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Incidence and comparative prognosis of cancers with metastasis to noncommon sites

A population-based study

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Abstract

Primary tumors have common sites of metastasis such as lymph nodes, bones, liver, lungs, and brain; however, they can also metastasize to other uncommon sites such as adrenals, bone marrow, and skin among others. Our study aimed to investigate the relationship between uncommon sites of metastasis at the time of diagnosis and median survival in a number of primary tumors using the Surveillance, Epidemiology, and End Results (SEER) database.

This retrospective cohort study conducted between September–October 2021 included patient-level SEER data for 2016–2018 using SEER Research Data, 9 Registries, Nov 2020 Sub (1975–2018). Descriptive analysis for complete cohort and median survival for each primary within the cohort was performed using *R* software.

A total of 25,345 patients (females, 51.4%) were diagnosed with primary tumors with metastasis to uncommon sites at the time of diagnosis; the mean age at diagnosis was 68 years. Lung and bronchus primaries constituted the largest proportion of cohort (41.9%) that metastasized to uncommon sites, followed by nonHodgkin lymphoma-nodal (7.4%), pancreas (6.6%), stomach (3.7%), and ovarian (3.4%). The incidence of metastasis to uncommon sites was most common in respiratory cancers in ages 61–80 years (25%) and least in breast primaries in ages 18–40 years (0.1%), and was higher in Whites compared to other races. Regarding median survival, liver cancer with metastasis to uncommon sites had the worst prognosis (1 month), whereas small intestine tumors were associated with a better prognosis, median survival of 13 months.

In this cohort study, the lung and bronchus cancers were the most common primaries metastasized to uncommon sites at diagnosis. The liver tumor had the worst survival compared to other tumors. These findings will help redirect the available screening tools to improve survival in patients with primary tumors with metastasis at diagnosis and may also play an essential role in future research and achieve a better prognosis for cancer patients.

Abbreviations: CNS = Central nervous system, GI = Gastrointestinal, GU=Genitourinary, LNs= Lymph nodes, NHL= Non-Hodgkin lymphoma, NOS = Not otherwise specified, SEER = Surveillance, Epidemiology, and End Results.

Keywords: cohort, SEER database, survival, prognosis, metastasis

1. Introduction

Cancers are among the leading causes of death worldwide. International Agency for Research on Cancer by the World Health Organization (WHO) reported the global incidence of cancers in 2020 being approximately 19.2 million, resulting in a mortality of 9.9 million annually.[1] By 2040, the number of new cancer cases is expected to rise to 30.2 million and the mortality to 16.3 million.[2] In the United States (US), the overall incidence of cancers was 442.4 per 100,000, and mortality was reported to be 158.3 per 100,000.[3]

The leading cause of death in most cancer patients is metastasis.[4] Morbidity and mortality associated with metastasis are often due to direct organ damage or compression secondary to growing lesions, paraneoplastic syndromes, or treatment complications.[4] Most metastatic lesions are surgically untreatable and may need chemotherapy, hormone therapy, and radiation therapy for palliative purposes to prolong survival.

Although various sites of tumor metastasis have been defined, some sites have a higher prevalence of metastasis than others. Liver is a common site of metastasis, especially for gastrointestinal tumors.[5,6] Erichsen et al reported an increased

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prevalence of liver metastasis through the decades with no improvement in prognosis.[7] Bone metastases have a high prevalence, especially in prostate, breast, and renal cancers.[8] Brain metastases are common in lung cancers, melanomas, and renal cancers.[9] Lung metastasis is common in cancers of head and neck, breast, stomach, pancreas, kidney, bladder, genitourinary tract, and sarcomas.[10] Lymph nodes (LNs) are also common sites of metastasis and may be a predictor of survival.[11]

Cancer preventive measures have been negatively affected during the COVID-19 pandemic with decreased numbers of screening tests and the subsequently reported number of new cases.[12] American Cancer Society recommended postponing all routine screening programs and elective procedures.[12,13] This led to a delay in the diagnosis of new cancer cases affecting the clinical management and prognosis due to late presentation. Therefore understanding the different sites of metastasis at the time of diagnosis and the associated survival may help to redirect the available resources to improve cancer care and improve the survival and the quality of life of cancer patients.

In our study, we used the Surveillance, Epidemiology, and End Results (SEER) database to identify the patients with uncommon sites (other than liver, bone, brain, lung, and distal lymph nodes) and calculated their associated survival in each primary to provide a comparative prognosis.

2. Methodology

2.1. Data source and cohort population

The SEER database (SEER Research Data, 9 Registries, Nov 2020 Sub (1975–2018)) included around 28% of the US population and was used to access all the patients presented with metastasis at diagnosis in uncommon sites between 2016 and 2018.[14] Uncommon sites of metastasis coded as other sites in SEER database are those that do not involve the liver, bone, brain, lung, and distal LNs. Some examples include but are not limited to the adrenal gland, bone marrow, pleura, malignant pleural effusion, peritoneum, and skin.

Patients with metastasis at diagnosis in uncommon sites were included in our study, without restrictions on age, race, year of diagnosis, or histological type. All included patients were with malignant behavior and known age and otherwise excluded. For survival analysis, patients with unknown survival months were excluded from the analysis.

Informed consent from patients was not obtained as the data is publicly available. No human or animal objects were directly involved thus ethical review was also not required.

2.2. Statistical analysis

National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat), version 8.3.9 was used to extract the data. Data were exported to *R* software to conduct the analysis.[15] Analysis was conducted showing the number of patients in different primaries, their proportions in the whole cohort, concomitant common sites of metastasis, and median survival in months. Primary tumors were subsequently sorted and combined into 6 main categories; respiratory, gastrointestinal (GI), genitourinary (GU), miscellaneous, lymph-blood-nervous, and breast to compare the different age groups, races, and gender. Primary tumors that fall under each category are summarized in **Table S1, Supplementary Material** http://links.lww.com/MD/G794. Patients in each broader category were divided into 4 groups according to age: 18-–40 years, 41–60 years, 61–80 years, and older than 80 years. Gender was divided into males and females. Race was divided into White, Black, and Other (American Indian/Alaska Native, Asian/Pacific Islander).

3. Results

3.1. Baseline characteristics

Our analysis showed 25,345 patients diagnosed with metastasis to uncommon sites with a mean age of 68 ± 17 years. There was a female predominance in our cohort of 13,033 (51.4 %). About 33.4%, 34.9%, and 32.5% of the patients were diagnosed in 2016, 2017, and 2018, respectively. There were 6144 (24.2%) patients who had concomitant bone metastasis, 6045 (23.8%) had liver metastasis, and 5232 (20.6 %) had lung metastasis. Incidence of concomitant distant LNs and brain metastasis was the lowest, 4903 (19.3%) and 2731(10.8%), respectively. Table 1 summarizes the baseline characteristics of our cohort.

3.2. The common sites and other sites of metastasis.

Lung and bronchus cancers were the most common tumors metastasized to uncommon sites with 10,612 (41.9%) patients. The most common type of systematic metastasis was bone with 3754 (35.4%), followed by the lung 2307 (21.7%). NHL (non-Hodgkin lymphoma)-nodal metastasized to uncommon sites in 1871 (7.9%) patients with a systemic metastasis to lung in 177 (9.5%) patients followed by liver in 167 (8.9%) patients. Pancreas metastasized to other sites in 1690 (6.7%) patients with concomitant systematic metastasis to liver (49.5%) and lung (20.3%). Stomach metastasized to uncommon sites in 940 (3.7%) patients with concomitant systematic metastasis to LNs (23.1%) and liver (22.4%). Finally, ovary metastasized to uncommon sites in 885 (3.4%) patients with concomitant systematic metastasis to liver (18.9%) and LNs (18.4%). Detailed numbers and analysis of the primary tumors with their median survival is represented in Table 2 and Figure 1A.

The most common subsites to metastasize to other sites are the upper lobe of the lung 4825 (19%), lower lobe of the lung 2610 (10.3%), lung, not otherwise specified 2020 (8%), and lymph nodes of multiple regions 906 (3.6%) (Fig. 1B).

Table 1

Baseline characteristics of the included cohort with metastasis to uncommon sites

Characteristic	Number	Percentage
Number of pts with Mets at DX-Other	25,345	100
Age	68 (17) *	
Sex		
Male	12,312	48.6
Female	13,033	51.4
Race		
White	19,372	76.4
Other (American Indian/Alaska Native, Asian/Pacific Islander)	2743	10.8
Black	3164	12.5
Unknown	66	0.3
Year of diagnosis		
2016	8463	33.4
2017	8640	34.9
2018	8242	32.5
Cause of death		
Dead (attributable to cancer dx)	14,628	57.7
Alive or dead of other cause	10,585	41.8
Dead (missing/unknown COD)	130	0.5
Co-existent Mets at DX†		
Mets at DX-Distant LN	4903	19.3
Mets at DX-lung	5232	20.6
Mets at DX-liver	6045	23.8
Mets at DX-bone	6144	24.2
Mets at DX-brain	2731	10.9

Mets at DX: metastasis at diagnosis; COD: cause of death; dx: diagnosis.

*Mean (SD).

†NB: the numbers are not summable because categories are not mutually exclusive.

Table 2

Incidence proportion and median survival of patients identified with uncommon or other sites of metastases by primary cancer site

Site	Number of patients with uncommon metastases at diagnosis	Incidence proportion of uncommon metastases among entire cohort (%)	Median survival among patients with uncommon metastases (mo, IQR)	Type of systemic metastasis	Number of patients*	(%)	Median survival (mo, IQR)
Lung and bronchus	10,612	41.9	3(7)	Distal LNs	1991	18.8	3(7)
				Lung	2307	21.7	2(6)
				Brain	2191	20.7	3(6)
				Bone	3754	35.4	3(6)
				Liver	2236	21.1	2(5)
NHL – nodal	1871	7.4	11(18)	Distal LNs	109	5.8	11(13)
				Lung	177	9.5	7.5(14)
				Brain	37	2	5(9)
				Bone	303	16.2	10(16)
				Liver	167	8.9	7(16.25)
Pancreas	1690	6.7	2(6)	Distal LNs	263	15.6	2(4)
				Lung	343	20.3	1(4)
				Brain	25	1.5	1.5(4.5)
				Bone	129	7.6	1(4)
				Liver	836	49.5	1(4)
Stomach	940	3.7	3(8)	Distal LNs	217	23.1	3(7)
				Lung	95	10.1	2(4)
				Brain	16	1.7	1(1.25)
				Bone	82	8.7	2.5(5)
				Liver	211	22.5	2(4)
Ovary	885	3.5	8(17)	Distal LNs	163	18.4	8(16)
				Lung	111	12.5	5(15)
				Brain	4	0.5	14(10)
				Bone	17	1.9	7(15)
				Liver	168	19	2(4)
Breast	770	0.3	7(15)	Distal LNs	295	38.3	7(14.5)
				Lung	276	35.8	6(11.75)
				Brain	81	10.5	4(10)
				Bone	449	58.3	7(14)
				Liver	183	23.8	4(10.5)
Corpus uteri	715	2.8	8(14)	Distal LNs	121	16.9	5(11)
				Lung	92	12.9	5.5(9)
				Brain	7	1	5(3)
				Bone	35	5	4(6.5)
				Liver	71	9.9	6(10.5)
Kidney and renal pelvis	618	2.4	5(11)	Distal LNs	199	32.2	4(8)
				Lung	329	53.2	4(9.25)
				Brain	69	11.2	2(6)
				Bone	212	34.3	4(7)
				Liver	131	21.2	4(10.5)
NHL - extranodal	433	1.7	12(19)	Distal LNs	31	7.2	9(15)
				Lung	31	7.2	10(18.5)
				Brain	4	0.9	5.5(14)
				Bone	37	8.6	5(10)
				Liver	23	5.3	4(12.5)
Cecum	404	1.6	7(13)	Distal LNs	64	15.8	5(12)
				Lung	60	14.9	3.5(9.25)
				Brain	1	0.2	3(0)
				Bone	15	3.7	3(8)
				Liver	160	39.6	4(12)
Melanoma of the skin	379	1.5	6(13)	Distal LNs	114	30.1	4(9)
				Lung	162	42.7	4(8)
				Brain	120	31.7	4(8)
				Bone	93	24.5	3(6)
				Liver	92	24.3	3.5(9.25)
Sigmoid colon	344	1.4	7(12)	Distal LNs	63	18.3	8(12)
				Lung	60	17.4	4(10.5)
				Brain	6	1.7	2.5(6.25)
				Bone	20	5.8	3.5(9.75)
				Liver	157	45.6	5(12)
Esophagus	327	1.3	3(7)	Distal LNs	131	40.1	3(5.5)
				Lung	88	26.9	2.5(4.25)
				Brain	21	6.4	2(4)
				Bone	110	33.6	3(6)
				Liver	127	38.8	2(4.5)

(*Continued*)

Table 2

(*Continued*)

Site	Number of patients with uncommon metastases at diagnosis	Incidence proportion of uncommon metastases among entire cohort (%)	Median survival among patients with uncommon metastases (mo, IQR)	Type of systemic metastasis	Number of patients*	(%)	Median survival (mo, IQR)
Prostate	290	1.1	10(16)	Distal LNs	117	10.3	9(17)
				Lung	41	14.1	7(14)
				Brain	8	2.8	2(5.75)
				Bone	184	63.5	9(14)
				Liver	32	11	5.5(14.5)
Liver	286	1.1	1(5)	Distal LNs	54	18.9	2(4.75)
				Lung	71	24.8	1(3)
				Brain	2	0.7	2(0)
				Bone	42	14.7	2(4)
				Liver	17	5.9	3(7)
Small intestine	271	1.1	13(19)	Distal LNs	30	11.1	8.5(23.5)
				Lung	21	7.8	3(10)
				Brain	3	11.1	5(13.5)
				Bone	10	3.8	10(12)
				Liver	104	38.4	11(18)
Appendix	258	1	11(15)	Distal LNs	15	5.8	5(12.5)
				Lung	9	3.5	6(7)
				Brain	0	0	NA
				Bone	2	0.8	1.5(.5)
				Liver	19	7.4	11(16)
Ascending colon	227	0.9	6(11)	Distal LNs	67	29.5	6(9.5)
				Lung	33	14.5	4(5)
				Brain	3	1.3	4(4.5)
				Bone	13	5.7	3(7)
				Liver	101	44.5	5(9)
Large intestine, NOS	227	0.9	2(9)	Distal LNs	38	16.7	3(5.5)
				Lung	47	20.7	2(5.5)
				Brain	3	1.3	1(2)
				Bone	17	7.5	1(6)
				Liver	98	43.2	2(7.75)
Rectum	222	0.9	6(12)	Distal LNs	66	29.7	3.5(7.75)
				Lung	54	37.8	4.5(13)
				Brain	9	4.1	2(6)
				Bone	34	14.3	4.5(7.75)
				Liver	105	47.3	5(12)
Intrahepatic bile duct	191	0.8	3(6)	Distal LNs	64	33.5	3.5(6)
				Lung	43	22.5	2(5.5)
				Brain	0	0	NA
				Bone	21	11	2(5)
				Liver	46	24.1	3(6)
Gallbladder	179	0.7	3(7)	Distal LNs	28	15.6	5.5(6.25)
				Lung	20	11.2	3(7)
				Brain	1	0.6	7(0)
				Bone	10	5.6	6.5(7.5)
				Liver	78	43.6	2(7)
Urinary bladder	179	0.7	2(6)	Distal LNs	49	27.8	2(4)
				Lung	47	26.3	1(2)
				Brain	8	4.5	5.5(10.75)
				Bone	36	20.1	1(5)
				Liver	42	23.5	1(2)
Cervix uteri	121	0.5	7(12)	Distal LNs	49	40.5	6(12)
				Lung	23	19	3(10)
				Brain	1	0.8	1(0)
				Bone	15	12.4	9(13)
				Liver	19	15.7	3(7)
Anus, anal canal and anorectum	28	0.1	5(12.25)	Distal LNs	8	28.6	9(16.5)
				Lung	2	7.1	3.5(1.5)
				Brain	0	0	NA
				Bone	4	14.3	3.5(2.25)
				Liver	7	0.3	4(2)

IQR: Interquartile range.

*The numbers are not summable because categories are not mutually exclusive.

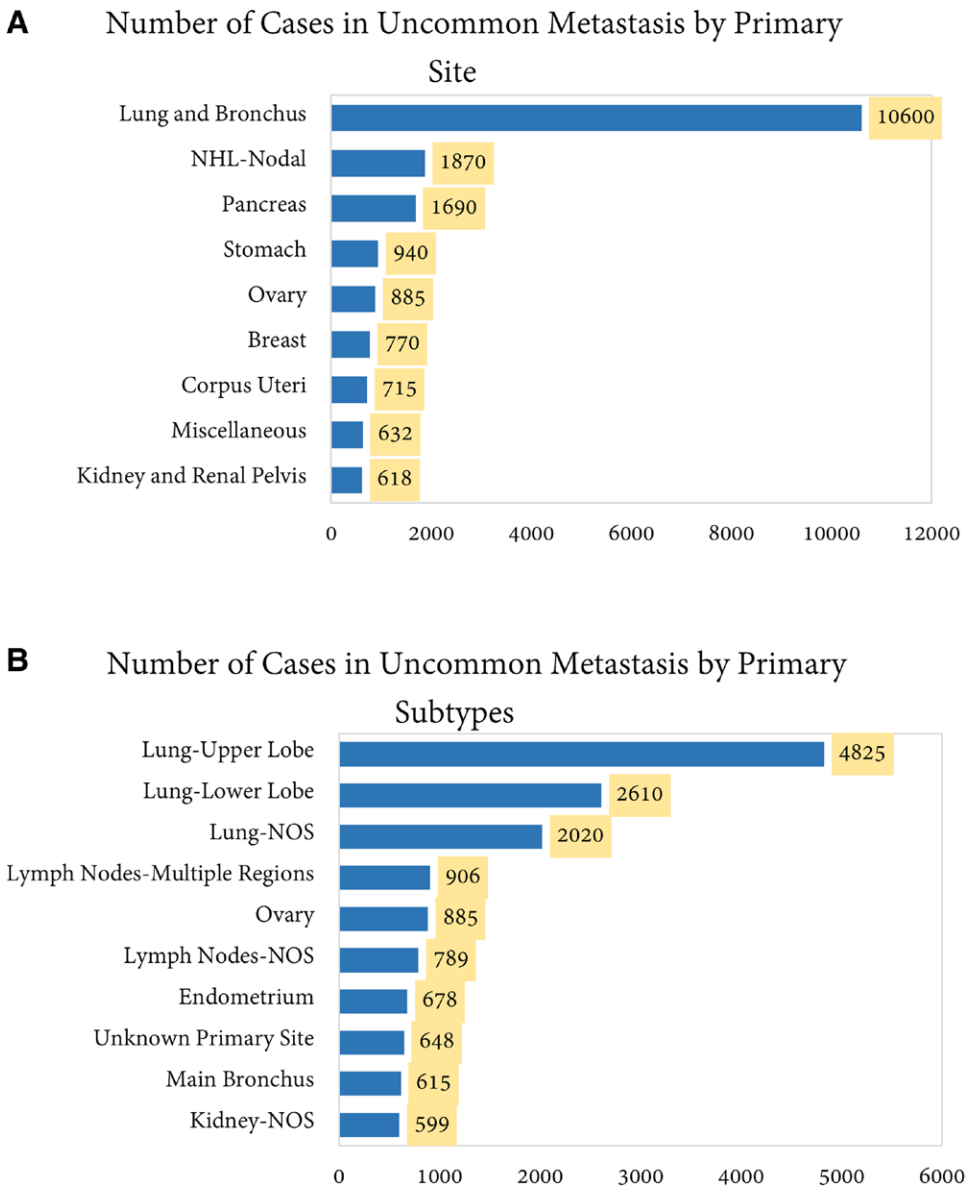

Figure 1. A: The number of patients with identified metastases to uncommon sites at diagnosis by primary cancer site. NHL = nonHodgkin lymphoma. B: The number of patients with identified metastases to uncommon sites at diagnosis by the subtypes of the primary cancer site. NOS = not otherwise specified.

3.3. Incidence proportion of patients with identified metastases to other sites at diagnosis by primary cancer site as stratified by age, race, and gender.

Incidence of metastasis to uncommon sites was most common in respiratory cancers in ages of 61-80 years and least in breast cancer primaries in young ages 18–40 years. GI and GU primaries still show a higher number in all ages with more predilection in 61–80 years (**Table S2, Supplementary Material** http://links.lww.com/MD/G794).

There was a noticeable higher number for metastasis to other sites with White race with the same order of incidence in primaries; respiratory primaries were the most common. Despite Black and other races (American Indian/Alaska Native, Asian/Pacific Islander) did not show a remarkable difference; there were higher incidences with Black race except for GI primaries and lymph, blood, and nervous primaries, which were higher in other races (**Table S3, Supplementary Material** http://links.lww.com/MD/G794).

The differences in incidence are somewhat minor between both sexes, with more prediction to higher incidence to males. Respiratory primaries are still the most common between both genders. (**Table S4, Supplementary Material** http://links.lww.com/MD/G794).

3.4. Survival

Liver cancer was associated with the worst prognosis, with a median survival of 1 month among patients with uncommon metastases. In the case of systemic metastasis, the median survival ranged between 1 month in LNs metastasis and 3 months in liver metastasis. The pancreas, large intestine, and urinary bladder followed by liver have a median survival of two months. Lung and bronchus, stomach, esophagus, intrahepatic bile duct gallbladder have a median survival of 3 months. Small intestine tumors were associated with a better prognosis than the aforementioned tumors, with a median survival of 13 months.

Survival was affected with concomitant systematic affection. For example, lung and bronchus primaries were associated with earlier death if metastasis to the liver. NHL-nodal showed worse survival if metastasized to the brain; 5 months while 11 months if metastasized to LNs. The detailed survival rates are represented in Table 2 and Figure 2.

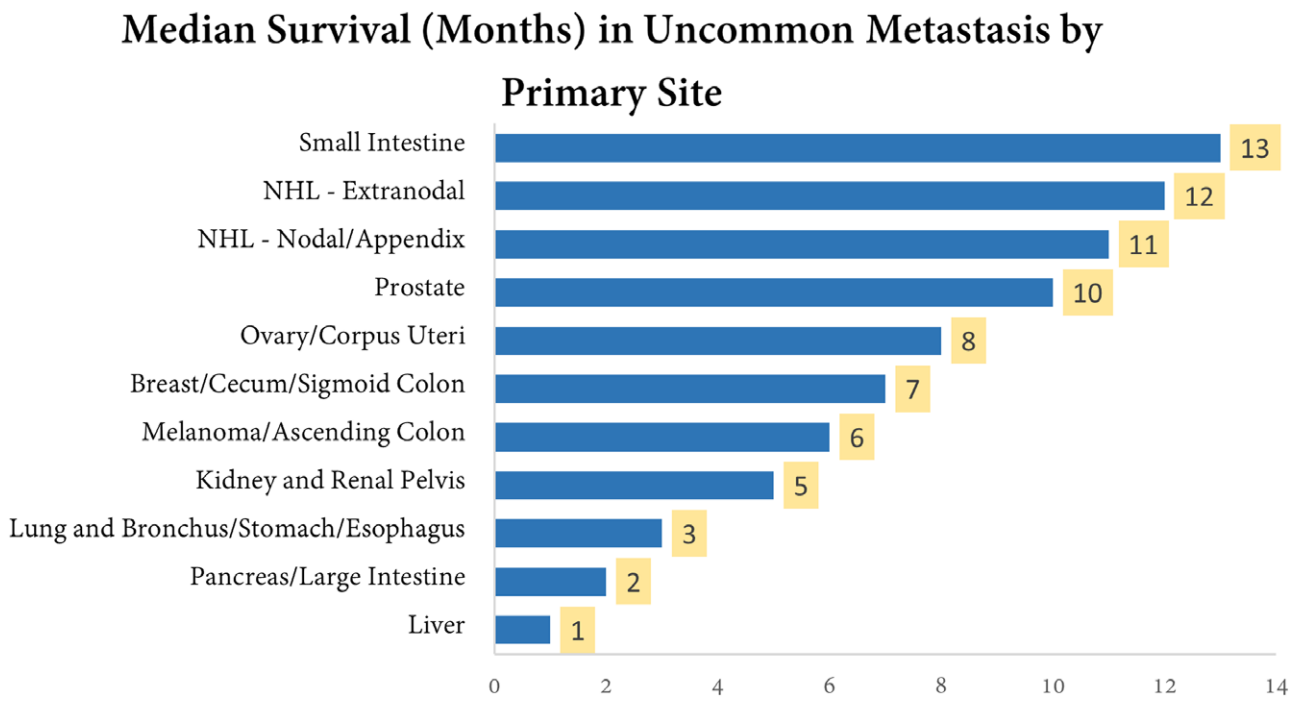

Figure 2. The median survival (in months) of the primary cancer site with identified metastases to uncommon sites at diagnosis. NHL = nonHodgkin lymphoma.

4. Discussion

Our study showed that the most common primaries metastasized to uncommon sites were the lung and bronchus cancers, followed by NHL-nodal, pancreas, stomach, and ovary. Demographically, metastasis to uncommon sites was more common among 61–80 years age group (55.6%), followed by the age group of 41–60 years (23.3%), which implicates the elderly to be a subset of the population, not only being at risk of developing cancer, but also developing metastasis to uncommon sites. In the USA, 80% of all cancers are diagnosed at the age of 55 years or older.[11] Respiratory, GI, GU, and lymph-blood-nervous categories showed a male predilection except for breast, which is more common in females. The incidence proportion of uncommon metastasis was highest for the White race, 76.6% of all incidence followed by African Americans (12.5%) and other races (10.9%). Such a high incidence proportion of uncommon metastasis correlates with the 76.3% of the cohort being White.

Lung and bronchus cancers accounted for the most common primary with uncommon metastasis at diagnosis, with a median survival of 3 months. Lung cancer, when are detected, is often in a metastatic stage IV.[16] Bone, brain, and liver are common sites of metastasis for respiratory cancers, which is consistent with our findings.[17–19] Heart and skin may be uncommon sites of metastasis.[20,21]

NHL is the second most common cancer with uncommon metastasis at diagnosis. Our findings suggest that the nodal form of NHL is more common than the extranodal form. Survival rates vary from 4 to 11 months. Our results showed the worse prognosis with liver and brain metastasis in nodal NHL meanwhile worse prognosis in liver and bones in extranodal NHL.

GI tumors had a high tendency to metastasize with the pancreas, followed by the stomach cancers found to commonly have metastasized at diagnosis. The liver was seen to be a common site of systemic metastasis for GI cancers which is supported by previous literature which is also consistent with our findings.[5,6] Lymph node metastasis is common, especially in stomach and esophageal cancers, which has prognostic value and is an important factor for surgical resection in high-grade stomach cancers.[22] Our findings suggested that the esophagus followed by stomach and large intestine tumors had the worse survival rates of 2 and 3 months, respectively. In most GI cancers, brain metastasis was found to have a lower survival rate.

Pancreatic cancer is often detected at an advanced stage due to the lack of highly sensitive screening techniques. Yachida et al reported that distant metastasis occurs late during the genetic evolution of pancreatic cancer, at least 5 years after the initial mutation. Still, the median survival is only 2 years once the metastasis occurs, which is diagnosed at an even later stage.[23] On the other hand, anorectal cancers have the least number of metastatic to other sites at diagnosis.

Ovarian cancers are commonly metastasized to the liver, lymph nodes, and lungs. Deng et al also reported the common sites of ovarian cancer metastasis are the liver, distant LNs, lung, bone, and brain.[24] Deng et al reported the site of distant metastases to be an independent prognostic factor with lung metastases having the worst overall survival and distant lymph node metastases had the best survival[24]; however, our study found liver metastasis to have the worse prognosis with a median survival of only 2 months and brain metastasis with a comparatively better prognosis with a median survival of 14 months. Breast cancer commonly metastasized to bone, followed by liver and lymph nodes. Tahara also reported bones as the most common sites of breast cancer metastasis.[25]

We also found that almost all the GU cancers metastasized to the liver, followed by LNs and bone. GU cancer mainly spreads to the LN basins before dispersing to the lungs and liver. Bone tends to be a common site of metastasis among lung, NHL, and breast cancers. The possible reason for this may be 2-fold- one being the small caliber of blood vessels in the bone, filtering the cancer cells, and another being the constant cell turnover rate in the bones providing a fertile home for cancer cells to proliferate. Central nervous system (CNS) essentially remains the site of least common metastasis among all the cancers except malignant melanoma, where significant patients present with brain metastasis is only second to the lung by a narrow margin. Supportive evidence came from Yashin et al, who reported that the blood-brain barrier's integrity must be compromised for melanoma cells to metastasize to the brain.[26] Another theory is that melanoma cells had the same embryonic origin as CNS cells and share common antigens such as MAG-1 and MAG-2, hence the CNS metastasis.[27]

Niu Fy et al studied uncommon metastasis in nonsmall cell lung cancer in 2872 patients. They postulated that metastasis to uncommon sites is rare because the microenvironment of these organs is not suitable for tumor survival.[28] For example, skin is a rare site for metastatic growth as it shares only 5% of cardiac output and is immunologically active against tumor cells.[29] Skeletal muscles also have a special microenvironment characterized by its changes in PH, blood flow, and pressures.[30] Spleen's high concentration of immune cells and its role as "immune surveillance" also makes it an unfavorable site of metastatic seeding. Anti-angiogenesis factors in the spleen further discourage metastatic growth.

Our study is limited by the national registries contributing to the SEER database. Over the years, some states have been excluded, like Mississippi, Nevada, North Dakota, due to unsatisfied criteria, contributing to missing numbers of advanced cancer. As the SEER includes only US patients only, biases were reported due to the lack of external validity of the results and the retrospective nature of the analysis. Also, Seeking expert care at an early stage of symptoms often is affected by the availability of premium cancer institutes and the affordability of the patients. These significantly impact the stage of diagnosis and course of treatment, thus affecting survival. Hence, the regional variations of cancer care and financial capacity lend to the disparity in the numbers over the years. Finally, summation of patients with different systematic affection will not equal the total population because patients may have concomitant multiple site affection.

5. Conclusions

The results of this study provide population-based estimates of the incidence and survival rate of the different tumors with metastasis to other sites at the time of diagnosis. We have shown that lung and bronchus cancers were the most common tumors metastasized to other sites at diagnosis, followed by NHL-nodal, pancreas, stomach, and ovary. We also found that the survival rate and prognosis were worse in the liver, pancreas, large intestine cancers. On the other hand, small intestine, NHL-extra nodal, anorectum, and appendix cancers had better survival and prognosis. These data can help clinicians justify the use of different screening tools, which may also play an essential role in future research and achieve a better prognosis for cancer patients.
The author(s) of this work have nothing to disclose.

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Writing – review & editing: All authors.

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