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Carcinoma lung with cutaneous metastasis: experience from an Indian institute

Running title: Carcinoma Lung with Cutaneous Metastasis

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Abstract

Background: Majority of lung cancer patients are presented with metastatic disease. However, cutaneous metastasis (CM) from lung carcinoma is a rare entity with very few case reports published in the Indian background. Moreover, outcome in these patients is dismal and no standard therapeutic approaches are there. Thus, a long-term analysis from a single institute in this infrequent occurrence holds scientific importance. The purpose of this study was to describe the clinico-demographic profile of patients having CM with lung primary and also to evaluate the survival outcomes in these patients.

Materials and methods: This was a retro-prospective study conducted over 5-year time period in an academic institute of India. Records of all histopathologically confirmed lung cancer patients were reviewed and patients having biopsy-proven CM were included in this analysis. Permission from Institutional Ethics Committee and informed consent from all the patients were taken. Data of these patients were collected and analysed using standard statistical software.

Results: Total of 25 cases of biopsy-proven CM were found in the stipulated time period. Mean age of patients was 57.6 years with high male predominance. Anterior chest wall was the most common site of skin involvement and squamous cell carcinoma was the most common primary histopathology. Overall, median survival was 4.9 months.

Conclusion: Once CM developed, survival of lung carcinoma patients become dismal. Goal of the treatment will be to palliate and to improve quality of life in these patients.

Understanding the clinical pattern and demographic profile of these patients will guide a standard treatment approach.

Key words: cutaneous metastasis; demography; lung carcinoma; palliation; survival

Introduction

Lung cancer was found to be the 2nd most frequently occurring cancer worldwide, surpassed by breast cancer only [1]. With approximately 1.8 million deaths in 2020, it stands out as the leading cause of cancer-related mortality globally [1]. In India, although lung cancer ranked 4th in the list of cancer incidence, the trend is ever increasing [1, 2]. Non-small cell lung cancer (NSCLC) comprises of 80-85% of all lung cancers, the rest being small cell lung cancer (SCLC) [3]. NSCLC is further divided into adenocarcinoma, squamous cell carcinoma (SCC) and large cell carcinoma [3]. Over half of patients with lung cancer at first visit are in stage IV, i.e., having distant metastasis [4]. The common sites where metastasis from lung cancer occurs frequently are the brain or central nervous system (CNS), bones, liver, adrenal gland, contralateral lung and distant lymph nodes [4, 5]. The relatively less common sites, where primary lung cancer can spread in rare occasions, are the gastro-intestinal tract (stomach and intestine), pancreas, thyroid, ovary, kidney and skin [5, 6].

Occurrence of cutaneous involvement from primary solid tumor is an infrequent entity [7]. Breast is the most common primary solid tumor in case of diagnosed cutaneous metastasis (CM) followed by lung. Other common sites include the gastro-intestinal tract (colon, stomach, gall bladder), ovary and head and neck [7, 8]. In terms of age, CM is mostly seen in patients with advanced age, mostly after their 50s. [9, 10]. In general, nodular lesion is most commonly found in cutaneous metastasis from primary solid tumors. However, clinical manifestation has a diverse entity and may present as rash, purplish patches, ulceration, eczema, zosteriform eruption and so on [11, 12]. The lesions of skin metastasis often mimic primary cutaneous malignancies or even benign skin lesions [10]. Hence, histopathological verification is often required to confirm the diagnosis, even in the presence of another primary tumor, as double primary with coexisting solid tumor and primary skin malignancy is not uncommon [13]. Fine needle aspiration cytology (FNAC) is employed as a first line modality to confirm a case of suspicious CM; biopsy with supplement from immunocytochemistry staining is conclusive in case of any doubt or unknown primary [9]. A panel of different immunohistochemical (IHC) markers is often used simultaneously to distinguish metastatic and primary skin malignancy as well as to identify primary site in the case of CM [10]. Location of CM can be a helpful guide to suspect the origin of primary

tumor. Overall, the most common location of CM is the chest wall, indicating the most common site of primary from breast or lung malignancy; followed by the abdominal wall (metastasizing from gastro-intestinal tract and ovarian tumor) [9]. Other frequent encountered sites are the scalp (head and neck malignancy, sarcomas), back and extremities (hepatocellular and renal cell cancer) and so on [8]. Still, it is worthy to remember that this location wise guidance is just a useful tool to search primary, never confirmatory; as any malignancy can harbour distant skin metastasis other than predictable sites.

Lung is the most common primary site for CM in males, and the second most common, after breast carcinoma, in females [10, 14]. Broadly, one third of CM cases origin from lung malignancy. With an average survival of 3 months, it has worse prognosis among other primary tumors [7, 15]. Obviously, non-small cell histology predominates over small cell variant and, overall, adenocarcinoma is the major subtype that metastasize to the skin [12, 16]. Among locations of CM originating from lung carcinomas, the anterior chest wall is the most common followed by the abdomen, head and neck, scalp and multiple sites in a few cases [8, 9, 17]. Uncommon sites involvement as CM with primary lung carcinoma has also been reported, like involvement of the nasal tip, fingers, scrotum and lip [17–19]. Skin lesions in case of advanced lung carcinoma traditionally present as painless, hard nodules, solitary or multiple, often ulcerated superficially; nevertheless, other manifestations mentioned earlier also appear [12, 18, 20]. In around 15% of cases, it was the first clinical sign in an undiagnosed patient of lung cancer. [21] By and large, CM was associated with multiple other site metastases and indicate very progressive disease course [14, 22]. Howbeit, patients with only CM having lung primary with a comparatively better survival were also encountered [19].

Treatment of primary lung carcinoma with skin involvement depends on several factors; including, but not limited to, histology of tumor, preceding treatment received for lung malignancy, time of appearance of skin lesions, other associated metastasis and, obviously, performance status or life expectancy of the patients. In majority of cases, where secondary cutaneous lesion appears after a due course of disease and along with multiple other site metastases, systemic therapy in the form of chemotherapy (1st line regimen or beyond that in resistant cases) or targeted therapy (mainly in adenocarcinoma) is the preferred modality, although response to chemotherapy seems to be poor probably due to lack of blood supply to the skin. [19] Regimen of chemo- and targeted therapy depends on histopathology of primary tumor. Local therapies, like radiation or surgical excision, can be used to ameliorate symptoms like pain, bleeding or compression [23]. In a few cases, where cutaneous

metastasis is the first sign of underlying lung carcinoma and primary tumor is treatment-naïve; treatment goal is directed both to metastatic lesions (systemic chemotherapy and/or local therapy) as well as to primary tumor, i.e., surgery and/or radiotherapy [24]. Still and all, it is worth mentioning, many of these patients present with a poor performance status and only a handful of treatment options, mostly palliative and supportive care are useful for them [20].

Outcome in patients of lung carcinoma having cutaneous metastatic lesion is discouraging, despite using all available modalities. Literature reveals median survival of around 3-4 months with highest survival being 27 months in the case of single site cutaneous metastasis in adenocarcinoma of lung [14, 24]. Survival benefit of a single cutaneous lesion over multiple cutaneous metastases was also reported [24]. In a 10-year long retrospective study, the only two factors found to be associated with significant survival benefit were performance status and chemotherapy efficacy [22].

Due to a relatively less incidence, documentation of secondary skin involvement in primary lung carcinoma in literature is smaller. Similar study from India is also limited. In this background, we designed this analysis with the intention to describe the comparatively rare event of cutaneous metastasis in primary lung cancer in Indian population. The objectives of this study were to describe the patients' characteristics and the patterns of cutaneous metastasis in lung primary as well as to evaluate the survival outcomes in these patients. These will help to learn the clinico-demographic pattern of this group of patients from India and to modify treatment approach to them.

Materials and methods

This was a retro-prospective analysis done over a period of 5 years in a referral academic cancer institute of India. Approval from the Institutional Ethics Committee (IEC) was taken. All the patients of primary lung carcinoma, with any histopathological variant, attended the institute between January 2017 and December 2021, and were identified and checked for any presence of clinical cutaneous involvement. Inclusion criteria were histologically proved lung malignancies, secondary cutaneous involvement confirmed by skin biopsy and patients' willing for treatment and regular follow-up. Patients not attending the hospital after the initial visit due to any cause and skin metastasis only suspicious based on clinical picture or imaging were excluded from the analysis. Detailed evaluations, including routine haematological (complete blood count) and biochemical profile (blood urea, serum

creatinine, liver enzymes), imaging (local and metastatic sites) were done in all patients to know overall disease burden, to stage the disease accurately and to identify other organ involvement. However, in case of multiple organ involvement by distant spread, biopsy from all sites was not done and high metabolic activity in whole-body positron emission tomography (PET) scan was considered conclusive. Biopsy specimens of all patients included in the analysis were re-evaluated for histology typing with the help of immunohistochemistry (IHC). Lung cancer biopsy specimens stained positive for cytokeratin 5/6 (CK5/6) and p63 were labelled as SCC; while CK7, TTF1 (thyroid transcription factor 1), and/ or napsin-A positivity was conclusive for adenocarcinoma; similarly, SCLC was diagnosed if chromogranin A and synaptophysin staining were found positive.

Treatment course of these patients was determined by their histopathological variant and other associated factors, like previous treatment received, overall metastatic burden, general condition of the patient, life expectancy, and did not change for this study purpose. Survival was calculated from the date of cutaneous metastasis diagnosed, either from the first date of visit or developed later, to the death of the patient; telephonic confirmation was taken from the attendants for those patients who expired outside the hospital.

Written informed consent was taken from all the patients or their family members to publish their clinical details and clinical photographs.

Data of these patients, having primary lung cancer with secondary skin involvement, were collected and entered in Microsoft Excel (version 2021) and analysed using Statistical Package for Social Sciences (SPSS) version 22 [IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp]. Patient characteristics, both demographic and clinical profile, were summarized using descriptive statistics. Quantitative data were presented as mean and standard deviation (SD), while qualitative data were presented as ratios and proportions. Student's t-test was used for quantitative data, while Chi-square test and Fisher's exact test were used for qualitative data whenever two or more than two groups were used to compare. Kaplan Meier method was used to calculate the median survival. The level of statistical significance was set as $p < 0.05$.

Results

A total number of 29 patients were identified in the stipulated time period, those were having primary lung carcinoma along with cutaneous involvement. However, 4 patients were excluded from this analysis as a result of no follow-up after the first visit (3 patients) and no

biopsy proven cutaneous metastasis (1 patient). Data regarding demographic profile and tumor characteristics of the rest 25-patients are elucidated in a tabulated format (Tab. 1).

Included patients ages ranged from 38 to 75 years (mean: 57.6, median: 59 and SD: 10.15). High male dominance was seen in our analysis with a male to female ratio being 5.25:1 ($p = 0.001$). Only 3 patients among them had a positive family history of malignancy in a first degree relative. Majority of the patients (68%) had average to poor general condition at the time of cutaneous metastasis development, i.e., Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2–3. It was found that primary tumor of the right lung had a greater tendency (60%) to skin metastasis in our analysis ($p = 0.006$). Also, a statistically significant higher number of CM was seen in smokers ($p = 0.043$). The most common histologic type of lung cancer diagnosed by IHC test, as mentioned earlier, with skin metastasis was found to be SCC (48%) in our analysis followed by adenocarcinoma ($p = 0.016$).

Regarding development of CM, maximum number of the patients (76%) developed skin involvement in the course of disease progression, termed as metachronous metastasis. Median time of metastasis development from the diagnosis of lung carcinoma was 5.3 months in these patients. Cutaneous lesion was seen on the anterior chest wall in 11 patients, anterior abdominal wall and back in 4 patients each, the skin of the scalp and the nose in one patient each and more than one site in three patients (Fig. 1). Regarding clinical presentation of metastatic cutaneous lesion, solitary or multiple nodular lesions, with or without ulceration, were most prevalent and found in 70% of patients. Other lesions include plaque in 3 patients, multiple papules in 2 patients, ulcerative macules and multiple pustules in one patient each. A few cutaneous lesions, especially those ulcerated, painful; and surrounding inflammation, were also present in 7 patients. Overall, 7 patients had multiple lesions and the rest have single lesion. A significant number of patients (72%) had metastasis to other distant sites along with skin involvement ($p = 0.043$). Among the other sites involved, most common were bones followed by liver and brain, in decreasing order.

Intent of treatment was palliative in nearly all patients. Radiation therapy (RT) was given to primary site i.e., thorax and mediastinum in all patients; dose-schedules differed from patients to patient but it was mostly palliative. Median prescribed dose of RT was 20 Gy given in 5 fractions, 4 Gy per fractions. All the patients were given systemic therapy in form of oral or intravenous chemotherapy or targeted therapy to control primary as well metastatic disease burden. Regimens or drug were selected according to histopathological typing, patients' general condition and disease status. Most common intravenous chemotherapy agent used

was cisplatin, combined with etoposide in case of small cell lung cancer, with paclitaxel in SCC and with premetexed in adenocarcinoma. Erlotinib, a tyrosine kinase inhibitor, was used in a few adenocarcinoma patients for maintenance targeted therapy. However, immunotherapy was not given to any patient. At the time of reporting the analysis, all the patients were expired. Median survival was 4.9 months, range 2.7 to 8.4 months (Fig. 2).

Discussion

The incidence of cutaneous metastasis from a lung carcinoma varies in different studies but usually ranges between 3–4%; nevertheless, a 24% incidence was also reported [16, 25]. Majority of the published articles on CM in lung carcinoma are case reports and a few of them are illustrated in a tabular form (Tab. 2) for better understanding the nature of both primary tumor and skin lesion [15, 26–39].

In our analysis, majority of the patients' characteristics grossly matched other studies published previously. Mean age and higher male preponderance were in line with the recently published North Indian lung cancer patients' data [40, 41]. Male predominance also matched the literature describing lung as the most common primary in cutaneous metastasis occurred in male patients [9, 14]. The number of smokers in our analysis (72%) is identical to north Indian lung cancer patients [42]. This also explained the male dominance in our patient cohort, as higher smoking prevalence is seen in Indian men than Indian women [42]. Mean time of primary tumor diagnosis to detection of CM was also compatible with the current study [25]. The right lung preponderance found in our analysis matched the large-scale Italian study [24]. Although no specific association was found, it can be due to shorter lymphatic channels of the right lung as compared to the left lung [43]. Majority of the patients (72%) had multiple metastatic lesions other than cutaneous involvement, which is surprisingly similar to the decade old global reports [24, 44]. Betlloch-Mas et al. also showed that 27% of their patients did not harbour another metastasis along with cutaneous metastasis [25]. Our analysis showed that almost the same number (28%) of patients had only skin-exclusive metastatic lesions. Surprisingly, the most common histology was squamous cell carcinoma (~50%), which is not the most common variety of lung cancer in North India [40, 41]. However, it is comparable with other study from the Eastern part of India and may be a reflection of higher smoking status in the study region [45]. Predominance of metachronous cutaneous lesions in our analysis was also in line with the analysis of the latest 18-year Spanish study [25]. Anterior chest wall was the most common site of skin secondaries which

also matched the literature [17, 44]. Rare site of presentation, like involvement of nose and scalp, was also seen in the study patients as mentioned in the literature [18, 44]. Multiple site skin involvement, as seen in 3 patients of our analysis, was also documented [44, 46]. As reported in previous studies, nodular cutaneous lesion was the most common clinical pattern in the patient cohort [11, 25, 39, 44]. Intent of treatment was palliative in all of them. Median survival was 4.9 months, which was also in agreement with other retrospective analyses and review articles [12, 14]. Various case reports and series also indicated that these patients had a poor survival of only a few months [16, 28, 37, 44].

Radiation therapy induced tumor control at the distant, non-irradiated site by means of systemic immune mechanism is termed as “abscopal effect” [47]. Although lung cancer has comparatively low immunogenicity, still a few cases of abscopal effects in lung carcinoma were documented in literature [48, 49]. Even regression of metastatic subcutaneous nodules after irradiation of primary lung tumor was also reported [48]. Furthermore, a handful of cases showed occurrence of abscopal response in metastatic melanoma, a malignant skin cancer [48, 50]. It can therefore be envisaged that cutaneous metastasis with primary lung cancer can be treated by irradiating primary tumor, taking into account the prevalence of abscopal effect in both lung cancer and malignant skin disease. However, in order to use this benefit clinically, further information is required.

There are a few limitations in our study. Among these, the significant drawback was the nature of the analysis which was descriptive, not a predefined clinical trial. The patients were treated according to their disease status and different radiotherapy schedules and different systemic therapies were administered without any uniformity. A small sample size, i.e., only 25 patients, was another major limitation as was minimal genetic mutation analysis of the patients leading to restricted interim analysis. On the other hand, the interesting trait of our study is its prospective nature and combining clinico-pathological features with respect to treatment outcome and survival.

Conclusion

Cutaneous metastasis from primary lung cancer is comparatively scattered and generally demarcate advanced stage of disease. Understanding the clinico-demographic pattern of these patients will enable such rare clinical cases to be identified and managed with right approach at an early stage. Our analysis showed several associative factors for occurrence of CM in

primary lung cancer, such as advanced age, male gender, smoking habits, right lung tumor, non-small cell histology (squamous and adenocarcinoma). A few prognostic markers were also revealed, such as multiple site metastasis, number of skin lesions and response to primary treatment. However, definitive conclusion cannot be drawn due to a small sample size and descriptive nature of the study. A post-hoc analysis with survival outcomes based on different prognostic factors is planned and currently ongoing. As per our knowledge, this is the first original, prospective study of lung carcinoma with CM from a tertiary cancer centre cum teaching institute in India. More prospective studies and case series, particularly multi-institutional analyses with a large number of patients will provide basis for the standard treatment. In the modern era, immunotherapy alone or in combination with radiotherapy, can bring more treatment response in these patients.

Conflict of interest

The authors declare no conflict of interests.

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Table 1. Baseline patient and tumor characteristics

Characteristics	Parameters	No of patients	Percentage (%)	p-value
Total Patients		25	–	–
Sex				
Male		21	84	0.001
Female		4	16	
Age				
≤ 40		2	8	0.2
41–50		4	16	
51–60		7	28	
61–70		10	40	
> 70		2	8	
Background				
Rural		17	68	0.11
Urban		8	32	
Smoking status				
No		7	28	0.043
Yes		18	72	
Laterality				
Left		8	32	0.006
Right		15	60	
Both		2	8	

Histopathology			
Adenocarcinoma	8	32	0.016
Small cell carcinoma	3	12	
Squamous cell carcinoma	12	48	
Others	2	8	
Stage			
IVA	11	44	0.69
IVB	14	56	
Metastasis to skin only			
No	18	72	0.043
Yes	7	28	
Number of skin lesion			
Single	22	88	0.001
Multiple	3	12	

Table 2. Summary of case reports on lung carcinoma with cutaneous metastasis

Study	Year	Site of metastasis	Tumor histology	Treatment given	Outcome
Beachkofsky et al. [15] (n = 1)	2009	Skin, brain	Adenocarcinoma	chemotherapy	Death within a few months
Barbetakis et al. [26] (n = 1)	2009	Skin	SCLC	Chemo-radiotherapy	Death at 12 months from diagnosis
Mego et al. [27] (n = 1)	2010	Skin, bone	Adenocarcinoma	Palliative radiotherapy and <i>i.v.</i> chemotherapy	Death at 13 months from diagnosis
Pathak et al. [28]	2013	Skin	Squamous cell carcinoma	–	–
Fratu et al. [29] (n = 1)	2014	Skin	Squamous cell carcinoma	Surgery, ??	Death at 2.9 months
Elfatoiki et	2015	Skin, liver,	Adenocarcinoma	–	Death at 1

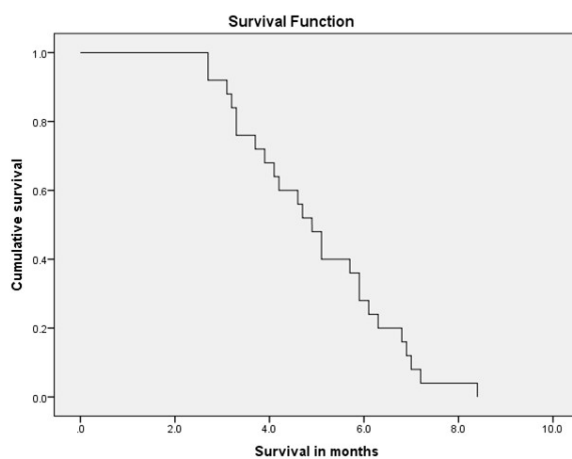
al. [30] (n = 1)		bone (vertebra)	a		month
Pajaziti et al. [31] (n = 1)	2015	Skin	SCLC	<i>i.v.</i> chemotherapy	Death at 4 months from diagnosis
Scott et al. [32] (n = 1)	2016	Skin, brain, liver	Adenocarcinoma	<i>i.v.</i> chemotherapy	Progressive disease
Khaja et al. [33] (n = 2)	2019	Skin	Squamous cell carcinoma	Chemo-radiotherapy and <i>i.v.</i> chemotherapy	Death
Yasokawa et al. [34] (n = 1)	2020	Skin, brain	Squamous cell carcinoma	Chemo-radiotherapy, Targeted therapy, surgical removal of cutaneous metastasis	Death at 16 months from diagnosis
Wang et al. [35] (n = 1)	2020	Multiple organ and skin metastasis	Adenocarcinoma	Targeted therapy	Stable disease
Gogia et al. [36] (n = 1)	2020	Skin, brain, breast, bone, left adrenal	Adenocarcinoma	Whole brain radiotherapy	Death at 1.2 months
Sharma et al. [37]	2021	Skin, brain, bone and multiple nodes	Adenocarcinoma	Palliative radiotherapy to brain and bone, palliative chemotherapy	-
Vouchara et al. [38] (n = 1)	2022	Skin, brain, spleen, right adrenal and	SCLC	<i>i.v.</i> chemotherapy	Death at 2 months from diagnosis

		multiple nodes			
Zhong et al. [39] (n = 1)	2022	Skin, mediastinal & hilar lymph nodes	Adenocarcinoma	Not mentioned	Not mentioned

Figure 1. Clinical photograph of cutaneous metastasis from lung primary showing different location of cutaneous metastasis; **A.** Anterior chest wall; **B.** Multiple lesions in anterior chest and abdominal wall; **C.** Anterior abdominal wall; **D.** Back



Figure 2. Kaplan-Meier survival curve of patients with cutaneous metastasis in primary lung carcinoma (from the diagnosis of cutaneous metastasis)



Supplementary File

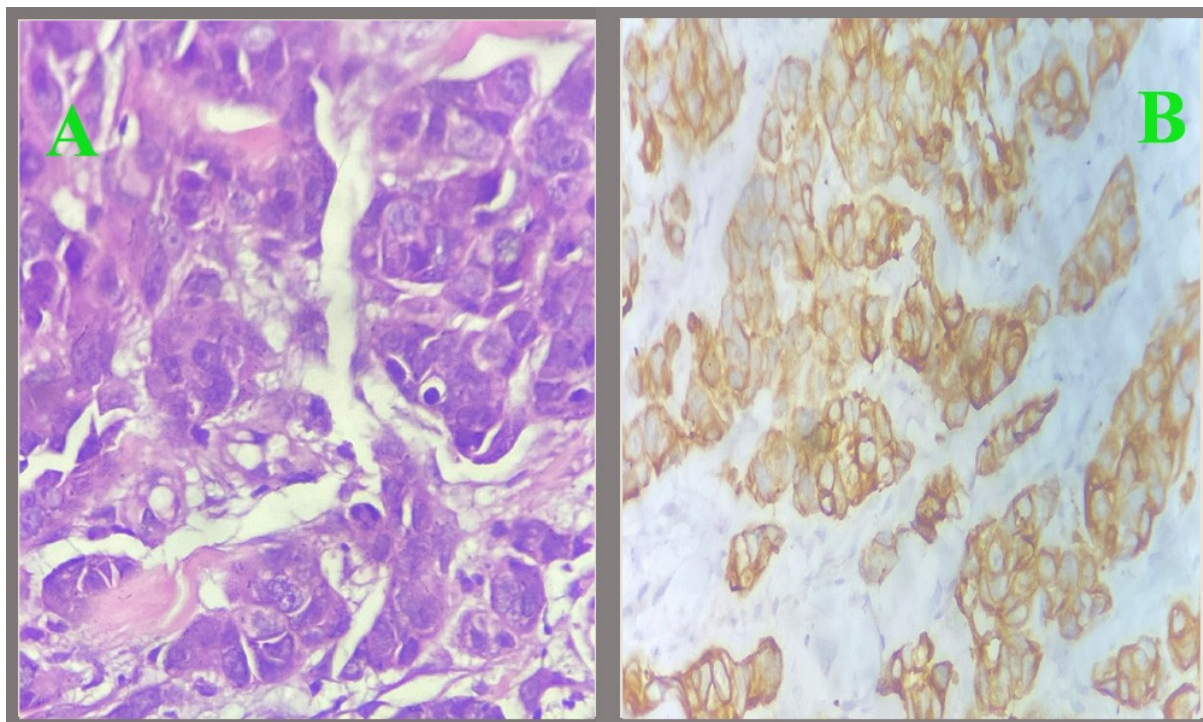


Figure 1S.