

# Clinical Profile and Treatment Outcomes of Metastatic Carcinoma with Unknown Primary: A Single Institution Experience

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**Background:** Cancer of unknown primary origin (CUP) is a heterogeneous group of cancers defined by the presence of metastatic disease with no identified primary. CUP has been reported to comprise approximately 2% to 5% of all cancer cases. With the availability of sophisticated imaging techniques and targeted therapies in the treatment of cancer, the extent of workup in CUP remains a challenge and should be based on the clinical presentation, radiological imaging, tumour biomarkers, pathology with immunohistochemistry and the patient's ability to tolerate therapy.

**Objectives:** To study the incidence, clinical presentation, histology, treatment modalities used, survival and lacunae in not establishing the diagnosis of primary.

**Materials & Methods:** This was a retrospective study done between January 2014 to December 2018. 650 patients of cancer of unknown primary at presentation were enrolled in this study. After going through various investigations, primary of 387 patients were detected & hence, were excluded from this study. Primary could not be detected in 263 patients even after going through comprehensive work up and henceforth, these were taken up for this study. Demographics, imaging, pathology and treatment data were analyzed from the case records retrospectively between 1st January 2014 to June 2017. The data was collected prospectively between July 2017 to December 2018. Patients with histopathological evidence of metastatic lesion were included and patients whose primary were detected after comprehensive work-up were excluded from this study.

**Results:** Incidence of unknown primary was 0.65 per 1 lakh population. Majority of the patients were from rural areas (77.9%) & most of the patients were in the age group of 61-80 years (47.1%). Male to female ratio was 1.45:1. Abdominal pain (29.7%) and bone pain (20.5%) were the most common clinical symptoms reported. Computed Tomography & PET-CT scans detected primary lesions in 156 out of 650 (24%) & 12 out of 33 (33.3%) patients respectively. Adenocarcinoma was the most common histology (58.6%). The most common treatment modality received by the patients was external beam radiotherapy (12.5%). The median survival of the studied patients was 6-12 months.

**Conclusion:** Patients presenting with metastatic carcinoma with unknown primary have poor outcomes. These patients need a patientcentred, streamlined, rapid diagnostic pathway. The outcome of these patients with standard chemotherapy remains poor. Larger studies with other therapeutic and novel agents are warranted to improve the treatment outcomes.

## Introduction

Carcinoma of unknown primary origin (CUP) is a diverse group of cancers that is defined by the presence of metastatic disease (biopsy proven) with no identified primary Tumour after comprehensive workup [1].

Unknown primary tumour (UPT) is an intriguing clinical phenomenon found in approximately 5% of all newly diagnosed patients with cancer [2-4]. With the availability of sophisticated imaging techniques and targeted therapies in the treatment of cancer, the extent of workup in CUP remains a challenge and should be based on the clinical presentation, radiological imaging, tumour biomarkers, pathology with immunohistochemistry and the patient's ability to tolerate therapy. The median age at diagnosis is reported to be 60 years and the occurrence is slightly higher in males. In the early 1970s, some researchers argued that diagnosis of cancer of unknown primary origin could only be made if the primary tumour was not found at autopsy [5]. More than 50% of CUP patients present with multiple sites of involvement while the rest have a single site, most commonly involving liver, lung, bone or lymph nodes [6]. CUP patients are classified into subgroups and specific risk categories according to the organs involved (disease stage) and histology in order to optimize patient management [7]. Notably it seems that CUP survivors have a higher risk of developing many subsequent cancers [8]. The overall prognosis of CUP patients is generally very poor with a median survival of 4-12 months. It has been reported that around 50% of patients alive at 1 year and 10% at 5 years from diagnosis [9].

## Materials and Methods

This retro-prospective study was conducted in the Department of Radiation Oncology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar (Jammu and Kashmir, India). The study included the histologically proven carcinomas of unknown primary only (metastatic non-epithelial unknown primary and those patients where primary site was identified were excluded) that were registered in Regional Cancer Centre (SKIMS) between January 2014 to December 2018. Six hundred & fifty patients (650) of cancer of unknown primary were initially enrolled in this study. After going through various investigations, 387 patients were excluded from this study. Primary could not be detected in 263 patients even after thorough & comprehensive work up and henceforth, these patients (n=263) were taken up for this study. All these patients had biopsy proven metastatic epithelial cancers.

## Data Analysis

Data analysis was done on an MS Windows-based PC computer. The data were first keyed into a Microsoft Excel spreadsheet and cleaned for any inaccuracies. Statistical analysis was done using IBM SPSS Statistics for Windows from IBM Corp. (released 2020, Version 27.0. Armonk, NY, USA). Categorical variables were shown in the form of frequencies and percentages.

## Ethics

The procedure in conducting the study was as per the institutional ethics committee guidelines and as per the Helsinki Declaration of 1964, revised in 2013. This study was approved by institutional ethics committee number IEC SKIMS protocol number RP-17/2019 dated 16-02- 2019. Informed consent was waived, as this was mainly a retrospective audit of the health records.

## Results

In our study, majority of the patients 124 (47.1%) were in the age group of 61-80 years followed by 99 (37.6%) in the age group of 41-60 years. 156 (59.3%) patients were males and 107 (40.7%) were

females with a male: female ratio of 1.45:1. Majority of our patients presented with abdominal pain 78 (29.7%) followed by bone pain 54 (20.5%) and 38 (14.4%) with generalized weakness (Table 1).

| Characteristic        | Category             | n (%)      |
|-----------------------|----------------------|------------|
| Age interval          | ≤ 20                 | 03 (1.1)   |
|                       | 21 - 40              | 34 (12.9)  |
|                       | 41 - 60              | 99 (37.6)  |
|                       | 61 - 80              | 124 (47.1) |
|                       | ≥81                  | 03 (1.1)   |
| Gender                | Female               | 107 (40.7) |
|                       | Male                 | 156 (59.3) |
| Clinical presentation | Cough                | 17 (6.5)   |
|                       | Abdominal Pain       | 78 (29.7)  |
|                       | Anorexia             | 13 (4.9)   |
|                       | Bone Pain            | 54 (20.5)  |
|                       | Chest Pain           | 14 (5.3)   |
|                       | Constipation         | 01 (0.4)   |
|                       | Fever                | 07 (2.7)   |
|                       | Generalized Weakness | 38 (14.4)  |
|                       | Headache             | 12 (4.6)   |
|                       | Haemoptysis          | 03 (1.1)   |
|                       | Palpable Lymph Nodes | 15 (5.7)   |
|                       | Weight Loss          | 11 (4.2)   |

**Table 1. Baseline Characteristics.**

Contrast Enhanced Computed Tomography (CECT) findings showed that 90 (34.2%) & 59 (22.4%) patients had liver & bone metastasis respectively.

Adenocarcinoma was the most common histological sub-type reported in both males as well as females (Table 2).

| Histology of metastasis         | n (%)      |
|---------------------------------|------------|
| Adenocarcinoma                  | 154 (58.6) |
| Poorly differentiated carcinoma | 59 (22.4)  |
| Squamous cell carcinoma         | 38 (14.4)  |
| Undifferentiated carcinoma      | 12 (4.6)   |

**Table 2. Histological Subtypes.**

Abdominal pain 50 (32.5%) and bone pain 39 (25.3%) were the main clinical symptoms in patients with the histology of adenocarcinoma. Most of the patients with liver metastasis on ultrasound had adenocarcinoma on histology. Most of the patients presented with liver metastasis (34.2%) followed by skeletal metastasis (22.4%) (Table 3).

| Site of metastasis | n (%)     |
|--------------------|-----------|
| Liver metastasis   | 90 (34.2) |
| Bone metastasis    | 59 (22.4) |
| Lymphadenopathy    | 43 (16.3) |
| Lung metastasis    | 36 (13.7) |
| Brain metastasis   | 23 (8.7)  |
| Pleural effusion   | 05 (1.9)  |
| Ascites            | 05 (1.9)  |

|                   |          |
|-------------------|----------|
| Spleen metastasis | 02 (0.8) |
|-------------------|----------|

**Table 3. Site of Metastasis.**

212 (80.6%) patients had not received any sort of treatment. 33 (12.5%) patients had received external beam radiotherapy, while 18 (6.84%) patients had received chemotherapy (Table 4).

| Treatment modality | Type                       | n (%)     |
|--------------------|----------------------------|-----------|
| Chemotherapy       | 5Fluorouracil+ Cisplatin   | 02 (0.8)  |
|                    | 5Fluorouracil+Oxaliplatin  | 10 (3.8)  |
|                    | Cisplatin + Etoposide      | 03 (1.1)  |
|                    | Erlotinib                  | 02 (0.8)  |
|                    | Gemcitabine+ Carboplatin   | 01 (0.4)  |
| Radiotherapy       | External Beam Radiotherapy | 33 (12.5) |

**Table 4. Treatment Modalities Received.**

On an average, 65% patients were alive at 6 months and 46% at one year after completion of chemotherapy (Table 5).

|          |              |            |
|----------|--------------|------------|
| Survival | At 6 months  | 173 (65.5) |
|          | At 12 months | 121 (46)   |

**Table 5. Survival Outcome.**

## Discussion

Patients with unknown primary must be subjected to all basic investigations that would lead to better management and early treatment & consequently better survival of these patients. Advanced imaging modalities and immunohistochemistry facilities should be made available in all tertiary care hospitals in our country for better assessment and management of these patients.

In our study, a rising trend in the incidence of unknown primaries was seen (46 patients registered in the year 2014 & 65 in 2018). Most of the patients belonged to the age group of 61-80 years, which is similar to studies by Brewster DH et al [10] and Levi F et al [11]. Majority of the studied patients were from rural areas (77.9%) & 58 (22.1%) patients belonged to urban areas. The possible reason for the difference could be the large population are residing in rural areas. Our study revealed that histology of most of carcinoma of unknown primary were adenocarcinoma 154 (58.6%) followed by poorly differentiated carcinoma in 59 (22.4%) and undifferentiated in 12(4.6%) and this is consistent with a study conducted by Greco FA et al [2] and another study by Lembersky BC et al [3]. PET scan was done in 33 patients and with it, primary site was identified in 12 (36.36%), which suggests that PET scan is a useful investigation modality, and this is found similar to a study conducted by Sève P, Billotey C, Broussolle C, et al [12] and another study by Moller AK et al [13]. However PET scan imaging was not performed on many patients 242 (92%), which might be due to lack of availability and affordability. Similarly, CT scan revealed primaries in 156 (24%) patients and similar percentage was seen in a study by Karsell PR et al [14] and another study by McMillan JH et al [15]. About 60% of patients had metastasis at multiple sites and the rest 40% showed metastasis at a single site (most commonly in liver, followed by lung, bone, brain and lymph nodes) which is consistent with the study conducted by Briasoulis et al [6].

Although majority of the patients (80.6%) had not received any sort of treatment, external beam radiotherapy (EBRT) remained the main modality of treatment received by 33 (12.5%) patients. 25 patients received EBRT to involved bones, 05 to brain and 03 to cervical lymph nodes. In all these patients who received EBRT, survival was slightly better than those who had not. The overall

prognosis of these patients was generally very poor with a median survival of 6-12 months in our set of patients. 121 (46%) patients were alive for one year from the time of diagnosis, which is similar with a study conducted by Hainsworth et al [9]. Majority of the patients had chemotherapy regimens contained platinum which is found in consistence with the study conducted by Fizazi et al [16]. The basic investigations for knowing the primary were not done by many patients, like endoscopy (58.94%), colonoscopy (22.81%) and bronchoscopy (30.04%), which if performed would have helped in detailed evaluation of knowing the primary. However, the reason for not performing these procedures is not mentioned in the records clearly. Similarly, Immunohistochemistry markers (IHC) were also not performed by the patients (99%), probably due to lack of availability.

In conclusion, patients presenting with metastatic carcinoma with unknown primary have poor outcomes. These patients need a patient-centred, streamlined, rapid diagnostic pathway. The outcome of these patients with standard chemotherapy remains poor. Larger studies with other therapeutic and novel agents are warranted to improve the treatment outcomes.

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