

Here is the metastasis - find the primary carcinoma for it: a large biopsy study

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ABSTRACT

Objectives: According to estimates, cancer of unknown primary origin (CUP) accounts for approximately 3 to 5% of new cancer cases annually in the United States. With early diagnosis, many CUP patients can achieve long-term remission. The aim of this study was to document the organ tropism for metastasis for tumors with a definite primary cancer. In addition, we sought to contribute to understanding organ tropism in tumors of unknown origin.

Methods: Retrospectively, biopsies of 492 metastatic cancers were evaluated. The required immunohistochemical panel was applied to determine the tumors' origins.

Results: A total of 492 patients with metastases were included in the study. The most common origins of metastasizing tumors were lung (25.4%), colon (18.9%), breast (15.4%) and stomach cancers (10.6%). The least metastatic tumors were the salivary gland, neuroendocrine, adrenal, tubal, nasopharynx, rectum and esophagus cancers (0.22% for all). The most common cancers that metastasized to the liver were colon cancer (29.0%), stomach cancer (18.6%) and pancreatic cancer (18.6%). The most common cancers that metastasized to the bone were lung cancer (58.0%), breast cancer (29.0%), and prostate cancer (13.9%). The most common types of tumors that metastasized to the lungs, the kidney (35.1%), colon (29.7%), and breast cancers (16.2%), were the most common. The most common tumors that metastasized to the brain were the lung (61.1%), the breast (16.7%), and kidney cancers (8.7%). The most common tumors metastasizing to the skin were lung (31.0%), breast (27.6%), and colon (13.8%) cancers.

Conclusions: Primary cancers have different metastatic patterns, which may help determine their causes. By involving distant anatomical structures and disrupting their function, tumor metastases increase the morbidity and mortality associated with the disease; thus, they affect staging, prognosis, and treatment. Metastases (or cancers from unknown primary sites) usually require extensive investigation to determine their primary source. Whether the cancer is tracked prospectively or retrospectively, a detailed observational template highlighting expected metastatic patterns would greatly assist in diagnosis and treatment.

Keywords: Cancer of unknown primary origin; organ tropism; metastasis

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Cancer of unknown primary origin (CUP) is cancer that cannot be traced back to its point of origin. It is one of the most common cancers, accounting for 3-5% of all cancer diagnoses [1, 2]. It is estimated that carcinomas with unknown primary origin (CUP) account for 10% of all cancers. Most CUP cases are diagnosed in patients over 50, with the median age at diagnosis being 65 years [3]. The most common sites of metastatic carcinoma are the lungs, liver, and brain. The lungs are the most common site of metastatic disease, accounting for approximately 50% of all cases. The liver is the second most common site of metastasis, accounting for about 30% of all cases. The brain is the third most common site of metastasis, accounting for approximately 20% of all cases [3, 4]. While the cause of CUP is unknown, it is believed to be the result of a mutation in a cell's DNA [5].

Several factors determine the distribution of metastatic carcinoma. The most crucial factor is the type of primary cancer. For example, breast cancer typically metastasizes to the bones, while lung cancer often spreads to the brain or liver [5]. Other factors include the stage of the tumor (early-stage cancers are more likely to spread), the tumor's size, and the primary tumor's location. Metastatic carcinoma can also influence the patient's age, gender, and overall health [3].

The prognosis for CUP patients varies depending on the cancer diagnosis stage. The outcome of patients with CUP relies on diagnosing the primary cause. A patient with CUP who can attribute the cause to a specific site has a better prognosis than a patient whose origin cannot be determined. Metastatic carcinoma is difficult to treat, and the chances of survival are often low. The best hope for a cure is early detection and treatment of the primary tumor. However, even with early treatment, the chances of survival are only about 50% [5]. A five-year survival rate of 25% is achieved by CUP patients who can identify the primary tumor site [6]. In contrast, only 5% is completed by patients unable to determine the primary tumor site. The use of immunohistochemistry is one of the most reliable, cost-effective, and widely available approaches to evaluating these lesions. An epidemiology and morphology-driven approach to tumor diagnosis and site of origin assignment cannot be completed without immunohistochemistry [5]. With early diagnosis and treatment, many patients with CUP can achieve long-

term remission [6]. It is crucial to know where metastases occur in unknown primary tumors so that additional clinical and pathological studies can be guided.

Our study aimed to describe the occurrence and location of metastases in many carcinomas with known primary carcinomas, seeking to drive cases with only metastases detected at the time of diagnosis and cases with unknown primary carcinomas for possible primary cancers.

METHODS

In this study, biopsies of 492 metastatic cancer patients between 2015 and 2022 were retrospectively analyzed. Samples of the cases included in the survey include biopsies taken from metastases that developed during the follow-up of the patients, metastasectomy materials, and metastasectomy materials performed in addition to the operation during the primary operation. The age, gender, and clinical information of the patients were obtained from the hospital information system. Routine follow-up was applied to all biopsies, embedded in paraffin, and stained with hematoxylin-eosin (HE). When cases are deemed necessary for each patient to determine tumors origins (pan-cytokeratin, vimentin, cytokeratin 7, cytokeratin 20, CDX2, CD45, TTF-1, estrogen receptor, progesterone receptor, chromogranin, synaptophysin, CD56, MELAN-A, S-100, HMB-45, thyroglobulin, HEPPAR, p40) were selected and an immunohistochemical panel was applied.

The method used in the immunohistochemical studies: Four micron-thick sections from tissues in appropriate paraffin blocks for each antibody were taken on poly-L-lysine coated slides. The antigen retrieval technique was used in IHC studies; the avidin-biotin-peroxidase complex method was applied. Antibodies were stained on a Leica band max automated immunohistochemical staining device. A Bond Polymer Refine Detection kit (Leica, DS9800) was used for each antibody. The necessary staining procedure was performed according to the datasheet of each antibody, and appropriate positive and negative controls were used for each antibody. After covering them with a coverslip ultra-mount, the prepared samples were examined under an Olympus BX51 model microscope. The origin of metastatic carcinoma, which was determined by evaluating histomorphological, immunohis-

Table 1. Metastasizing organs for primary cancers

Metastasis location	n	%
Liver	210	42.7
Bone	116	23.6
Lung	37	7.5
Brain	36	7.3
Skin	29	5.9
Bone marrow	14	2.8
Ovary	13	2.6
Surrenal	9	1.8
Colon	6	1.2
Pleura	5	1.0
Other	17	3.5
Total	492	100.0

tochemical, and clinical findings in pathology reports, was recorded.

The Clinical Research Ethics Committee approved the study (number: 2022/369. dated 01.07.2022).

Statistical Analysis

The PASW Statistics 18.0 package program was used for statistical analysis. In descriptive statistics, categorical data are shown as percentage frequency, and continuous variables as mean, standard deviation, minimum, and maximum.

RESULTS

A total of 492 patients with metastases were included in the study. The mean age of the patients was 59.97 ± 11.73 years of age (min: 27-max: 97). In total, 57.1% (n = 282) of the patients were males. Tumors were detected by excisional methods in 52.3% (n = 272) and incisional methods in 44.7% (n = 220) of the patients. Metastases were detected primarily in the liver (47.2%), bone (23.6%), and lung (7.5%). The amounts detected in other organs (kidneys (0.4%), endometrium (0.4%), and stomach (0.4%) were minimal. Among the bone metastases, 56.9% (n = 66) were in the vertebrae, 22.4% (n = 26) in the femur, 6.9% (n = 8) in the humerus, and 3.4% (n = 4) in the ribs. The organs of the patients with metastases are listed in frequency in Table 1.

The most common origins of metastasizing tumors were lung (25.4%), colon (18.9%), breast (15.4%), and stomach cancers (10.6%). Among other tumors that metastasized the least was the salivary gland (0.22%), neuroendocrine (0.22%), adrenal (0.22%), tuba (0.22%), nasopharynx (0.22%), rectum (0.22%) and esophagus cancers (0.22%). Men's most common metastasizing tumors were lung, colon, stomach, and pancreas, while in women, breast, colon, stomach, and lung were observed. Table 2 shows the frequency distribution of primary tumors that metastasize by gender.

Table 3 summarizes the origins of tumors that metastasize to the liver and bone based on frequency.

Table 2. Origin of primary metastasizing tumors and the distribution by gender

Origin	Total		Male		Female	
	n	%	n	%	n	%
Lung	125	25.4	107	85.6	18	14.4
Colon	93	18.9	54	58.1	39	41.9
Breast	76	15.4	3	3.9	73	96.1
Stomach	52	10.6	32	61.5	20	38.5
Pancreas	43	8.7	27	62.8	16	37.2
Kidney	32	6.5	19	59.4	13	40.6
Prostate	22	4.5	21	95.5	1	4.5
Gall bladder	11	2.2	2	18.2	9	81.8
Bladder	10	2.0	6	60.0	4	40.0
Ovary	7	1.4	0	0.0	7	100.0
Liver	5	1.0	4	80.0	1	20.0
Thyroid	4	0.8	1	25.0	3	75.0
Endometrium	3	0.6	0	0.0	3	100.0
Other	9	1.8	5	55.6	4	44.4

Table 3. Cancers most commonly metastasizing to the liver and the bone

Metastasis to the liver			Metastasis to the bone		
Metastasis origin	n	%	Metastasis origin	n	%
Colon	61	29.5	Lung	50	58.0
Stomach	39	18.6	Breast	25	29.0
Pancreas	39	18.6	Prostate	12	13.9
Lung	31	14.8	Kidney	9	10.4
Breast	17	8.1	Stomach	4	4.6
Gall bladder	7	3.3	Colon	3	3,5
Bladder	4	1.9	Pancreas	3	3,5
Kidney	3	1.4	Thyroid	3	3,5
Ovary	3	1.4	Ovary	2	2.3
Prostate	2	1.0	Gall bladder	2	2.3
Neuroendocrine	1	0.5	Endometrium	1	1,2
Surrenal	1	0.5	Bladder	1	1,2
Tubal	1	0.5	Nasopharynx	1	1,2
Total	210	100.0	Total	116	100.0

The most common cancers that metastasized to the liver were colon cancer (29.0%), stomach cancer (18.6%), and pancreatic cancer (18.6%). The most common cancers that metastasized to the bone were lung cancer (58.0%), breast cancer (29.0%), and prostate cancer (13.9%).

A list of the most common tumor origins that metastasize to the lung and the brain is presented in Table 4. Among the most common types of tumors that metastasized to the lungs, the kidney (35.1%), colon (29.7%), and breast cancers (16.2%) were the most common. The most common tumors that metastasized to the brain were the lung (61.1%), the breast (16.7%), and kidney cancers (8.7%).

The most common tumor origins that metastasize to the skin and bone marrow are given in Table 5. The most common tumors metastasizing to the skin were lung (31.0%), breast (27.6%), and colon (13.8%) cancers. The tumors that most frequently metastasized to the bone marrow were breast (28.6%), lung (21.4%), and stomach cancers (21.4%), respectively.

DISCUSSION

Several questions arise when discussing metastasis, many of which remain unanswered. What causes metastasis? Does the primary tumor need a certain size

Table 4. Cancers most commonly metastasizing to the lung and the brain

Metastasis to the lung			Metastasis to the brain		
Metastasis origin	n	%	Metastasis origin	n	%
Kidney	13	35.1	Lung	22	61.1
Colon	11	29.7	Breast	6	16.7
Breast	6	16.2	Kidney	3	8.3
Bladder	2	5.4	Liver	2	5.6
Endometrium	1	2.7	Bladder	2	5.6
Liver	1	2.7	Prostate	1	2.8
Stomach	1	2.7			
Prostate	1	2.7			
Testis	1	2.7			
Total	37	100	Total	36	100

Table 5. Cancers most commonly metastasizing to the skin and the bone marrow

Metastasis to the skin			Metastasis to the bone marrow		
Metastasis origin	n	%	Metastasis origin	n	%
Lung	9	31.0	Breast	5	35.8
Breast	8	27.6	Stomach	3	21.4
Colon	4	13.8	Lung	3	21.4
Kidney	3	10.3	Prostate	2	14.3
Stomach	2	6.9	Pancreas	1	7.1
Endometrium	1	3.4			
Bladder	1	3.4			
Salivary gland	1	3.4			
Total	29	100.0	Total	14	100.0

to be able to leave and migrate? Do tumor cells move randomly from the tumor or are these selective clones genetically different from the dominant clone? Do carcinoma cells move individually or collectively? These issues have been extensively discussed in the literature. There have been many studies that have examined the metastatic patterns of different types of cancers. No recent studies, however, provide quantitative analyses of such patterns arising from a broad range of cancers based primarily on primary surgical and biopsy-diagnostic tissue analyses. To guide further clinical and pathological studies, it is essential to know where metastatic sites occur in unknown primary tumors. To guide patients with only metastases found at the time of diagnosis and those with unknown primary carcinomas on possible primary cancers, our study described the occurrence and locations of metastases in many carcinomas with known primary carcinomas. In this study, we attempted to contribute to understanding organ tropism in tumors of unknown origin.

Our review of data from biopsies performed between 2015 and 2022 on 492 metastatic cancer patients, comprising 20 different primary cancers and 13 different metastatic sites, demonstrated that: Based on the data collected during the 29 years during which a postmortem study conducted by Disibio and French [5], findings provided a comprehensive analysis of metastatic behaviors in both common and uncommon cancers. In addition to providing a sensitive, quantitative baseline of metastatic patterns among the analyzed malignancies, these findings were derived from

actual postmortem tissue analyses from the largest cohort of autopsies reported to date in the medical literature [5].

In our study, the most common primary cancers were, in descending order, lung (25.4%), colon (18.9%), breast (15.4%), stomach (10.6%), and pancreas (8.7%). Several large clinical and autopsy studies have reported a different ranking. Presumably, essential characteristics of primary cancers and population-specific differences will need to be studied. According to a large autopsy study conducted in the USA on metastatic patterns of primary cancers, the most common primary cancers were reported as rectum (11.4%), breast (11.3%), cervix (10.9%), stomach (9.1%), and prostate (5%) [5]. The timeline as well as the population is a determining factor for the distribution of primary cancers. According to the results of the first large series autopsy study of 1000 cases presented in 1950 from New York Montefiore Hospital, the most common primary cancers were reported as breast (16.7%), lung (16.0), stomach (11.9%), colon (11.6%) and rectum (8.9%).

As a primary neoplasm, lung cancer was the primary lead cancer, accounting for 25.4% of all the cases and 85.65% for males. Cancers of the lung are another common metastatic site for breast, melanoma, and thyroid cancers. The rate of lung tropism in our study was 7.5%. The physiology of the lung makes it ideal for colonization and metastasis. The broad surface area and numerous capillaries allow cancer cells to adhere, extravasate and colonize.

Our study found colon cancer to be the second

most frequently metastasizing cancer type, with a rate of 18.9%. In cancers with known primary sites, the rate of metastasis to the colon was 1.2%. In their large autopsy study, Disibio and French [6] reported colon metastasis rates of approximately 4% and metastasis to the large intestine as < 1%. The difference may be because that study separated rectal cancer: the rate for rectal cancers was 11%.

As a primary neoplasm, breast cancer was the third common type and accounted for 15.4% of our study, and as a metastatic target, it accounted for only 0.7% of all metastases. According to the literature, the ratio differs from the second to third most common malignancy [5, 6]. Worldwide, breast cancer is the fifth most common cause of death due to cancer (502 000 deaths per year), followed by lung (1.3 million deaths per year), stomach (1 million deaths per year), liver (662 000 deaths per year), and colon (655 000 deaths per year) [7, 8]. In this study, breast cancer metastasized robustly: Both accounted for a high proportion (15.4%) of all primary malignancies and generated many metastases. As a result, breast cancer contributed 15.4% to all metastases, the highest number among all analyzed malignancies. Consistent with the difficulty of treating primary breast cancer and identifying breast primaries among cancers that initially manifest as metastases from unknown primary sites, this tendency toward widespread metastasis occurs.

The breast was a rare metastatic target in this data set, receiving only 0.7% of all metastases. Yet 87.1% of all metastases to the breast were classified as having originated from the breast itself in the archival data set. Because it is difficult at present to determine whether breast lesions are metastases from contralateral primary malignancies or secondary (ipsilateral) primary malignancies, this finding is of interest. Retrospectively, it appears likely that the former assumption was made when the data were collected, and caution should be exercised in evaluating them.

The liver is a favorite metastatic site for solid tumors such as breast, lung, and gastrointestinal cancers [9, 10]. Similarly, in our study, 42.7% of all metastases were to the liver.

Different types of cancer disseminate to bone at different rates. Cancers of the breast and prostate are the most common cancers that metastasize to the bones. The other rates of primary metastasis of cancers

are as follows prostate 90.1%, breast 71%, melanoma 48.6%, renal 44.5%, lung 34%, pancreas 25%, thyroid 13 %, colon 8%, liver 8% and ovarian 3% [10-12]. The bone ranked second among metastatic organotropism, with a rate of 23.6% of all metastasis targeting the bone. Like other studies, our study determined that the cancers that metastasized to the liver most frequently were cancers of colorectal origin. However, in our study, this rate was found to be 29% and relatively lower; in other studies, it is 46.1% and 48%, respectively [5, 13]. Our research suggests that ethnic, geographical, and genetic factors strongly influence the rate of metastasis. Cancer research should consider the specific characteristics of each race and region based on this experiment. Our study's second most common cancers metastasizing to the liver were the stomach and pancreas, while the pancreas and breast metastasized in another study [5].

There has been much interest in bone cancer in terms of organ tropism and metastatic niche. After the liver and lung, bone is the most common metastatic site [14], but our study found it to be the second most common site after the liver. The first three cancers metastasizing to the bone most frequently were lung, breast, and prostate [15]. Similarly, the first three cancers that metastasized to the bone most frequently in our study were lung, breast, and prostate. Nevertheless, our study's percentage of patients with metastatic lung cancer was significantly higher: 58% developed bone metastases. According to the previous study [15], bladder-derived metastases ranked fourth after kidney-derived metastases. Our study, however, found gastrointestinal metastases more frequent than bladder metastases. Endometrium, bladder, and nasopharynx metastasized to bone the least in our study.

Most cancers metastasize to the lungs as the third organ in the chain. Colorectal tumors commonly metastasize to the parenchyma and the endobronchial nich [15, 16]. Breast cancer usually metastasizes to the bone, liver, and lung, and the rate of metastasis to these organs is around 25% [16]. Like nowhere else in the body, the brain consists of two major microenvironments, a variety of parenchymal cells and leptomeninges filled with cerebrospinal fluid. The two microenvironments differed both cellular and metabolically. A cancer cell must cross and adapt to both environments to metastasize to the brain [16]. Adaptation may even lead to the acquisition of brain-like

characteristics [17]. As tumor cells cross the blood-brain barrier, they also carry inflammatory cells. There is also the possibility that metastatic tumor cells can adapt to the brain as an immune microenvironment [18]. Lung, breast, malignant melanoma, and kidney tumors are the most common cancers that metastasize to the brain [19, 20]. According to our study, lung, and breast cancers were the first to metastasize to the brain. A small percentage of hepatocellular carcinomas metastasize to the brain; two of our cases were hepatocellular carcinomas (5.6%). Detection of prostate cancer metastatic to the brain from autopsies and case series in the literature is extremely rare [21]; its incidence ranges from 0.4 to 2% [22]. In our study, one out of 36 cases (2.8%) of prostate adenocarcinoma metastasized to the brain. Metastasis of solid organ cancers to the skin is rare. Skin metastasis may be the first sign of advanced cancer or an indicator of cancer recurrence. Metastasis to the skin is rare; its rate varies between 0.2-9% among all metastases [17, 18]. In our study, the rate of skin metastasis was 5.9%, which was consistent with the literature. Among the organs that metastasize to the skin, the breast was the most common primary origin in some studies, and the lung in some studies [22]. In our study, breast carcinoma was the two most common organs that metastasized to the skin after lung carcinoma. In our study, metastases originating from the colon and kidney, breast, and lung were at a later frequency. In the later order of frequency and among cancers that metastasize to the skin, the cancers with the least origin are quite different [18]. Endometrial cancer and salivary gland-derived cancers are present in some studies but not at all in some studies [19]. Our study detected salivary gland metastasis, which is a rare report.

One of the organs in which the concepts of the metastatic niche are best defined is the bone marrow [20]. Breast carcinomas are the most common tumors metastasizing to the bone marrow [20]. Sometimes, surprisingly, even sarcomas can metastasize to the skin: in some studies, gastric carcinomas are the most frequently metastasized cancers [21, 22]. In our study, the breast was found to be the most common among primary cancers that metastasized to the bone marrow. According to the previous study of our team on bone marrow metastases, their chances of receiving effective chemotherapy decrease when a patient is diag-

nosed with bone marrow cancer [16]. Cancer patients do not show direct evidence of bone marrow involvement. Despite the common involvement of bone marrow in solid tumors bone marrow tumors are uncommonly diagnosed. Solid malignancy staging does not routinely use bone marrow biopsy. A clinical warning sign is unexplained hematological findings and thrombocytopenia. In the diagnosis of solid tumor-related bone marrow involvement, as well as in the detection of hematological malignancies, bone marrow biopsy is an effective, inexpensive, and applicable method.

Despite the uniqueness of each distant organ, certain general principles underlying organotropism emerge. The prerequisite for understanding the molecular level of these mechanisms knows the most common metastasis tropisms of primary tumours.

Our study is definitive proof of which organ is the primary focus in metastatic cancers. Because the cases in our study were those whose primary cancer was known, followed up and biopsied from the metastasis. In addition, the primary organ was supported with an immunohistochemical panel. Cases with diffuse metastases who did not undergo biopsy were not included in our study.

CONCLUSION

As expected, different primary cancers tended to metastasize to different sites with a different frequency. By looking at these varying metastatic patterns, it may be possible to deduce the origins of cancers whose primary sites are unclear at the presentation. Furthermore, this baseline provides a foundation for further studies that will clarify the clinical and molecular characteristics of specific malignancies cited in this study, especially those that occur less frequently.

Authors' Contribution

Study Conception: ÇÖ, MB, HD; Study Design: ÇÖ, MB; Supervision: YS, MB; Funding: N/A; Materials: MOA, ÇÖ; Data Collection and/or Processing: MOA, ÇÖ; Statistical Analysis and/or Data Interpretation: YŞ; Literature Review: ÇÖ; Manuscript Preparation: ÇÖ, MB and Critical Review: HD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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