

**CLINICOPATHOLOGICAL PATTERNS OF CUTANEOUS METASTASES- A SEVEN-YEAR STUDY**Saji Francis<sup>1</sup>, Cherukattil Hazeena<sup>2</sup>, Sathi P. P.<sup>3</sup><sup>1</sup>Associate Professor, Department of Pathology, Government Medical College, Idukki, Kerala.<sup>2</sup>Assistant Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala.<sup>3</sup>Professor, Department of Pathology, Government Medical College, Kozhikode, Kerala.**ABSTRACT****BACKGROUND**

Cutaneous metastases are rare and occur in only 0.6%-10.4% of all malignancies.<sup>1,2</sup> Though they are more often seen in the advanced stage of cancer, it may be the first sign of malignancy and can lead to diagnosis of the primary tumour. The magnitude and distribution of cutaneous metastases in North Kerala is not well known. We aimed to categorize the different primaries of the skin metastases and study the demographic and clinicopathological characteristics of cutaneous metastases.

**METHODS**

All cases of cutaneous metastases diagnosed either by histopathology or Fine Needle Aspiration Cytology (FNAC) in the Department of Pathology, Government Medical College, Kozhikode, during the seven-year period between October 2010 and September 2017 were studied. Data was retrieved from case records and analysed with the help of computer software SPSS.

**RESULTS**

Of 125 cases of cutaneous metastases, 74 cases were diagnosed by FNAC and 51 by histopathology. Most common metastatic deposits were adenocarcinoma (73.6) and squamous cell carcinoma (12%). Primary was unknown in 28.8% cases. The most common primary tumours in males were lung, hepatobiliary system, gastrointestinal (GIT) system and head & neck. In females; breast, genital system, lung, hepatobiliary and GIT were the common primaries. The commonest site of skin deposits was the chest wall. Other common sites included abdominal wall and scalp/head.

**CONCLUSIONS**

Skin is an important site of metastatic disease, particularly in patients with carcinoma of breast, lung, hepatobiliary and gastrointestinal systems. FNAC is a rapid and easy technique to diagnose skin metastases. Immunohistochemistry is an efficient ancillary aid in the detection of its origin.

**KEYWORDS**

Cutaneous Metastases, Histopathology, Fine Needle Aspiration, Immunohistochemistry.

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**BACKGROUND**

Cancer is one of the leading causes of morbidity or mortality worldwide. Now the burden of cancer has shifted to less developed countries, which account for about 57% of cases and 65% of cancer deaths worldwide.<sup>3</sup> Cutaneous metastases are rare but it may be seen in the advanced stage of cancer or even manifest as the presenting sign of malignancy. As per the literature, the incidence of cutaneous metastases has increased drastically from 2.7% in 1969 to 4.5% in 1993, and currently to 10%. Growing awareness of this condition, shooting up of cancer rates or increased survival of patients with malignancy may be the possible factors leading to the increase in the rates.<sup>4</sup>

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*Corresponding Author:*

*Dr. Hazeena C,*

*Assistant Professor,*

*Department of Pathology,  
Government Medical College,  
Kozhikode-673008, Kerala.*

*E-mail: hazeenac@gmail.com*

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There is paucity of data regarding the magnitude and distribution of cutaneous metastases in North Kerala. This study aimed to analyse the clinicopathologic features of skin metastases diagnosed in the department of pathology, Govt. Medical College Kozhikode over a period of seven years.

**Aims and Objectives**

1. To categorize the different primaries of the skin metastases.
2. To study the demographic and clinicopathological characteristics of cutaneous metastases.

**METHODS**

Demographic and clinical data were retrieved from case records. Histopathology/cytology slides were reviewed. Special stains including immunohistochemistry (IHC) were done to identify the primary wherever needed or feasible.

**Setting and Design**

This was a Retrospective study conducted at the Department of Pathology, Government Medical College Kozhikode; during the seven-year period between October 2010 and September 2017.

**Inclusion Criteria**

All patients of cutaneous metastasis diagnosed by either FNAC or histopathology from the Department of Pathology, Govt. Medical College Kozhikode between 1<sup>st</sup> October 2010 and September 30<sup>th</sup> 2017, during a period of 7 years were included in the study.

**Exclusion Criteria**

Cutaneous involvement by direct extension of the tumour and cases with incomplete data were excluded.

**Ethics**

This study has been approved by Institutional Ethics Committee of Government Medical College, Kozhikode.

**Statistical Analysis**

The statistical analysis was done using SPSS software, version 18. Qualitative variables were presented as frequencies and percentages. The association of qualitative variables was tested by chi square test. A p value of  $\leq 0.05$  was considered as statistically significant.

**RESULTS**

Out of 143 cases of cutaneous metastases reported in the study period, complete clinical data were available in 125 cases and only these were taken for statistical analysis. Of these 125 cases, 74 cases were diagnosed by FNAC and 51 by biopsy. 58% (72) were males and 42% (53) were females. The male to female ratio was 1.4:1. The age of the patients at the time of diagnoses ranged from 7 to 84 years. The maximum number of patients were seen in the 40-59 year age group (Figure 1). Only 2 patients were below 20 years.

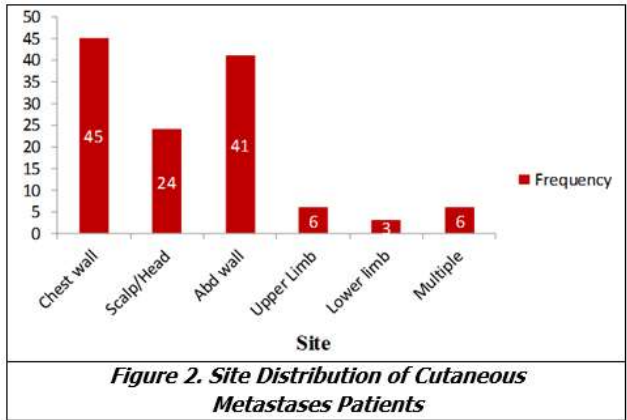
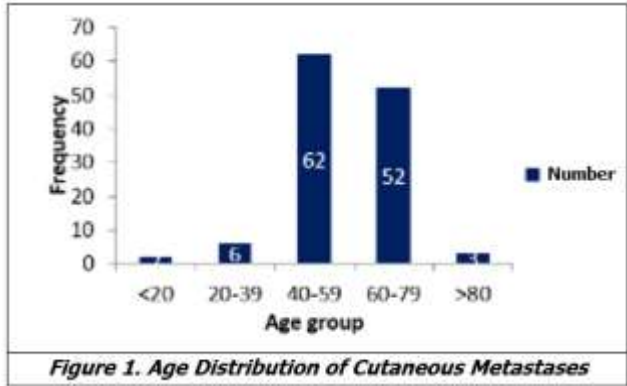
The commonest sites of skin involved were chest wall in 45 patients (36%), abdominal wall in 41 patients (32.8%) and scalp/head in 24 patients (19.2%). In 115 cases (92%), only a single site was involved as compared to multiple sites in 10 cases (8%) (Figure 2). Clinically these lesions presented as papules, macules, vesicles, nodular lesions etc., with nodules predominating. In 95 cases, a clinical diagnosis of cutaneous metastases had been made, while in 22 cases, no specific diagnoses were given. 8 cases were diagnosed clinically as primary skin pathology; two of which are shown in figures 3 and 4.

Majority of cases (41.6%) had tumour size less than 2 cm, as shown in table 1. The primary site was unknown at time of presentation in 36 patients (28.8%). Gender wise distribution of the different primaries is outlined in table 2. The commonest primary tumours which metastasized to skin were carcinoma breast in females and lung carcinoma in males.

Majority of cutaneous metastases were from adenocarcinoma followed by squamous cell carcinoma and poorly differentiated carcinoma (Table 3). There were four cases of leukemia, one of which is shown in figure 5. Adenocarcinoma was most commonly seen on the abdominal wall while squamous cell carcinoma and poorly differentiated carcinoma were often seen over the chest wall with a significant p value of  $<0.001$  (Table 4). Sites of

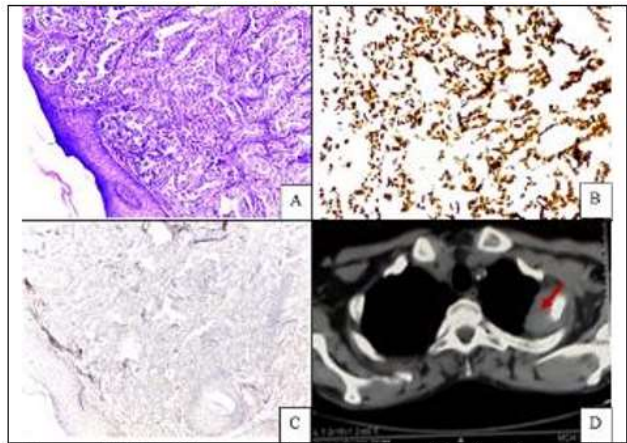
cutaneous metastases of the various primary tumours are shown in Table 5.

Breast and lung tumours showed predilection for chest wall while hepatobiliary, gastrointestinal and female genital tract tumours metastasized more to abdominal wall. This was statistically significant with a p value of less than 0.001. It was noted that these tumours tended to metastasize to the cutaneous site nearest to it. Umbilical nodules were the presenting feature in four cases of cutaneous metastases. Two of these cases originated from carcinoma stomach, one from carcinoma colon and in one case, the primary was unknown. Three out of five cases of urinary tract tumours metastasized to scalp, of which there were two cases of renal cell carcinoma and one case of carcinoma urinary bladder. Figure 6 portrays the case of a male 74 years. He presented with a cystic lesion scalp of one-month duration. This patient was a diagnosed case of transitional carcinoma, urinary bladder. FNAC from the scalp lesion revealed "cercariform" cells which is a clue to the diagnosis of metastatic transitional cell neoplasms. These cells have a nucleated globular body and a cytoplasmic process with fishtail-like end.<sup>5</sup>

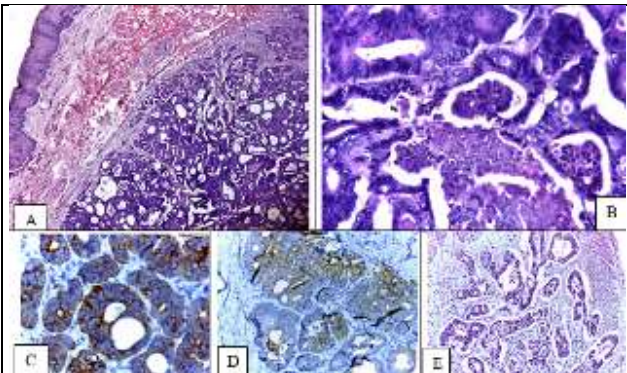


Size (cm)	Number of Tumours	Percentage
<2	52	41.6
2- 3.9	47	37.6
≥4	26	20.8

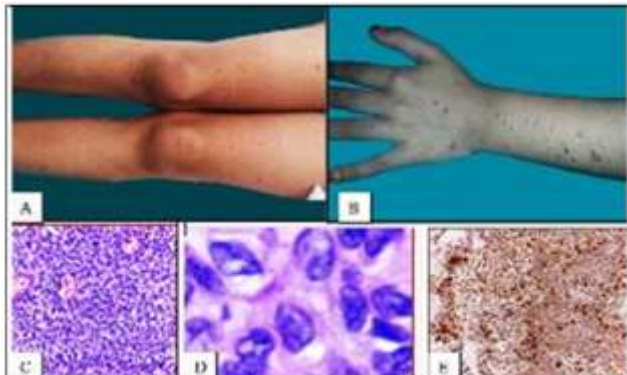
Table 1. Distribution by Size of Cutaneous Metastases



**Figure 3-** Male 75 years with ulcer penis clinically diagnosed as carcinoma. **(A)** Skin biopsy displays a neoplasm in a glandular pattern in the dermis. Adenocarcinoma was diagnosed but since epidermis was normal, metastasis was suspected (Haematoxylin-eosin stain, original magnification X 200). **(B & C)** IHC for TTF positive & CK20 negative indicating lung primary. (Original magnification X 200) **(D)** CT scan of lung revealed a lesion in apical segment of upper lobe of left lung (red arrow) thus confirming diagnosis of carcinoma lung.



**Figure 4-** Male 66 years with a lesion upper lip, clinically diagnosed as salivary gland tumour **(A)** Lip biopsy shows a neoplasm in a glandular pattern. Mucosa lined by squamous epithelium is normal (Haematoxylin-eosin stain, original magnification X 100). **(B)** Adenocarcinoma with necrosis (Haematoxylin-eosin stain, original magnification X 400). **(C)** IHC for CK7 showing diffuse positivity (Original magnification X 400). **(D)** IHC showing positivity for CK 20(Original magnification X 200). Metastasis from GIT was suspected. **(E)** Further enquiry elicited the history of surgery for periampullary carcinoma, a few years back; histopathology of which demonstrates the same glandular pattern as that of the lip lesion (Haematoxylin-eosin stain, original magnification x200).



**Figure 5 (A & B).** Female 7 yrs with multiple lesions on arms and legs. **(C)** Skin biopsy showing diffuse infiltrate of small cells (Haematoxylin-eosin stain, original magnification X 200). **(D)** Demonstrates leukemic cells with cleaved nuclei (Haematoxylin-eosin stain, original magnification X 400). **(E)** IHC showing diffuse CD3 positivity confirming T cell origin (Original magnification X 200).

Primary	Number of Patients (%)		
	Total 125 (100%)	Males 72 (57.6%)	Females 53 (42.4%)
Unknown primary	36 (28.8%)	24 (19.2%)	12 (9.6%)
Breast	18 (14.4%)	0	18 (14.4%)
Lung	15 (12%)	11 (8.8%)	4 (3.2%)
Hepatobiliary	13 (10.4%)	10 (8%)	3 (2.4%)
Gastrointestinal system (GIT)	12 (9.6%)	9 (7.2%)	3 (2.4%)
Female genital system (FGS)	9 (7.2%)	0	9 (7.2%)
Head & Neck	7 (5.6%)	6 (4.8%)	1 (0.8%)
Urinary	5 (4%)	5 (4%)	0
Leukemia	4 (3.2%)	2 (1.6%)	2 (1.6%)
Malignant melanoma	2 (1.6%)	1 (0.8%)	1 (0.8%)
Soft tissue sarcoma	1 (0.8%)	1 (0.8%)	0
Bone sarcoma	1 (0.8%)	1 (0.8%)	0
Adrenocortical carcinoma	1 (0.8%)	1 (0.8%)	0
Male genital system	1 (0.8%)	1 (0.8%)	0

**Table 2. Distribution of Different Primaries**

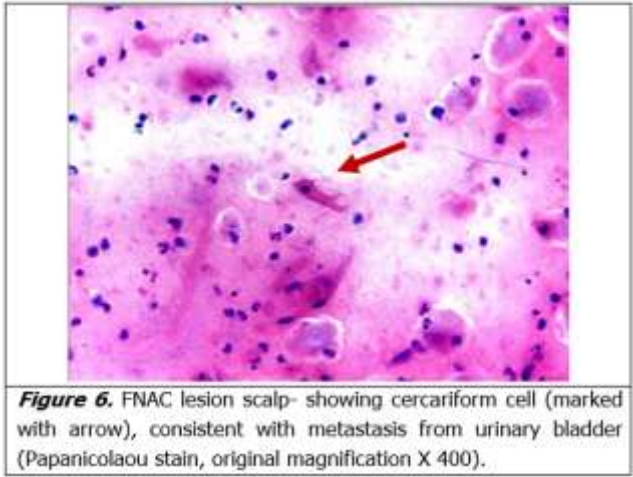
Pathological Diagnosis	Frequency	Percentage
Adenocarcinoma	92	73.6
Squamous cell carcinoma	15	12
Poorly differentiated carcinoma	9	7.2
Leukemia	4	3.2
Melanoma	2	1.6
Ewing's sarcoma	1	0.8
Soft tissue sarcoma	1	0.8
Gastrointestinal stromal tumour	1	0.8

**Table 3. Frequency of Different Pathological Diagnosis**

Pathological Diagnosis	Site						Total
	Chest	Scalp/ Head	Abdominal Wall	Upper limb	Lower limb	Multiple Sites	
Adenocarcinoma	29	18	36	3	1	5	92
Squamous cell carcinoma	10	3	2	0	0	0	15
Poorly differentiated carcinoma	6	1	1	1	0	0	9
Leukemia	0	0	0	2	1	1	4
Malignant melanoma	0	0	1	0	1	0	2
Ewing sarcoma	0	1	0	0	0	0	1
Soft tissue sarcoma	0	1	0	0	0	0	1
Gastrointestinal stromal tumour	0	0	1	0	0	0	1
<b>Total</b>	<b>45</b>	<b>24</b>	<b>41</b>	<b>6</b>	<b>3</b>	<b>6</b>	<b>125</b>

**Table 4. Distribution of Pathological Diagnoses in Various Sites**





Primary Site of Malignancy	Site of Metastases						Total
	Chest	Scalp/Head	Abdominal Wall	Upper Limb	Lower Limb	Multiple Sites	
Unknown	15	6	12	1	0	2	36
Breast	6	6	2	2	0	2	18
Lung	10	2	2	0	0	1	15
Hepatobiliary	3	3	7	0	0	0	13
Gastrointestinal	0	1	10	1	0	0	12
Female Genital	1	0	7	0	1	0	9
Head & Neck	7	0	0	0	0	0	7
Urinary	2	3	0	0	0	0	5
Haematopoietic	0	0	0	2	1	1	4
Skin	0	0	1	0	1	0	2
Adrenal	0	1	0	0	0	0	1
Soft tissue	0	1	0	0	0	0	1
Bone	0	1	0	0	0	0	1
Male genital system	1	0	0	0	0	0	1

**Table 5. Sites of Cutaneous Metastases of the Various Primary Tumours**

Men		Females	
Brownstein et al n=482/724	This study n=72/125	Brownstein n=242/724	This study n=53/125
Lung (24%)	Lung (15.3%)	Breast (69%)	Breast (34%)
Colon (19%)	Hepatobiliary (13.9%)	Colon (19%)	Female genital tract (17%)
Melanoma (13%)	Gastrointestinal (11.1%)	Melanoma (5%)	Lung (7.6%)
Carcinoma of oral cavity (12%)	Head & Neck (8%)	Lung (4%), Ovary (4%)	Gastrointestinal (5.7%) Hepatobiliary (5.7%)

**Table 6. Comparison of Frequency of Primary Sites of Malignancy**

DISCUSSION

Though skin is the largest organ in human body, cutaneous metastases occupies only 8th place among the metastatic sites in cancer.<sup>6</sup> In 28.8% of our cases, primary was unknown at time of clinical presentation, with females (9.6%) constituting only half the number of males (19.2%). Brownstein et al studied the patterns of cutaneous

metastasis in 724 patients and reported that it was the presenting picture in 27% of men and only 6% of women. They explained these differences based on the fact that carcinoma of the lung and kidney tended to metastasize to skin early, and are relatively common in men but uncommon in women, whereas carcinoma of the breast is common in women, but rarely presents as cutaneous metastasis.<sup>7</sup> The review article by Nashan et al. reported that in 22% of cases, cutaneous metastases led to diagnosis of primary tumour.<sup>4</sup>

Brownstein et al also noted that the source of cutaneous metastases tended to be the same tumours that were most frequent in the general population and that the sex of the patient was one of the most important factors relating to the patterns of cutaneous metastasis. When the data was presented combining the sexes, the underlying pattern was more likely to be obscured.<sup>6</sup> Lung and breast cancer are the most prevalent malignant neoplasms and leading causes of cancer deaths, both worldwide and in less developed countries among males and females respectively. Our data show that they are also the main source of cutaneous metastasis. However, in more developed nations, the most frequently diagnosed cancer among men is prostate cancer though lung malignancy is the leading cause of cancer death among both men and women. No case of metastasis from prostate was noted in our study. Table 6 shows the comparison of the most frequent primary tumours in this study and that reported by Brownstein et al.

The commonest sites of skin involved were chest wall (36%) followed by abdominal wall (32.8%) and head especially the scalp (19.2%).

Sariya et al. too reported that upper trunk and abdomen were the most frequent sites for metastasis followed by the head and neck (particularly the scalp). Metastases to the extremities were uncommon.<sup>8</sup> A meta-analysis of skin metastases from patient tumour registries and autopsy studies showed that chest was most frequently involved (28.4%) followed by abdomen (20.2%). Scalp involvement was seen in 6.9% of all metastases. High vascularity, immobility, and the warmth of the region may be the reason for the predilection to scalp.<sup>9</sup> Tumours of urinary system and breast were the most common malignancies which metastasized to scalp in our study. Some were unknown in origin. Many studies show that the scalp is the most common site of metastasis of renal cell carcinoma.<sup>2,10</sup> Four cases in our study presented with umbilical nodule, two of which originated from carcinoma stomach, one from carcinoma colon and one was of unknown primary. Umbilical metastases are widely described in literature as "Sister Mary Joseph nodule" in honor of the person who first identified it. Most common primary sites of umbilical metastases were stomach, ovary, colon, rectum, or pancreas.<sup>11</sup> There were five cases of cutaneous metastases in our study from urinary tract malignancies. Mueller et al noted that these occurred only in 1% of patients with advanced urinary tract disease.<sup>12</sup>

Clinical presentations were varied including nodules, plaques, and ulcers.<sup>13</sup> In most studies nodules were the most frequent presentation as in ours although inflammatory, cicatricial, and bullous lesions were also noted.<sup>2</sup> The majority

of cases (41.6%) in this study had skin lesions with tumour size less than 2 cm. Hussein MRA in his review article noted that cutaneous metastases vary in size from so tiny as to be of 'miliary lesions' to as large as 'Hen's egg size'.<sup>14</sup> Distinguishing metastases from a primary cutaneous tumour is not always easy. Histologic features such as bottom-heavy distribution of tumour within the deep dermis and subcutis, lymphovascular invasion, and lack of connection of tumour with the overlying epidermis have been mentioned in literature as indicative of metastasis. A continuum of changes from benign to malignant may be seen in primary adnexal neoplasm.<sup>15</sup>

Children rarely have cutaneous metastases probably because carcinoma is not common in this age group. Looking bill et al. observed that neuroblastoma and leukemia are the most frequent causes of skin metastases in children.<sup>2</sup> A thirty year study of non-hematopoietic cutaneous metastases in children and adolescents found that the most common primary tumours in this age group were rhabdomyosarcoma and neuroblastoma.<sup>16</sup> We had only one pediatric patient, a child of seven years who had leukemic infiltrate in the upper limb. Another adolescent patient of fifteen years had scalp secondaries from Ewing Sarcoma.

Of the histologic types, in our study, the largest proportion of cases was adenocarcinoma (73.6%), followed by squamous cell (12%) and poorly differentiated carcinoma (7.2%). The largest review of skin metastases in the United States in the past 25 years by Wong et al identified the most common histological types of tumours as adenocarcinoma (41.4%), squamous cell carcinoma (12.2%) and malignant melanoma (5.2%).<sup>17</sup> In the study by Saeed et al., commonest was adenocarcinoma (40.3%), followed by melanoma (18.2%), and squamous cell carcinoma (15.6%).<sup>15</sup> Skin metastases most frequently occur in the vicinity of the primary tumour. Breast and lung cancers frequently metastasize to the chest wall, whereas cancers of the bowel, ovary, and bladder most often metastasize to the abdominal wall.<sup>2</sup> A similar pattern was seen in our study too.

FNAC is a preferred first line modality in suspected cases of cutaneous metastasis which often renders unnecessary other invasive diagnostic procedures.<sup>18</sup> In this study a significant proportion of cases (59%) were diagnosed by using Fine Needle Aspiration Cytology only.

## CONCLUSIONS

Cutaneous metastases are underdiagnosed and clinically challenging. It may occur as the first sign of malignancy. Skin is an important site of metastatic disease, particularly in patients with carcinoma of breast, lung, hepatobiliary and gastrointestinal systems. FNAC is a rapid and easy method of diagnosis. Immunohistochemistry is an efficient ancillary aid in the detection of its origin.

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