS

After followup of 0.5 to 2 years data were compared among various groups, various disease related factors like volume of disease, staging of neck node, extracapsular spread in final HPE report and various patient related factors like age and sex of patient, performance status of patient, and presence of comorbidities were compared with final outcome in terms of recurrence or disease free survival with less complications.

CONCLUSION

1. Most prominent tumour related prognostic factors were low volume nodal disease in the neck and absence of extracapsular spread. Patients with TNM stage I (TON1M0) were associated with lower recurrence and less complication postoperatively as compared to advanced stage disease (TON2M0 and TON3M0).
2. In our study, patient related variables associated with superior patient outcomes in terms of locoregional recurrence or disease free survival were good performance status, females, young age, absence of weight loss, non-smoker without any comorbidity.

KEYWORDS

CUPS– Carcinoma of Unknown Site; RT, CT– Radiotherapy and Chemotherapy;

CPD– Chronic Obstructive Pulmonary Disease; DM– Diabetes Mellitus; UADT– Upper Aerodigestive Tract.

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BACKGROUND

A histologically confirmed malignancy in a cervical node without an identified primary tumour is classified as carcinoma of unknown primary site (CUPS).¹ Cancer registries around the world report the incidence of CUPS in the range of 2% – 10% of all cancer diagnosed and CUPS

therefore ranks among the top 10 commonest malignancies. According to the USA Surveillance, Epidemiology and End Results data, CUPS accounts for 2.3% of all cancers in both sexes or ~30 000 patients each year.² Squamous cell histology is the most common type representing 75% of cases followed by undifferentiated carcinoma and adenocarcinoma.³

These constitute about 0.5% of all cancer diagnoses, and 3% - 4% of all head-neck malignancies. When the upper/mid-jugular nodes are involved, most of these are squamous cell carcinomas (SCC) or poorly differentiated carcinomas. In 1957, the first definition of cervical lymph node metastasis of an unknown primary site was reported by Comess et al. According to Comess et al, it should include 1) No history of previous malignancy or cancer ablation of

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Corresponding Author:

Dr. Vishal Pathania,

#101, T7, CHD Avenue 71, Gurgaon.

E-mail: drvpathania@gmail.com

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any indeterminate lesion, 2) No history of definite symptoms related to a specific organ system, 3) No clinical or laboratory evidence of a primary neoplasm, 4) One or more cervical masses proved histologically or cytologically to be carcinoma.⁴ Cancer of unknown primary site (CUPS) has been traditionally considered as metastatic cancer in the absence of a clinically detectable anatomically defined primary tumour site after an 'adequate' diagnostic evaluation.⁵

Pathogenesis of CUPS is poorly understood. In the majority of patients, the primary tumour site is very small and clinically undetectable, yet has metastasised to yield clinically detectable metastases. This is apparent from autopsy studies, particularly in carcinomas where small clinically undetectable primaries are found in ~75% of these patients.⁶ In 25% of patients, the primary is not evident even at autopsy: In these, the primary was either missed or spontaneously resolved or there remains another explanation for the metastatic cancer. These other explanations include various theories including stem cell and embryologic migration hypotheses.⁵

A painless and unilateral cervical mass is the most common clinical presentation. The site of palpable cervical lymphadenopathy could be useful in suggesting the possible primary tumour site. In patients with squamous cell histotype the jugulodigastric and mid-jugular lymph nodes are most commonly involved, whereas metastatic adenocarcinoma is more frequently diagnosed in the low cervical or supraclavicular areas. In addition based on the metastatic lymph node level, several probable sites of the primary tumours can be predicted, for Ex:

- a. If submandibular nodes (Level I) are involved, the primary site could be in the floor of the mouth, lips and anterior tongue;
- b. If jugulodigastric or upper jugular nodes (Level II) are affected, search for primary tumour in epipharynx, base of the tongue, tonsils, nasopharynx and larynx;
- c. If middle and lower jugular nodes (Levels III and IV) are involved, the most likely primaries are located in hypopharynx or larynx; and
- d. If supraclavicular nodes (Level V) are the metastatic sites, the possible primary tumours could be derived from the lungs, thyroid, breast, gastrointestinal or genitourinary system.^{7,8}

A study carried out by Calabrese et al in Feb 2005- "Diagnosis and management of neck metastases from an unknown primary" published that metastases in the upper and middle neck (Levels I-II-III-V) are generally attributed to head and neck cancers, whereas the lower neck (Level IV) involvement is often associated with primaries below the clavicles.⁹

Many of these patients are tobacco/alcohol users, have dietary deficiencies and poor oral hygiene. They usually have a history of chronic tobacco or alcohol use.¹⁰ Non-smokers and non-drinkers respond better to radiotherapy and survive longer.³

MATERIALS AND METHODS

1. General Setting: The study was done in a tertiary care hospital setting.
2. Place of Study: ENT- Head and Neck Services.
3. Timeline:
 - a. Preliminary actions ---- 03 months
 - b. Data collection ---- 18 months
 - c. Analysis and write up ---- 03 months
 Total time ---- 24 months

A prospective study carried out among patients presenting for management for CUPS neck to Dept. of ENT-Head and Neck Surgery, Base Hospital, Delhi Cantt.

4. A detailed head and neck examination is carried out in these patients. The characteristics of the nodal disease, including the levels affected are noted.
5. The data was analysed to evaluate the patient factors, disease factors associated with improved outcomes following treatment in patients with CUPS Neck. The association between the factors (patient and disease related factors) and outcomes in terms of disease free survival and complications impacting quality of life were determined.
6. Quantitative parameters were analysed using paired 't' test and qualitative parameters were analysed using Chi-square test. P < 0.05 was taken as statistically significant. SPSS software was used for analysis.

Inclusion Criteria- Patients with proven metastatic squamous cell carcinoma in the neck without an identified primary in the UADT (Upper Aerodigestive Tract).

Exclusion Criteria- Patients who failed to complete post-treatment followup of at least one year.

Paediatric Patients- History of previous tumours in the UADT (Upper Aerodigestive Tract).

RESULTS

After followup of 0.5 to 2 years, data were compared among various groups. Results are discussed below-

1. Association with gender- The study included 32 patients, out of which 30 were male and 2 were female. During followup period of 2 years, 5 out of 30 male patients had recurrence of disease. Above data suggested that males were predominantly affected and associated with poor patient outcomes (p value is .53).
2. Association with Age- The study shows that 13 out of 32 patients were below 60 years and 19 patients were above 60 years. During followup, 5 patients had locoregional recurrence, 1 out of them was below 60 yrs. and 4 patients were above 60 yrs. It shows poor patient outcomes are associated with advancing age (p value .375).
3. Association with size of neck node- The study shows that patients with neck node size more than 3 cm are associated with higher recurrence rate and poor patient outcomes; 3 out of 18 patients with neck node size < 6

cm had recurrence, whereas 2 out of 14 patients with neck node size > 6 cm had recurrence (p value- .427).

4. Association with performance status (as per Karnofsky scale)- As per study, patients with poor performance status were associated with higher recurrence rate; 20 out of 32 patients had performance status above 90 and 12 patients had performance status below 90. Recurrence was seen in 2 patients with performance status > 90 and 3 patients had recurrence with performance status < 90 (p value- .395).
5. Association with tobacco use- 31 out of 32 patients were chronic tobacco users. Disease was mainly affecting the people who were chronically exposed to tobacco and recurrence was also common in this group of patients, but statistically no significant association was found between tobacco use and recurrence (p value- .662).
6. Association with comorbidities- Study shows 7 out of 32 patients had comorbidities like COPD, DM, hypertension etc. 2 out of 7 patients with comorbidities had recurrence. Above data suggested that patients with known comorbidities were associated with poor outcomes in terms of recurrence, but statistically significant association was not found between comorbidity and recurrence (p value- .286).
7. Association with clinical staging- Clinical staging as per TNM Classification, 4 out of 32 patients were in T0N1M0 stage, 14 out of 32 patients were in T0N2aM0 stage and 14 patients were in T0N3M0 stage. During followup, 2 patients with T0N2M0 and 3 patients with T0N3M0 had recurrence. Although higher recurrence rates were seen with clinically advanced disease, but statistically no significant relation was found between clinical staging and recurrence (p value- .684).
8. Association with extracapsular spread and multiple node involvement in HPE report- Multiple neck nodes were found positive for squamous cell carcinoma in final HPE report in 19 out of 32 cases. Extracapsular spread was seen in 8 out of 32 cases. During followup patients with multiple positive neck node and 3 out of 8 patients with extracapsular spread had locoregional recurrence. Multiple neck node involvement and extracapsular spread both were associated with poor patient outcomes in terms of recurrence, but statistically significant relationship was not found (P value- .211). After followup of 0.5 to 2 years data were compared among various groups, various disease related factors like volume of disease, staging of neck node, extracapsular spread in final HPE report and various patient related factors like age and sex of patient, performance status of patient, presence of comorbidities were compared with final outcome in terms of recurrence or disease free survival with less complications. Although, results were statistically not significant (as p value was > .05), but strong clinical correlation were seen between various patients and disease related factors and final outcome in terms of recurrence or disease free survival with less

complications. Insignificant 'p' value might be due to small sample size and short duration of followup.

DISCUSSION

This study was conducted in a tertiary care centre. It involved 32 patients of carcinoma of unknown primary with cervical metastasis; 22 out of them underwent surgery (neck dissection) and 31 patients underwent radiotherapy (post-op RT and RT + CT) and 26 patients had received adjuvant chemotherapy too.

Age and sex distribution is similar to other studies. In our study, 4 patients were of less than 50 years of age and 28 more than 50 years. 30 patients were males (94%) and 02 were females (6%). Similar to other studies where males were predominantly affected, almost 80% of the patients were male. In our study, median age of patients was around 59 to 63 years, similar to other studies where median age was 57 to 60 years.¹⁰

All 32 patients included in study were chronic bidi/cigarette smokers. Similar to other studies, patients usually have history of tobacco or alcohol use. 97% patients included in study had performance status between 80 and 90 (as per Karnofsky scale), 7 patients were associated with comorbidities like HTN, COPD and CAD.

In our study, patients with good performance status without any comorbidities were associated with superior patient outcomes. This conclusion is also similar to other studies where good performance status, young age and absence of weight loss were favourable prognostic factors.¹¹

All patients had unilateral single node involvement at the time of presentation. Level of involved neck node was similar to other studies. In our study most common site was level II and III involved in 44% cases. Next most commonly affected level was level II alone (34%), then level II, III, and IV. Level III and IV neck node was involved only in 22% cases. Overall, level II lymph node was the most common site of involvement (approximately 90% of level II alone and along with level III and IV) and next is level III neck node. As in other studies most common involved cervical lymph node was jugulodigastric (71%) followed by mid-jugular node (22%).³

In our study, median size of involved lymph node was 5 cm (range 2.5 to 7 cm). Findings were similar to other studies, where the median nodal size was 5 cm (range 2 - 14 cm) and there is an apparent prevalence of N2 cases.^{12,13} In our study, most prominent tumour related prognostic factors related with superior patient outcomes in terms of locoregional recurrence were-

1. Lymph nodal stage or low volume nodal disease in the neck.
2. Absence of Extracapsular spread.

In our study, patient related variables associated with superior patient outcomes in terms of locoregional recurrence or disease free survival were good performance status, females, young age, absence of weight loss, non-smoker and without any comorbidity were favourable prognostic factors.

CONCLUSION

1. Important disease related factors, which were associated with superior patient outcomes in terms of locoregional recurrence or disease free survival were low volume nodal disease and absence of extracapsular spread, perineural or perivascular invasion. Size of neck node more than 3 cm, N2 and N3 disease and multiple positive neck nodes were associated with poor patient outcomes.
2. Patient related factors associated with superior patient outcomes in terms of locoregional recurrence or disease free survival were good performance status, females, young age, absence of weight loss, non-smoker and absence of any comorbid conditions.

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