Distribution of primary site of hepatic metastases and prognosis of hepatic metastases at different primary sites

Huangbao Li
First Hospital of Jiaxing https://orcid.org/0000-0003-1537-6951
Jun Zhou
First Hospital of Jiaxing
Fengqing Zhao
First Hospital of Jiaxing
Quan Cheng
Xiangya Hospital Central South University
Xiang Zhu (zhuxiang2018@tom.com)

Research article

Keywords: hepatic metastases, prognosis, primary site, SEER, lung cancer, colorectum cancer, pancreas cancer

Posted Date: August 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.13470/v1

Abstract

Background Most of the time, the primary tumor of hepatic metastases is easy to find. However, sometimes this is a confusing question. The present study aimed to explore the distribution of primary sites of hepatic metastases and the prognosis of hepatic metastases at different primary sites. Methods Data on patients with hepatic metastases were obtained from the surveillance, epidemiology, and end results (SEER) database between 2010 and 2016. Descriptive statistics was used to analyze the distribution of primary sites, life table to calculate survival rate, Kaplan-Meier method to plot survival curves, and Cox univariate regression and multivariate regression analysis to assess prognostic factors. Results The median age of 151,821 patients was 67 years; 58.7% of the primary sites were derived from the digestive system, followed by the respiratory system (25.6%) and other sites (15.8%). Ten leading primary sites were lung (25.4%), colorectum (24.1%), pancreas (19.8%), stomach (4.5%), breast (4.1%), gallbladder and biliary system (3%), esophagus (2.7%), kidney and renal pelvis (2.1%), ovary (1.8%) and primary sites unknown (2%). The overall survival probability of patients with hepatic metastases at 6 months, 1 year, and 3 years was 44.5%, 28.7%, and 9.9%, respectively, with a median survival of 4 months. The prognosis of hepatic metastases from lymphoma (Hodgkin and non-Hodgkin), the small intestine, breast, and colorectum was relatively better, and that from primary sites unknown, urinary system (bladder, urethra), lung, and pancreas was quite poor. Conclusion The distribution of primary sites of hepatic metastases was different under different grouping conditions, but the lung, colorectum and pancreas were the top three sources. The prognosis of hepatic metastases from different primary sites varied greatly.

Background

The primary site of the tumor determines its biological behavior and metastatic characteristics [1-3], and different tumors have completely different morbidity and mortality [4]. According to the conventional strategy, doctors need to develop individualized treatment plans based on factors, such as the primary site, metastasis, and comorbidities of a tumor. However, in the actual clinical process, many tumors are found not because of the symptoms of the primary site, but the symptoms of metastases or accidentally found metastases, rather than primary sites during routine physical examination [5]. With the increasing accuracy of ultrasound, computed tomography, and magnetic resonance imaging, especially contrast-enhanced examinations, even small hepatic tumors are easily detected during routine examinations [6-8].

Due to the generally poor prognosis of patients with hepatic metastases, it is critical to quickly identify the primary site of tumor and promptly treat it. The liver is the most predominant metastatic organ of various tumors, such as pancreatic cancer [9], colorectal cancer [10], and stomach cancer [11]. According to this characteristic, when hepatic metastasis is suspected, we often check primary lesions in these organs. Most of the time, the primary tumor is easy to find. However, sometimes this is a confusing question. Although positron emission tomography–computed tomography or systemic diffusion-weighted imaging [12] can be of great help in finding metastases or primary lesions, doctors still have difficulty in exploring the primary site.

So far, by consulting the literature, we have not found a study on the distribution characteristics of the primary site of hepatic metastasis. Therefore, we extracted the clinical characteristics of patients with hepatic metastasis from the surveillance, epidemiology, and end results (SEER) database, with the purpose of analyzing the distribution of the primary site and the survival status of each tumor type with hepatic metastasis; thus, providing guidance to help physicians to design imaging or other examinations to find the primary site, and to make decisions regarding curative-intent interventions.

Methods

Data

Data were derived from the SEER database which started to release metastatic information related to liver, lung, bone, and brain in 2010. From the latest version of April 2019, the most recent follow-up cutoff date was December 31, 2016.

Hepatic metastasis diagnosis was identified using International Classification of Diseases for Oncology (ICD-O-3), which defined the primary site. Variables extracted from the database included patient ID, sex, age, marital status, race, primary site, histological code (ICD-O-3), grade, surgical approach, lung metastasis, bone metastasis, hepatic metastasis, survival time, and overall survival (OS) status.

The inclusion criteria were the following: the period of diagnosis (2010-2016); and with hepatic metastases (SEER Combined Mets at DX-liver (2010) = 'Yes'). The exclusion criteria included those aged <18 years and those with missing follow-up information.

The colorectum was defined as originating from the cecum and ending at the rectum, including the entire large intestine, with ICD-O-3 coded as C180-C209, C260. Other digestive systems were located in the gastrointestinal tract but not specifically recorded (C268, C269, C488). In the primary site classified by system, “others” refers to all systems except the digestive system and respiratory system (excluding myeloma and leukemia). Surgery of primary site was defined when the primary site received surgical interventions, regardless of whether it was partial or radical resection, or whether the metastases which were treated was unknown. Combined metastases was defined when hepatic metastasis was accompanied by at least one or more of lung metastasis, bone metastasis, and brain metastasis. Age at diagnosis was categorized as younger than 45 years, 45 to 64 years, and 65 years and older.

Statistical Analysis

Cox regression analysis and descriptive statistics of patients' demographic and tumor characteristics were summarized by SPSS 25 (IBM Corp., Armonk, NY). Survival probability and survival curves were calculated and plotted using the R “survival” and “survminer” package; the pie chart and forest plot were also drawn using R (https://www.r-project.org/). Statistical significance was set at two-sided $P < 0.05$.

Results

Patients' characteristics

Table 1 shows demographic data and clinical baseline characteristics of a total of 151821 patients with hepatic metastases (80352 men and 71469 women, 1.12:1) were investigated. The median age was 67 years (IQR 58–76) and the median follow-up time was 3 months (IQR 1–11). Among them, 58.7% of the primary sites were derived from the digestive system, followed by the respiratory system (25.6%) and other sites (15.8%). Also, 80.4% of patients did not receive surgical-related interventions and 41.2% of patients had metastases in other sites, such as the lungs, bones, or brain. Other specific information is shown in Table 1.

Distribution of the primary site

Table 2 shows number and percentage of the specific distribution of the primary site, in which there were no patients with hepatic metastasis in myeloma and leukemia. At the same time, we conducted a subgroup analysis based on sex and age. Ten leading primary sites for the hepatic metastasis by sex and age were arranged in order, as shown in Figure 1.

In general, the ten leading primary sites for hepatic metastases were lung and bronchus (25.4%), colorectum (24.1%), pancreas (19.8%), stomach (4.5%), breast (4.1%), gallbladder and biliary system (3%), esophagus (2.7%), kidney and renal pelvis (2.1%), ovary (1.8%), and primary sites unknown (2%), which account for 89.5% of the total (Figure 1A). The lung, colorectum, and pancreas were the mostly common primary sites of hepatic metastasis, accounting for 69.3%.

From a sex perspective, in men, the five leading primary sites for hepatic metastases were lung and bronchus (26.4%), colorectum (25.4%), pancreas (20.2%), stomach (5.9%), and esophagus (4.3%) (Figure 1B). However, in women, the five leading primary sites for hepatic metastases were lung (24.3%), colorectum (22.6%), pancreas (19.3%), breast (8.7%), and ovary (3.8%). It is important to note that organs associated with sexual characteristics, such as the breast, ovary, and uterus were relatively common (Figure 1C). In addition, the esophagus and kidney were more common in men than the gallbladder and biliary tract, but this trend was opposite in women.

In terms of age, the primary sites of patients of different ages varied greatly. The most common primary sites for patients younger than 45 years were colorectum (36.2%), breast (12.7%), pancreas (10.1%), and genital organs (ovaries, uterus, and male or female genital organs) (Figure 1D). The primary sites common to patients younger than 65 years were the colorectum (27%), lung and bronchus (22.9%), and pancreas (18.2%) (Figure 1E). In patients aged 65 years or older, the common primary sites were the lung and bronchus (28.5%), pancreas (21.6%), and colorectum (21.2%) (Figure 1F). With increasing age, the proportion of primary sites of colorectal, breast, and genital system decreased, but the proportion of pancreas, lung and bronchus, gallbladder, and biliary system gradually increased.

Prognosis of patients with hepatic metastases

Table 3 shows the 1-year OS of patients with hepatic metastases at each primary site. The overall survival rates of patients with hepatic metastases at 6 months, 1 year, and 3 years were 44.5%, 28.7%, and 9.9%, respectively, with a median survival time of 4 months (Figure 2A). The prognosis of hepatic metastases from lymphoma (Hodgkin and non-Hodgkin), small intestine, genital system (breast, ovary, and other male or female genital organs), retroperitoneal tissues, and colorectum and anus was relatively better. The prognosis of hepatic metastases from primary sites unknown, urinary system (bladder, urethra), lung, pancreas, hepatobiliary system, and esophagus was quite poor (Supplementary Figure 1).

Table 4 shows the risk factors for the prognosis of hepatic metastases. Through Cox univariate and multivariate analysis, we found that sex, age, marital status, ethnicity, primary site, grade, presence of surgery, and presence of combined metastases were independent risk factors for prognosis. Figure 2 shows the Kaplan-Meier survival curves for patients with hepatic metastases under different conditions. Supplementary Figure 2 shows a forest plot based on univariate Cox regression analysis of the effects of surgery on the prognosis of each primary site. Most of hepatic metastases benefitted from surgical intervention at the primary site, except for the anus, non-Hodgkin lymphoma, prostate, eye and orbit, and other nonepithelial skin except melanoma of the skin.

Discussion

In this study, we depicted the distribution of primary sites of hepatic metastases and demonstrated that there were significant differences in the distribution of primary sites of hepatic metastases under different conditions. The prognosis of hepatic metastases from different primary sites varied greatly. Surgical intervention at most of the primary sites can benefit the patient's survival with hepatic metastases.

Metastasis is the process that includes local invasion by the primary tumor cells, intravasation into the blood (hematogenous) and/or lymphatic system (lymphatic), arrest at a distant organ, and metastatic colonization [13].It is also the process by which a localized cancer becomes a systemic disease [14] and the cause of about 90% of cancer-associated deaths [15]. The preferred sites of metastasis for a given type of cancer often include the first capillary beds downstream of the primary tumor [15]. The liver is rich in blood and is supported by both the hepatic artery and the portal vein. Therefore, it becomes a target organ for hematogenous metastasis and is threatened by all malignant tumors that produce circulating tumor cells (CTCs).

CTCs originating from the lungs can enter the liver through the hepatic artery, so the liver is the target organ of lung cancer. There were approximately 228,150 estimated new lung cancers in 2019, far more than other organs [4]. Therefore, although the proportion of lung cancer metastasized to the liver in the four most common target organs of lung, bone, brain, and liver is the least, this value is about 16%-17% [16]. However, due to the large number of the patients suffering from lung cancer, 49.3% of whom have had distant metastases at the time of diagnosis [17], the absolute sum of patients with hepatic

metastasis is tremendous. In the present study, when sorted by organs, tumors originating from the lung accounted for 25.6% of the total, ranking the first.

The digestive system delivers blood to the liver through the portal system. When a digestive tract tumor exists, the portal circulation, the most common route of dissemination of the digestive system tumor, contains both nutrients and CTCs that cause hepatic metastasis [18]. Therefore, the liver becomes the most preferred target organ for digestive system tumors, such as those of the colorectum [10], pancreas [9], stomach [11], and extrahepatic bile-duct [19]. In the present study, primary tumors derived from the digestive system accounted for 58.7% of the total (Table 1); the predominant sites in the system were the colorectal, pancreas, stomach, and gallbladder and other biliary tumors.

The influence of sex on the origin of the primary site was evident, and this difference could be due to the demographic and clinical characteristics of the primary tumor. Esophageal cancer [20], stomach cancer [21], and kidney cancer [22] are more common in men than in women, especially esophageal cancer (about 3:1). In men, the proportion of these three tumors is higher than that in women. In contrast, gallbladder and biliary tract tumors are more common in women [23], so hepatic metastases from the gallbladder and other biliary tumors in women are more common than that in men. In addition, the sum proportion of metastases in female-specific sexual organs, such as the breast, ovary, and uterus are relatively large (17.9%). As it is a specific feature of women, we should pay attention to it for women with hepatic metastases. Although morbidity of prostate cancer is the first one in men, primary tumor originating from the organ is rare because only about 7.53% of patients have metastases at diagnosis and the liver is not the preferred metastatic site for it [24].

The origins of the primary sites of different age groups show different characteristics, and the reasons for these differences may be the same as sex. At present, we have not found any research that can provide a perfect explanation of this discovery. We speculate that the reason colorectal, breast, pancreatic, and genital system-related tumors occupy a large proportion in young patients is that the number of colorectal cancer or breast cancer patients is large [4], and the liver is the preferred metastatic organ of colorectal cancer [10] and pancreatic cancer [9]. Furthermore, pancreatic cancer has a very high rate of hepatic metastasis [9], and the median age of breast cancer [25] and genital system-related tumors is relatively low (less than 65 years) [26,27].

The difference in prognosis of hepatic metastases originating from different sites, with 1-year OS as an example, from 12.2% of the primary site unknown to 78.7% of Hodgkin's lymphoma, is very significant (Table 3 and Supplementary Figure 1). Multivariate analysis found that sex, age, marital status, ethnicity, primary site, grade, presence of surgery, and presence of combined metastases were independent risk factors for prognosis. The reason for the poor prognosis of patients with unidentified primary sites is that if the primary tumor is not found, we cannot provide special treatments, such as surgery, radiotherapy, or chemotherapy. In contrast, chemotherapeutics of Hodgkin's lymphoma has changed its prognosis from being relatively incurable to one in which patients have a high likelihood of long-term survival [28].

This study found that surgical intervention at most of the primary sites can benefit patient's survival with hepatic metastases. In patients with a better prognosis as described in the previous paragraph, the primary site received a higher rate of surgical intervention (Supplementary Figure 2). Other studies have found that hepatectomy for synchronous gastric cancer hepatic metastases may carry survival benefits in selected patients [29]. In patients with colorectal hepatic metastases, surgical resection represents the only chance of long-term survival [30]. In patients with pancreatic cancer, hepatectomy is a procedure with a potential survival benefit for carefully selected patients, particularly those with metachronous metastases [31]. Primary tumor resection in metastatic breast cancer was associated with survival improvement [32], while hepatectomy combined with systemic treatment can provide a chance of long-term survival [33].

Although this study systematically described the origin of the primary site of hepatic metastases and the survival status of patients with hepatic metastases, there are still some limitations. First, the dataset used for this study did not include data regarding number, size, anatomical location, or distribution of hepatic metastases, which are important factors that can affect the survival results presented in this study [29]. Second, it was limited by the dependence on hospital administration, such as the lack of agreement between workers on diagnosis codes, which could lead to registration errors [34].

Conclusions

This study systematically described the distribution of the primary site of hepatic metastases and performed a subgroup analysis based on sex and age. From the results, we conclude that there were significant differences in the distribution of primary sites of hepatic metastases under different conditions. In addition, this study also evaluated the prognosis of patients with hepatic metastases from different primary sites. We believe that this work will have a positive impact on guiding clinicians to find the primary site of hepatic metastases and formulating treatment strategies.

Abbreviations

SEER the surveillance, epidemiology, and end results

CTCs circulating tumor cells

CI Confidence interval

OS overall survival

Declarations

Acknowledgments

The authors thank the Surveillance, Epidemiology, and End Results (SEER) program database for access to open data.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Jun Zhou and Xiang Zhu contributed to the idea and design. Huang-bao Li, Feng-qing Zhao, Jun Zhou and Xiang Zhu contributed to the data acquisition and analysis. Huang-bao Li, Feng-qing Zhao, Jun Zhou and Xiang Zhu contributed to the manuscript writing and revision. All authors contributed to data acquisition and analysis and to manuscript writing and revision, and agreed to all aspects of the work.

Funding

The work is supported by the Science and Technology Project of Jiaxing (grant number 2018AY32015)

Ethics approval and consent to participate

All procedures performed in the study involving human participants were in compliance with the Helsinki Declaration and First Hospital of Jiaxing (Approval Number:LS2018-176).

References

1. Wick MR. Metastases of malignant neoplasms: Historical, biological, & clinical considerations. Semin Diagn Pathol. 2018;35(2):112-122.doi:10.1053/j.semdp.2017.11.009.
2. Aygun N. Biological and Genetic Features of Neuroblastoma and Their Clinical Importance. Curr Pediatr Rev. 2018;14(2):73-90.doi:10.2174/1573396314666180129101627.
3. Friberg S, Nystrom A. Cancer Metastases: Early Dissemination and Late Recurrences. Cancer Growth Metastasis. 2015;8:43-49.doi:10.4137/CGM.S31244.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.doi:10.3322/caac.21551.
5. Dietrich CF, Sharma M, Gibson RN, Schreiber-Dietrich D, Jenssen C. Fortuitously discovered liver lesions. World J Gastroenterol. 2013;19(21):3173-3188.doi:10.3748/wjg.v19.i21.3173.
6. Danila M, Sporea I. Ultrasound screening for hepatocellular carcinoma in patients with advanced liver fibrosis. An overview. Med Ultrason. 2014;16(2):139-144

7. Chang CC, Chen HH, Chang YC, Yang MY, Lo CM, Ko WC, Lee YF, Liu KL, Chang RF. Computer-aided diagnosis of liver tumors on computed tomography images. Comput Methods Programs Biomed. 2017;145:45-51.doi:10.1016/j.cmpb.2017.04.008.
8. Van Beers BE, Daire JL, Garteiser P. New imaging techniques for liver diseases. J Hepatol. 2015;62(3):690-700.doi:10.1016/j.jhep.2014.10.014.
9. Oweira H, Petrausch U, Helbling D, Schmidt J, Mannhart M, Mehrabi A, Schob O, Giryes A, Decker M, Abdel-Rahman O. Prognostic value of site-specific metastases in pancreatic adenocarcinoma: A Surveillance Epidemiology and End Results database analysis. World J Gastroenterol. 2017;23(10):1872-1880.doi:10.3748/wjg.v23.i10.1872.
10. Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget. 2015;6(36):38658-38666.doi:10.18632/oncotarget.6130.
11. Qiu MZ, Shi SM, Chen ZH, Yu HE, Sheng H, Jin Y, Wang DS, Wang FH, Li YH, Xie D, et al. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. Cancer Med. 2018;7(8):3662-3672.doi:10.1002/cam4.1661.
12. Paruthikunnan SM, Kadavigere R, Karegowda LH. Accuracy of Whole-Body DWI for Metastases Screening in a Diverse Group of Malignancies: Comparison With Conventional Cross-Sectional Imaging and Nuclear Scintigraphy. AJR Am J Roentgenol. 2017;209(3):477-490.doi:10.2214/AJR.17.17829.
13. Turajlic S, Swanton C. Metastasis as an evolutionary process. Science. 2016;352(6282):169-175.doi:10.1126/science.aaf2784.
14. Cheung KJ, Ewald AJ. A collective route to metastasis: Seeding by tumor cell clusters. Science. 2016;352(6282):167-169.doi:10.1126/science.aaf6546.
15. Labelle M, Hynes RO. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. Cancer Discov. 2012;2(12):1091-1099.doi:10.1158/2159-8290.CD-12-0329.
16. Yang J, Zhang Y, Sun X, Gusdon AM, Song N, Chen L, Jiang G, Huang Y. The prognostic value of multiorgan metastases in patients with non-small cell lung cancer and its variants: a SEER-based study. J Cancer Res Clin Oncol. 2018;144(9):1835-1842.doi:10.1007/s00432-018-2702-9.
17. Chen VW, Ruiz BA, Hsieh MC, Wu XC, Ries LA, Lewis DR. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. Cancer. 2014;120 Suppl 23:3781-3792.doi:10.1002/cncr.29045.
18. Bird NC, Mangnall D, Majeed AW. Biology of colorectal liver metastases: A review. J Surg Oncol. 2006;94(1):68-80.doi:10.1002/jso.20558.
19. Wang X, Yu GY, Chen M, Wei R, Chen J, Wang Z. Pattern of distant metastases in primary extrahepatic bile-duct cancer: A SEER-based study. Cancer Med. 2018;7(10):5006-5014.doi:10.1002/cam4.1772.
20. Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis. J Gastroenterol Hepatol. 2016;31(6):1141-

1146.doi:10.1111/jgh.13289.

21. Wang J, Sun Y, Bertagnolli MM. Comparison of gastric cancer survival between Caucasian and Asian patients treated in the United States: results from the Surveillance Epidemiology and End Results (SEER) database. Ann Surg Oncol. 2015;22(9):2965-2971.doi:10.1245/s10434-015-4388-4.
22. Tan HJ, Chamie K, Daskivich TJ, Litwin MS, Hu JC. Patient function, long-term survival, and use of surgery in patients with kidney cancer. Cancer. 2016;122(24):3776-3784.doi:10.1002/cncr.30275.
23. Kim YJ, Kim K. Conditional survival in patients with gallbladder cancer. Chin J Cancer. 2017;36(1):85.doi:10.1186/s40880-017-0252-1.
24. Shou J, Zhang Q, Wang S, Zhang D. The prognosis of different distant metastases pattern in prostate cancer: A population based retrospective study. Prostate. 2018;78(7):491-497.doi:10.1002/pros.23492.
25. Derks MGM, Bastiaannet E, van de Water W, de Glas NA, Seynaeve C, Putter H, Nortier JWR, Rea D, Hasenburg A, Markopoulos C, et al. Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial. Eur J Cancer. 2018;99:1-8.doi:10.1016/j.ejca.2018.04.009.
26. Sozen H, Vatansever D, Topuz S, Iyibozkurt C, Kandemir H, Yalcin I, Onder S, Yavuz E, Salihoglu Y. Clinicopathological analysis of borderline ovarian tumours and risk factors related to recurrence: experience of single institution. J Obstet Gynaecol. 2019;39(2):253-258.doi:10.1080/01443615.2018.1499076.
27. Kataki AC, Sharma JD, Krishnatreya M, Baishya N, Barmon D, Deka P, Kalita M. A survival study of uterine cervical patients in the North East India: Hospital-cancer registry-based analysis. J Cancer Res Ther. 2018;14(5):1089-1093.doi:10.4103/0973-1482.184516.
28. Koshy M, Fairchild A, Son CH, Mahmood U. Improved survival time trends in Hodgkin's lymphoma. Cancer Med. 2016;5(6):997-1003.doi:10.1002/cam4.655.
29. Markar SR, Mackenzie H, Mikhail S, Mughal M, Preston SR, Maynard ND, Faiz O, Hanna GB. Surgical resection of hepatic metastases from gastric cancer: outcomes from national series in England. Gastric Cancer. 2017;20(2):379-386.doi:10.1007/s10120-016-0604-6.
30. Akgul O, Cetinkaya E, Ersoz S, Tez M. Role of surgery in colorectal cancer liver metastases. World J Gastroenterol. 2014;20(20):6113-6122.doi:10.3748/wjg.v20.i20.6113.
31. Antoniou E, Margonis GA, Sasaki K, Andreatos N, Polychronidis G, Pawlik TM, Pikoulis E. Is resection of pancreatic adenocarcinoma with synchronous hepatic metastasis justified? A review of current literature. ANZ J Surg. 2016;86(12):973-977.doi:10.1111/ans.13738.
32. Vohra NA, Brinkley J, Kachare S, Muzaffar M. Primary tumor resection in metastatic breast cancer: A propensity-matched analysis, 1988-2011 SEER data base. Breast J. 2018;24(4):549-554.doi:10.1111/tbj.13005.
33. Ruiz A, Sebagh M, Wicherts DA, Castro-Benitez C, van Hillegersberg R, Paule B, Castaing D, Vibert E, Cunha AS, Cherqui D, et al. Long-term survival and cure model following liver resection for breast cancer metastases. Breast Cancer Res Treat. 2018;170(1):89-100.doi:10.1007/s10549-018-4714-1.

34. Lyu HG, Haider AH, Landman AB, Raut CP. The opportunities and shortcomings of using big data and national databases for sarcoma research. Cancer. 2019.doi:10.1002/cncr.32118.

Tables

Table 1 Baseline characteristics of patients with hepatic metastases

Characteristic	No. (%) or M (IQR)
Sex	
Male	80352 (52.9)
Female	71469 (47.1)
Age (year)	67 (58-76)
Age (year)	
<45	7062 (4.6)
<65	56719 (37.4)
>=65	88040(58.0)
Race	
White	119762 (78.9)
Black	20093 (13.2)
Others	11590 (7.6)
Unknown	376 (0.2)
Marital status (married)	
Yes	75956 (50.0)
No	68178 (44.9)
Unknown	7687 (5.1)
Primary site	
Digestive system	89067(58.7)
Respiratory system	38821(25.6)
Others	23933(15.8)
Histology	
Adenocarcinoma	74786 (49.2)
Others	77035 (50.8)
Grade	
Well differentiated	3959 (2.6)
Moderately differentiated	27072 (17.8)
Poorly differentiated	27606 (18.2)
Undifferentiated	5610 (2.6)
T-, B-, or NK cell	309 (0.2)
Unknown	87265 (57.5)
surgery of primary site	
Present	26201 (17.3)
Absent	122083 (80.4)
Unknown	3537 (2.3)
Combined metastases	
Present	62600 (41.2)
Absent	85982 (56.6)
Unknown	3239 (2.1)

M (IQR): median (inter-quartile range)

Table 2: Distribution of primary sites of liver metastases under different conditions

Site	Total	Sex		Age (year)		
		Male	Female	<45	<65	>=65
All sites	**151821 (100)**	**80352 (100)**	**71469 (100)**	**7062 (100)**	**56719 (100)**	**88040 (100)**
Oral cavity & pharynx	**556 (0.4)**	**435 (0.5)**	**121 (0.2)**	**37 (0.5)**	**289 (0.5)**	**230 (0.3)**
Digestive system	**89067 (58.7)**	**50565 (62.9)**	**38502 (53.9)**	**4285 (60.7)**	**34266 (60.4)**	**50516 (57.4)**
Esophagus	4076 (2.7)	3482 (4.3)	594 (0.8)	129 (1.8)	1833 (3.2)	2114 (2.4)
Stomach	6817 (4.5)	4764 (5.9)	2053 (2.9)	366 (5.2)	2486 (4.4)	3965 (4.5)
Small intestine	2316 (1.5)	1222 (1.5)	1094 (1.5)	144 (2)	983 (1.7)	1189 (1.4)
Colorectum	36576 (24.1)	20433 (25.4)	16143 (22.6)	2556 (36.2)	15340 (27)	18680 (21.2)
Anus, anal canal, & anorectum	446 (0.3)	184 (0.2)	262 (0.4)	32 (0.5)	228 (0.4)	186 (0.2)
Liver & intrahepatic bile duct	1845 (1.2)	1076 (1.3)	769 (1.1)	88 (1.2)	763 (1.3)	994 (1.1)
Gallbladder & other biliary	4533 (3)	1927 (2.4)	2606 (3.6)	152 (2.2)	1490 (2.6)	2891 (3.3)
Pancreas	30026 (19.8)	16246 (20.2)	13780 (19.3)	714 (10.1)	10335 (18.2)	18977 (21.6)
Peritoneum & Retroperitoneum	374 (0.2)	125 (0.2)	249 (0.3)	36 (0.5)	142 (0.3)	196 (0.2)
Other digestive organs	2058 (1.4)	1106 (1.4)	952 (1.3)	68 (1)	666 (1.2)	1324 (1.5)
Respiratory system	**38821 (25.6)**	**21370 (26.6)**	**17451 (24.4)**	**571 (8.1)**	**13076 (23.1)**	**25174 (28.6)**
Lung & bronchus	38603 (25.4)	21210 (26.4)	17393 (24.3)	533 (7.5)	12999 (22.9)	25071 (28.5)
Other respiratory organs	218 (0.1)	160 (0.2)	58 (0.1)	38 (0.5)	77 (0.1)	103 (0.1)
Bones & joints	**59 (0)**	**37 (0)**	**22 (0)**	**17 (0.2)**	**20 (0)**	**22 (0)**
Soft tissue (including heart)	**639 (0.4)**	**337 (0.4)**	**302 (0.4)**	**101 (1.4)**	**245 (0.4)**	**293 (0.3)**
Skin	**1478 (1)**	**1039 (1.3)**	**439 (0.6)**	**118 (1.7)**	**538 (0.9)**	**822 (0.9)**
Melanoma of the skin	1372 (0.9)	958 (1.2)	414 (0.6)	114 (1.6)	521 (0.9)	737 (0.8)
Other nonepithelial skin	106 (0.1)	81 (0.1)	25 (0)	4 (0.1)	17 (0)	85 (0.1)
Breast	**6237 (4.1)**	**41 (0.1)**	**6196 (8.7)**	**896 (12.7)**	**3069 (5.4)**	**2272 (2.6)**
Genital system	**6122 (4)**	**1374 (1.7)**	**4748 (6.6)**	**638 (9)**	**2346 (4.1)**	**3138 (3.6)**
Uterine	1729 (1.1)	NA (0)	1729 (2.4)	160 (2.3)	835 (1.5)	734 (0.8)
Ovary	2691 (1.8)	NA (0)	2691 (3.8)	177 (2.5)	1027 (1.8)	1487 (1.7)
Other female Genital Organs	328 (0.2)	NA (0)	328 (0.5)	30 (0.4)	110 (0.2)	188 (0.2)
Prostate	1030 (0.7)	1030 (1.3)	NA (0)	3 (0)	316 (0.6)	711 (0.8)
Other male Genital Organs	344 (0.2)	344 (0.4)	NA (0)	268 (3.8)	58 (0.1)	18 (0)
Urinary system	**4676 (3.1)**	**3037 (3.8)**	**1639 (2.3)**	**175 (2.5)**	**1655 (2.9)**	**2846 (3.2)**
Urinary bladder	1229 (0.8)	886 (1.1)	343 (0.5)	21 (0.3)	316 (0.6)	892 (1)
Kidney & renal pelvis	3190 (2.1)	2007 (2.5)	1183 (1.7)	151 (2.1)	1284 (2.3)	1755 (2)
Ureter & other urinary organs	257 (0.2)	144 (0.2)	113 (0.2)	3 (0)	55 (0.1)	199 (0.2)
Eye & orbit	**77 (0.1)**	**47 (0.1)**	**30 (0)**	**3 (0)**	**30 (0.1)**	**44 (0)**
Brain & other nervous	**19 (0)**	**11 (0)**	**8 (0)**	**3 (0)**	**8 (0)**	**8 (0)**

system						
Endocrine system	**462 (0.3)**	**212 (0.3)**	**250 (0.3)**	**66 (0.9)**	**195 (0.3)**	**201 (0.2)**
Thyroid	198 (0.1)	87 (0.1)	111 (0.2)	16 (0.2)	66 (0.1)	116 (0.1)
Other endocrine	264 (0.2)	125 (0.2)	139 (0.2)	50 (0.7)	129 (0.2)	85 (0.1)
Lymphoma	**345 (0.2)**	**214 (0.3)**	**131 (0.2)**	**57 (0.8)**	**109 (0.2)**	**179 (0.2)**
Hodgkin lymphoma	44 (0)	20 (0)	24 (0)	15 (0.2)	13 (0)	16 (0)
Non-Hodgkin lymphoma	301 (0.2)	194 (0.2)	107 (0.1)	42 (0.6)	96 (0.2)	163 (0.2)
Primary site unknown	**3096 (2)**	**1519 (1.9)**	**1577 (2.2)**	**85 (1.2)**	**823 (1.5)**	**2188 (2.5)**
Mesothelioma	**167 (0.1)**	**114 (0.1)**	**53 (0.1)**	**10 (0.1)**	**50 (0.1)**	**107 (0.1)**

A line of bold characters used to mark a system or an independent organ

Table 3: Prognosis of patients with hepatic metastases from different primary sites

Site	1-year OS (95% CI, %)	Median OS (month)
All sites	28.8 (28.5-29.0)	**4**
Oral cavity & pharynx	37.3 (33.3-41.8)	7
Digestive system		
Esophagus	21 (19.7-22.3)	4
Stomach	25.8 (24.7-26.9)	4
Small intestine	62.3 (60.3-64.4)	28
Colorectum	50.3 (49.8-50.8)	12
Anus, anal canal, & anorectum	50.8 (46.2-55.9)	12
Liver & intrahepatic bile duct	18 (16.2-20)	3
Gallbladder & other biliary	18.2 (17.1-19.5)	3
Pancreas	16.1 (15.6-16.5)	2
Peritoneum & Retroperitoneum	58 (53-63.4)	16
Other digestive organs	19.8 (18-21.6)	2
Respiratory system		
Lung & bronchus	14.8 (14.5-15.2)	2
Other respiratory organs	29.3 (23.5-36.5)	7
Bones & joints	37.5 (26.8-52.5)	5
Soft tissue (including heart)	35.1 (31.4-39.2)	6
Skin		
Melanoma of the skin	23.3 (21.1-25.8)	4
Other nonepithelial skin	25.7 (18.2-36.3)	6
Breast	55.5 (54.3-56.8)	15
Genital system		
Uterine	30.4 (28.2-32.8)	5
Ovary	49.4 (47.5-51.4)	11
Other female Genital Organs	45.6 (40.3-51.7)	9
Prostate	43.7 (40.6-47)	9
Other male Genital Organs	58.9 (53.6-64.7)	19
Urinary system		
Urinary bladder	13.5 (11.6-15.8)	2
Kidney & renal pelvis	21.2 (19.8-22.8)	3
Ureter & other urinary organs	12.3 (8.7-17.5)	2
Eye & orbit	32.4 (22.9-45.7)	7
Brain & other nervous system	39.5 (22-70.8)	10
Endocrine system		
Thyroid	38.3 (31.8-46.3)	6
Other endocrine	33.3 (27.8-39.9)	6
Lymphoma		
Hodgkin lymphoma	78.7 (65.2-95.2)	NA
Non-Hodgkin lymphoma	57.2 (50.5-64.8)	28
Primary sites unknown	12.2 (11-13.6)	1
Mesothelioma	26.2 (20.2-34.2)	3

OS: overall survival; CI: confidence interval.

The ten leading primary sites with the best prognosis or the worst prognosis are presented in **Supplementary Figure 1**.

Figures

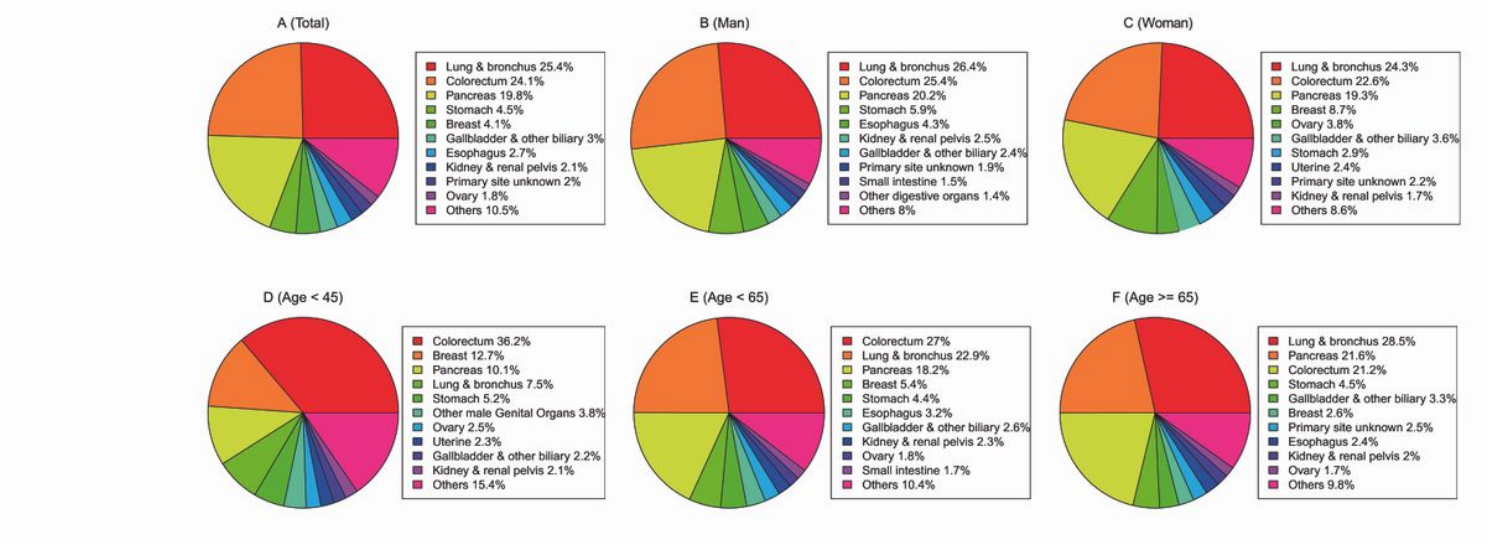

Figure 1

Ten leading primary sites for hepatic metastases. A: Total; B: Men; C: Women; D: <45 years old; E: <65 years old; F: >= 65 years old

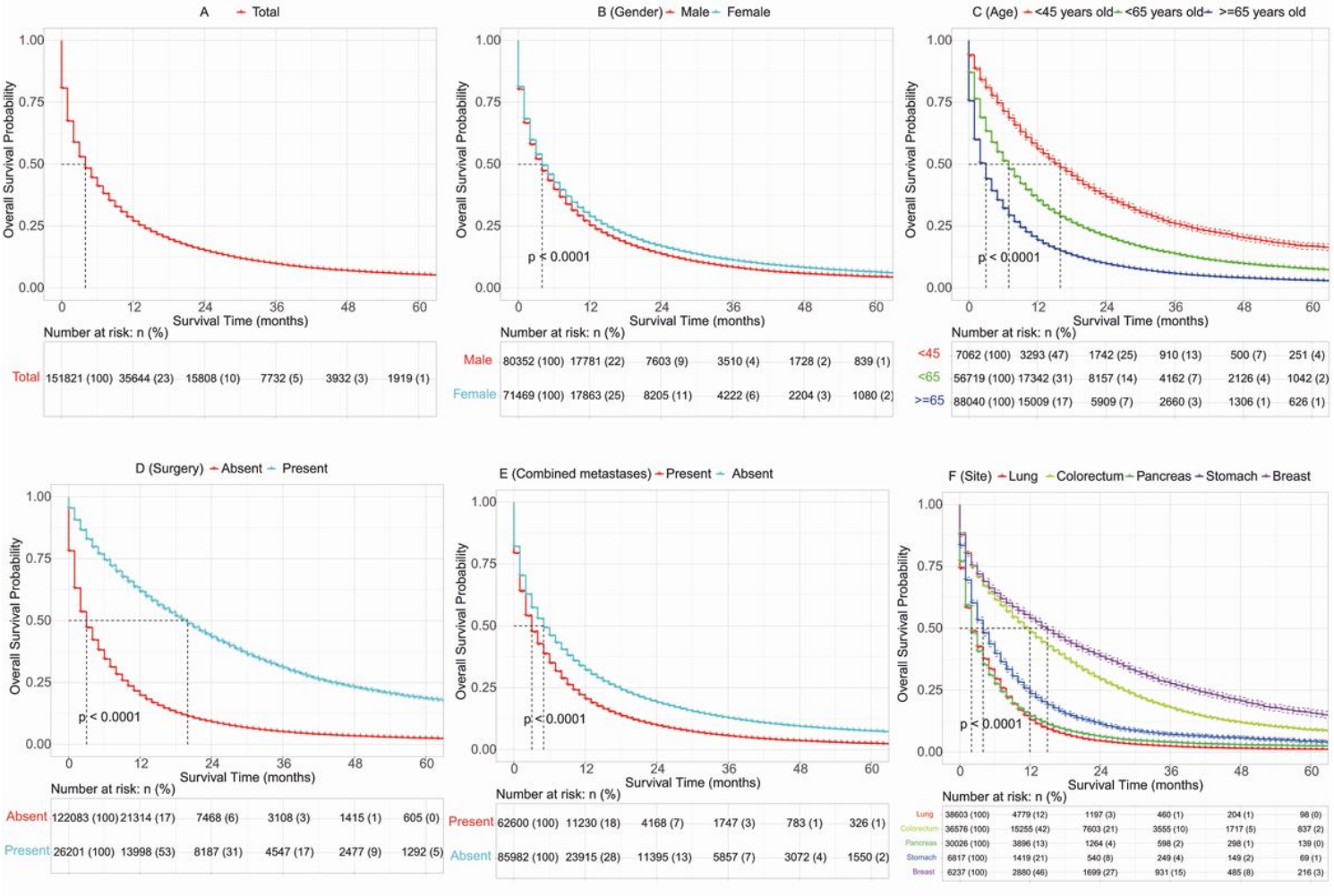

Figure 2

Kaplan-Meier survival curves for patients with hepatic metastases. A: Total; B: Sex; C: Age; D: Presence of surgery; E: Presence of combined metastases; F: Five leading primary sites for hepatic metastases.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.eps
- supplement2.eps