SITE-SPECIFIC SURVIVAL RATES FOR CANCER OF UNKNOWN PRIMARY (CUP) ACCORDING TO LOCATION OF METASTASES

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Novelty. The paper described nation-wide site-specific survival data for 9,306 CUP patients according to the metastatic location. CUP is uniquely suitable for the study of metastatic process because both the metastatic location at diagnosis and the site-specific cancer death are recorded and can be used to deduce metastatic pathways. The data show that the location of metastases predicts site-specific cancer deaths which in turn may point to the hidden primary tumor.

ABSTRACT

Cancer of unknown primary (CUP) is diagnosed at the metastatic stage and despite extensive diagnostic work-up the primary tumor often remains unidentified. Limited population-based survival data are available for metastatic location and none are available that link the location with the cause of death, which might give clues about the tissue of origin. A total of 9,306 CUP patients with extranodal metastases of adenocarcinoma and undifferentiated histology were identified from the Swedish Cancer Registry. Hazard ratios (HRs), mean survival times and Kaplan-Meier survival curves were provided according to CUP location at diagnosis and cause of death. The median survival was shortest (2 months) for patients with liver and longest (5 months) for those with nervous system metastases. Lung cancer was the most common cause of death in patients with CUP metastasis in the respiratory system, nervous system, bone and skin, with a median survival of 3 months. Patients with peritoneal/retroperitoneal and pelvical metastasis died of ovarian cancer, with a favorable median survival of 8 months, but also of pancreatic and colorectal cancers. Patients with pancreatic, liver, biliary and colorectal cancers with liver metastasis succumbed quickly. The data show that the location of metastases predicts site-specific cancer deaths which in turn may point to the hidden primary tumor. The results should facilitate the management of CUP in proposing that the diagnostic arsenal should target the lungs when metastases are diagnosed in the respiratory or nervous system, bone or skin; ovarian tumors should be suspected after diagnosis of pelvical metastases.

INTRODUCTION

Cancer of unknown primary site (CUP) is one of the most fatal cancers with a median survival of about 3 months based on population-based data [1,2]. CUP accounts for some 3% of all cancer in the Swedish Cancer Registry but even higher percentages have been cited elsewhere [3,4]. CUP patients are diagnosed through metastatic tissue and the primary tumor remains frequently undetected because it is small and dormant or it has disappeared [5-7]. Because the treatment is guided by the primary tumor, extensive diagnostic work-up is applied in order to identify the tissue-of-origin [8]. The current arsenal of diagnostic methods includes immuno-histochemical and gene expression profiling together with advanced imaging techniques [9-12]. Autopsy data have shown that the lung, liver, pancreas and gastrointestinal tract are common sites for primary tumors [10,13]. Even if the general prognosis remains poor some clinicopathological features identify subgroups with a more favorable outcome [10,11,14]. Adenocarcinoma is the main histological type accounting for some 70% all cases while undifferentiated cancer accounts for 20% [1,15]. At diagnosis, for some 10% of CUP patients metastases are confined to lymph nodes while for the remaining patients the diseases has spread to extranodal internal organs [1,2].

In the present study we address site-specific survival of CUP patients who present with metastases at different locations. Diagnostic data are obtained from the Swedish Cancer Registry and death causes from the Cause of Death Register from year 1993 through 2008. CUP offers unique opportunities to study the metastatic process because, firstly, the location of metastases is given, and secondly, the site-specific cause of death is given. Thus, if CUP metastases at diagnosis are located in the brain and the patient dies of lung cancer, as judged by the death registrar, both events are recorded. This might suggest that the hidden primary was actually in the lung and it started to grow after metastasizing to the brain [16]. This is much more informative than the recording of primary cancers, for which the TNM classification only states if metastases were present (M0, M1) and the cause of death is the primary cancer, irrespective of the distant metastases that killed the patient. Death certificates for Swedish cancer patients are of high quality because 85% of patients die in hospitals and, for over 90% of cancer deaths, examination at hospital prior to death has been the basis on which the death certificate was issued [17,18].

No previous study on extranodal CUP has tried to link the location of metastases to the cause of death. Instead, the previous papers have considered the location of metastasis and the overall mortality, including the MD Anderson Cancer Center series of 1000 patients collected up to year 1994 [14,19,20] and our earlier population based study from Sweden [1]. The present study covers 9306 CUP patients diagnosed with adenocarcinoma or undifferentiated cancer. The location of metastasis predicts the site-specific cause of death which may suggest the tissue-of-origin. These data should facilitate the diagnostic search for the primary tumor.

PATIENTS AND METHODS

The research dataset used in this study is the latest update of the Family-Cancer Database of year 2008, which was created by linking the Multigeneration Register of Statistics Sweden with the Swedish Cancer Registry, covering 12.1 million individuals. It has been used in recent studies on CUP [8,15,21]. National Census Data and the Swedish population register were incorporated into the dataset to obtain socioeconomic status information for individuals. CUP patients diagnosed between 1993 and 2008 were retrieved from the Swedish Cancer Registry, which is based on a compulsory notification of cases. The completeness of cancer registration was estimated to be over 90% [22]. Tumors were identified according to the tenth revision of the International Classification of Diseases (ICD-10) available since 1993. The ICD-10 codes define the location of metastasis according to the affected organs [23]. Only patients with one reported metastatic site were included. Only data for adenocarcinoma and undifferentiated cancer were used and these were presented together because our previous analyses showed that these histologies were largely similar and that there were too few undifferentiated cases to stand alone [1]. Causes of death were obtained from the Swedish Causes of Death Register, which coded deaths according to ICD-9 in 1987-1996, and ICD-10 since 1997. The cause of death in CUP patients is the organ-specific cancer which kills the patient, as judged by the death registrar. Deaths from cancer of the mediastinum included pleura and thymus. Death from "other cancers" included death from any other cancer than those that were analyzed separately.

4

The Swedish Cancer Registry applies the accepted definition of CUP, i.e. diagnosis of a metastatic cancer for which the primary site cannot be found, despite a standardized diagnostic work-up. If the primary site is found during the work-up, the diagnosis is changed from CUP to that cancer. The ICD-10 codes define the location of CUP metastases; among 9306 CUP deaths, the unspecified CUP (no specific location) was the largest group (3085 patients), followed by CUP with liver metastases (2311) or with peritoneal/retroperitoneal metastasis (1788). The cause of death data for each patient was obtained from the Causes of Death Register, based on the data delivered by a medically qualified death registrar. In a vast majority of cases this person was well aware of the clinical course of the disease because for over 90% of cancer deaths examination at hospital prior to death was the basis on which the death certificate was issued [17,18]. For all account, the cause of death assessment is highly qualified and we report in Results the concordance of the causes to the results of autopsy which is the golden standard. Among 8791 cancer deaths in CUP patients, 5807 were defined by a site-specific death (e.g., lung cancer) while for 2987 site was not given (CUP unspecified).

Survival from CUP was estimated, depending on the location of CUP and the cause of death. Survival curves for the cancer deaths were created via the Kaplan-Meier method (PROC LIFETEST, SAS Version 9.3, SAS Institute). Hazard ratios were calculated using a Cox regression model (PROC PHREG, SAS Version 9.3, SAS Institute).

The study was approved by the ethics committee at Lund University.

RESULTS

Table 1 gives the ICD codes used, the numbers of cancer deaths from extranodal metastases, median ages at diagnosis and median survival times in a total of 9306 patients with adenocarcinoma and undifferentiated histologies. Unspecified CUP was the largest death cause, accounting for 32.1%, followed by lung (12.5%), pancreatic (10.0%), ovarian (6.5%) and colorectal (6.3%) cancers. The median diagnostic ages (overall 72 years) ranged from 64 years for breast cancer to 76 years for mediastinal and 'other' cancers and 77 years for prostate cancer.

5

The median survival times (overall 2 months) were 2 months for many fatal cancers compared to the relatively favorable 10 months for breast and 12 months for prostate cancers.

Table 2 gives the numbers of cancer deaths, median diagnostic ages and median survival times (in months) according to the location of CUP metastases. Unspecified locations, i.e., the last column, were associated with the largest number (3085) of cancer deaths. For specified metastatic locations, the case numbers varies from the highest of liver (2311) and peritoneum/retroperitoneum (1788) to the lowest of nervous system (207), pelvis (200) and skin (130). The bottom line 'All' shows that the median diagnostic ages ranged between 62 years (nervous system) and 75 years (respiratory system and pelvis). Similarly, the median survival times ranged from 2 months (liver) to 5 months (nervous system). Survival times differed extensively both by location of metastases and cause of death. The extremes by location were pelvical metastases for which survival ranged from 1 month for many cancer deaths to 25 months for prostate cancer and 35 months for peritoneal cancer. Even though the median survival for bone metastases were only 3 months, breast (15 months) and prostate (23 months) cancer survival was relatively favorable.

We tried to compare the distribution of metastatic sites and causes of death among CUP patients who had been autopsied, however, the case numbers were small. When CUP was localized to the respiratory system, in 80% (16/20, not including unspecified CUP) of the cases the death cause was lung cancer, compared to 79.5% in Table 2. For liver metastasis, 45% (13/29) were considered to be due to liver or biliary deaths, compared to 37.5% in Table 2. In autopsied cases of peritoneal/retroperitoneal and pelvical metastases, ovarian cancer was the most common cause of death, identical to Table 2; all patients with bone metastases died of lung cancer (N=2). The only apparent discrepancy between autopsy data and Table 2 was for nervous system metastases, autopsies giving lung cancer deaths only at 19% (3/16) compared to 76% in Table 2; autopsies reported 50% of the deaths due to brain tumor which may be considered a matter of judgment.

Table 3 shows HRs for site specific cancer death by the location of CUP metastasis. Lung cancer deaths from respiratory system metastasis were used as a reference and HRs were

6

adjusted for age and gender. Bolding shows significant increases and underlining significant decreases in HR. When the cause of death was undefined CUP, the HRs tended to be increased. When CUP was diagnosed through respiratory system metastases, survival was more favorable in patients with ovarian cancer as cause of death (0.57) than in those with lung cancer. Liver metastases conveyed an unfavorable prognosis in patients with lung (1.74), pancreatic (1.65) and some other cancers as cause of death, notably in stomach cancer (2.14). Peritoneal/retroperitoneal metastases resulted in an increased hazard of death from some gastrointestinal cancers, including biliary but not liver cancers, and even from prostate cancer. For bone metastases, lung cancer HR was not changed but breast and prostate cancer HRs were decreased. For nervous system metastases, only the HR for mediastinal cancer was increased. Metastasis on skin was also an unfavorable sign, with death following in 1 month in ill-defined gastrointestinal cancer deaths or in 2 months in lung or CUP deaths.

Fig. 1A shows Kaplan-Meier plots for survival in four most common death causes in patients with CUP diagnosed in respiratory organs. The data illustrate, in agreement with Table 2, that the survival in pancreatic, lung and mediastinal cancers was fairly similar, with a median survival of 4 to 5 months, while the survival in ovarian cancer was markedly better (median survival 9 months). Fig. 1B shows survival in lung cancer depending on the location of CUP metastases. Patients with skin and liver metastases who died from lung cancer had a median survival of 2 months, compared to 4 months for bone and 5 months for nervous system metastases.

Fig. 2 shows similarly Kaplan-Meier plots of death causes in patients who were diagnosed with CUP liver metastases (A) and liver cancer deaths depending on the location of the initial metastases (B). Only breast cancer survival (A) deviated from other fatal courses.

DISCUSSION

The present study included a recent (1993-2008) nation-wide CUP population of 9,306 extranodal CUP patients diagnosed with adenocarcinoma and undifferentiated cancer, which according to our recent study show identical survival trends [1]. Previous studies on affected organs have been limited to fewer than 1,000 extranodal patients and have been hospital-based,

7

with selected patient groups [14,20,24]. The inclusion of all patients from diagnosis onwards is extremely important for trustworthy clinical risk assessment because the dramatic death rate for CUP in the first months after diagnosis would otherwise bias the results. Referral hospitals receive surviving patients, which for fatal forms of CUP may be substantially less than the initial patient population. We discussed this point in our previous paper referring to the different survival times for cancer registry-based and hospital-based studies [1]. Even cancer registries may miss fragile old patients who die outside the health care system [22].

A basic tenet of the present approach is that causes of death are correct. Death certificates are of high quality in Sweden because 85% of cancer patients die in hospitals and, for over 90% of cancer deaths, examination at hospital prior to death has been the basis on which the death certificate was issued [17,18]. We have previously discussed this issue and presented some data to prove the point [25]. Firstly, familial risks of many cancers were found to be equally high irrespective of incidence or death certificate data. Secondly, data on CUP melanoma agreed between these two sources of data indicating that the death registrar must have known the histology of metastatic tumor, most likely through access to up-to-date patient journals [1]. In the present study, we compared autopsy data from CUP patients; the available case numbers were small but these essentially agreed regarding metastatic location and the main causes of death.

The salient differences from our previous survival data considering overall survival instead of cancer-specific survival were shown in Table 2. While median overall survival by site of CUP metastasis ranged only from 2 to 5 months, the range in cancer-specific survival was larger. For respiratory metastases, ovarian cancer deaths showed a median survival of 9 months; patients with liver metastases survived for 5 months before succumbing to breast cancer and those with peritoneal/retroperitoneal metastasis survived for 12 months before death from breast cancer. In general, survival in breast and prostate cancers was longer compared to other CUP-related cancers. The appearance of CUP metastasis on the skin was associated with poor survival (median survival 3 months). Median survival was 1 month for ill-defined gastrointestinal cancer and 2 months for lung cancer or CUP.

The data have mechanistic implications as the cause of death may point to the tissue of origin, as we suggested in our study of CUP deaths after diagnosis of metastases limited to lymph nodes [16]. In that study, the cause of death was frequently cancer in the organ drained by the lymph nodes and this was lung cancer in 50% of the cases. Lung cancer was the most common cause of death in the present series of extranodal cases, barring the unspecific CUP as a cause of death. Lung cancer was the overwhelming cause of death after respiratory tract metastases but also after nervous system, bone and skin metastases. Ovarian cancer cause of death dominated when metastases were found in the peritoneum/retroperitoneum or in the pelvis. It is often thought that liver metastases are the messenger of death. This was true for the present study but a large number of deaths in patients initially diagnosed with liver metastatic CUP were eventually ascribed to other organs, including the pancreas and colorectum, implying that new evidence emerged between diagnosis and issuing of the death certificate, which allowed a more accurate determination of the tumor type. If it were true that most of nervous system, bone and skin metastases originate from the lungs, why do diagnostic methods, including imaging and immuno-histochemistry, not find the link [9,11,12]. Furthermore, if brain, bone or skin metastases were detected at diagnosis without evidence of lung metastases so how is it explained that the patient was dead in 2 months with lung cancer. These are some unanswered questions on the conundrum CUP [11,12,16,25].

What is the clinical relevance of the present data? When a patient presents with adenocarcinoma or undifferentiated cancer metastases in the respiratory system the most likely primary site is the lung even if it cannot be found. However, more surprisingly, a detection of CUP metastases in the nervous system, bone or skin should also raise the suspicion that the lungs are the tissue of origin, and the suspicion should be stronger among relatively young patients. The suspicion has also empirical bases because the nervous system and the bone are the most common metastatic sites from primary lung cancer [26]. Lung tumors can be detected by modern imaging techniques, including positron emission computed tomography (PET-CT) or breathing-synchronized high resolution spiral CT. However, sensitivity is low for tumors smaller than 1cm [8,12,13,27,28]. The suspicion of finding lung tumors should prompt the targeting of the diagnostic arsenal to this organ in order to obtain a quick diagnosis. However, even if the primary tumor could be found it remains to be seen how great the survival advantage will be, given the poor observed survival (4

9

months for respiratory organ and bone metastases and 5 months for nervous system metastases). Nevertheless, finding tumors early could help improve these statistics and the recent progress in the treatment of some lung cancer subtypes give hope of therapeutic advances in this fatal cancer [29,30]. Also, without a specific diagnosis many patients' treatment is probably replaced by fruitless diagnostic procedures and waiting for them. Even if speculation about the site of the fatal cancer being the tissue of origin proves not to be true, an expedient decision would streamline therapeutic efforts, given the dire prognosis. Thus, our data could eventually result in a survival advantage to some CUP patients.

In summary, the present study, based on recent population-based data on patients diagnosed with extranodal CUP, shows that the median survival varied only from 2 to 5 months between the common metastatic locations. However, the causes and timing of death varied between the metastatic locations according to three main groups. Patients with CUP metastasis diagnosed in the respiratory system, nervous system, bone and skin largely died of lung cancer. Patients with peritoneal/retroperitoneal and pelvical metastasis died of ovarian cancer and, less frequently, pancreatic and colorectal cancers. Finally, patients with liver metastasis succumbed in pancreatic, liver, biliary and colorectal cancers as the final cause of death. Since metastases from the liver to the pancreas or intestine seem unlikely, these cases suggest more accurate classification at death than at diagnosis. We believe that the present data on the cause of death may provide a roadmap to the tissue-of-origin and should be used to guide the diagnostic arsenal for early detection and initiation of therapy.

AUTHOR CONTRIBUTIONS

KH and MR conceived the study, KS provided the dataset and MR carried out the analyses, supervised by KH. AH provided oncological expertise and KH wrote the manuscript which was revised and commented by all authors.

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CONFLICT OF INTEREST

None

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11

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LEGEND TO FIGURES

12

Figure 1. Kaplan-Meier survival curves indicating cause of death for patients with CUP metastases in respiratory organs (A) or indicating location of metastases in CUP patients with lung cancer as cause of death (B).

Figure 2. Kaplan-Meier survival curves (A) for patients with CUP liver metastases with respect to cause of death. (B) Survival in patients with liver cancer as death cause, depending on location of CUP metastases at diagnosis.

Table 1. Causes of death, median age at diagnosis (years), and median survival (months) in all CUP patients (N=9306 cases). ICD-9 and ICD-10 codes were used for identifying deaths 1993-1996 and 1997-2008, respectively.

Cause of death	ICD-9	ICD-10	N	% of all	Age	Survival
Lung	162	C34	1159	12.5%	67	3
Mediastinum, pleura	163,164	C37, C38, C45	197	2.1%	76	5
Pancreas	157	C25	931	10.0%	69	2
Ovary	183	C56	602	6.5%	73	8
Colorectum	153, 154.0-1	C18-20	583	6.3%	71	2
Liver	155	C22	517	5.6%	73	2
Biliary system	156	C23,C24	472	5.1%	70	2
Ill-defined gastrointestinal	159	C26	345	3.7%	72	2
Urinary system	188,189	C64-68	151	1.6%	73	4
Stomach	151	C16	143	1.5%	70	2
Peritoneum	158	C48	108	1.2%	70	5
Breast	174	C50	85	0.9%	64	10
Prostate	185	C61	59	0.6%	77	12
Small intestine	152	C17	45	0.5%	71	4
Other cancer	140-239	C, D0x-4x	397	4.3%	76	2
CUP, unspecified	196-9	C75-80	2987	32.1%	74	2
Any cancer			8781	94.4%		
Non-cancer cause			525	5.6%	76	1
Total			9306	100.0%	72	2

Table 2. Median age (years) at diagnosis and median survival (months) in patients with CUP (N=9306 cases), depending on location of CUP and cause of death. Cases were included from Table 1 when at least two patients had died of the defined cancer. OS = Overall survival.

	Respiratory			Liver			Peritoneum/ Retroperitoneum			Nervous system			Bone			Pelvis			Skin			CUP, Unspecified		
	N	Age	OS	N	Age	OS	N	Age	OS	N	Age	OS	N	Age	OS	N	Age	OS	N	Age	OS	N	Age	OS
Cause of death																								
	289	71	4	82	67	2	13	71	2	110	61	5	128	65	4	2	73	1	35	70	2	439	68	3
Mediastinum, pleura	125	77	5	0			6	69	11	3	78	1	2	71	8	1			2	44	6	53	79	4
Pancreas	16	71	4	365	67	2	199	71	2	1			10	77	5	1			16	72	3	302	70	2
	17	76	9	19	73	3	329	74	10	0			1			72	73	8	4	63	7	141	72	8
Colorectum	8	76	4	205	72	2	124	69	2	5	78	4	12	73	3	11	69	5	5	69	4	178	72	2
	6	69	2	319	73	2	23	76	2	0	65	10	9	68	2	3	69	2	0			155	73	2
Biliary system	6	64	3	215	71	2	76	70	3	0			4	62	8	5	79	1	3	74	6	156	71	2
Ill-defined gastrointestinal	5	84	2	112	80	2	71	71	2	0			10	68	2	1			2	73	1	126	72	1
Urinary system	13	73	4	14	73	2	8	75	5	4	65	10	29	71	5	5	79	1	6	81	4	57	74	3
Stomach	5	59	4	27	71	1	46	72	2	2	58	10	3	63	3	1			2	75	4	45	70	3
Peritoneum	3	75	3	1			56	70	5	0			0			5	73	35	0	0		33	68	6
Breast	5	80	3	12	62	5	4	74	12	1			14	72	15	0			3	61	12	39	60	11
Prostate	1			3	77	0	2	68	1	2	77	27	16	75	23	2	73	25	2	85	7	28	78	10
Small intestine	1			9	66	2	13	72	3	0			0			1			0			17	70	7
Other cancer	21	79	2	41	76	1	92	77	3	17	67	5	18	74	4	38	75	6	5	77	7	134	76	2
CUP, unspecified	152	78	2	797	74	1	654	76	2	45	61	5	203	71	3	45	78	2	30	71	2	973	73	2
	724	75	4	2311	72	2	1788	74	3	207	62	5	501	70	3	200	75	4	130	73	3	3085	72	2

15

Table 3. Hazard ratios for death. 9,306 patients with specific CUP locations and specific causes of death were compared. CUP of respiratory organ with lung cancer as cause of death was used as the reference.

	Location of CUP																			
	Respiratory system				Liver				Peritoneum/retroperitoneum				Bone				Nervous system			
Cause of death	N	HR	95 % CI		N	HR	95 % CI		N	HR	95 % CI		N	HR	95 % CI		N	HR	95 % CI	
Lung	289	1	1	1	82	**1.74**	1.36	2.22	13	1.55	0.89	2.70	128	1.14	0.93	1.40	110	1.02	0.82	1.27
Mediastinum	125	0.83	0.67	1.02	0				6	0.54	0.24	1.21	2	1.05	0.26	4.22	3	**3.71**	1.19	11.58
Pancreas	16	1.37	0.83	2.27	365	**1.65**	1.41	1.93	199	**1.51**	1.26	1.81	10	1.13	0.60	2.12	1			
Ovary	17	0.57	0.35	0.92	19	1.25	0.79	1.99	329	0.67	0.57	0.78	1				0			
Colorectum	8	1.12	0.56	2.27	205	**1.54**	1.28	1.84	124	**1.29**	1.04	1.59	12	1.44	0.81	2.57	5	1.92	0.79	4.64
Liver	6	1.80	0.80	4.05	319	**1.58**	1.35	1.85	23	0.94	0.61	1.44	9	1.90	0.98	3.68	0			
Biliary system	6	2.14	0.95	4.80	215	**1.59**	1.33	1.90	76	**1.39**	1.08	1.80	4	0.91	0.34	2.45	0			
Ill-defined gastrointestinal	5	1.67	0.69	4.05	112	**2.00**	1.61	2.49	71	**1.59**	1.23	2.06	10	1.81	0.96	3.39	0			
Urinary system	13	0.80	0.46	1.40	14	**1.80**	1.06	3.09	8	0.71	0.35	1.43	29	0.97	0.66	1.41	4	0.55	0.21	1.48
Stomach	5	1.27	0.52	3.06	27	**2.14**	1.44	3.18	46	**1.87**	1.37	2.55	3	2.03	0.65	6.32	2	0.90	0.22	3.60
Peritoneum	3	1.64	0.53	5.11	1				56	0.73	0.56	0.95	0				0			
Breast	5	1.25	0.52	3.04	12	1.12	0.63	1.99	4	0.64	0.24	1.73	14	0.41	0.24	0.70	1			
Prostate	1				3	2.55	0.82	7.96	2	**4.33**	1.08	17.39	16	0.35	0.21	0.58	2	0.43	0.11	1.72
Small intestine	1				9	1.59	0.82	3.10	13	1.23	0.70	2.14	0				0			
CUP	152	**1.35**	1.11	1.64	797	**2.15**	1.88	2.47	654	**1.49**	1.29	1.71	203	**1.42**	1.19	1.70	45	1.18	0.86	1.61

Bolding shows that the HR is significantly increased (95%CI does not overlap with 1.00); underlining shows that the HR is significantly decreased.
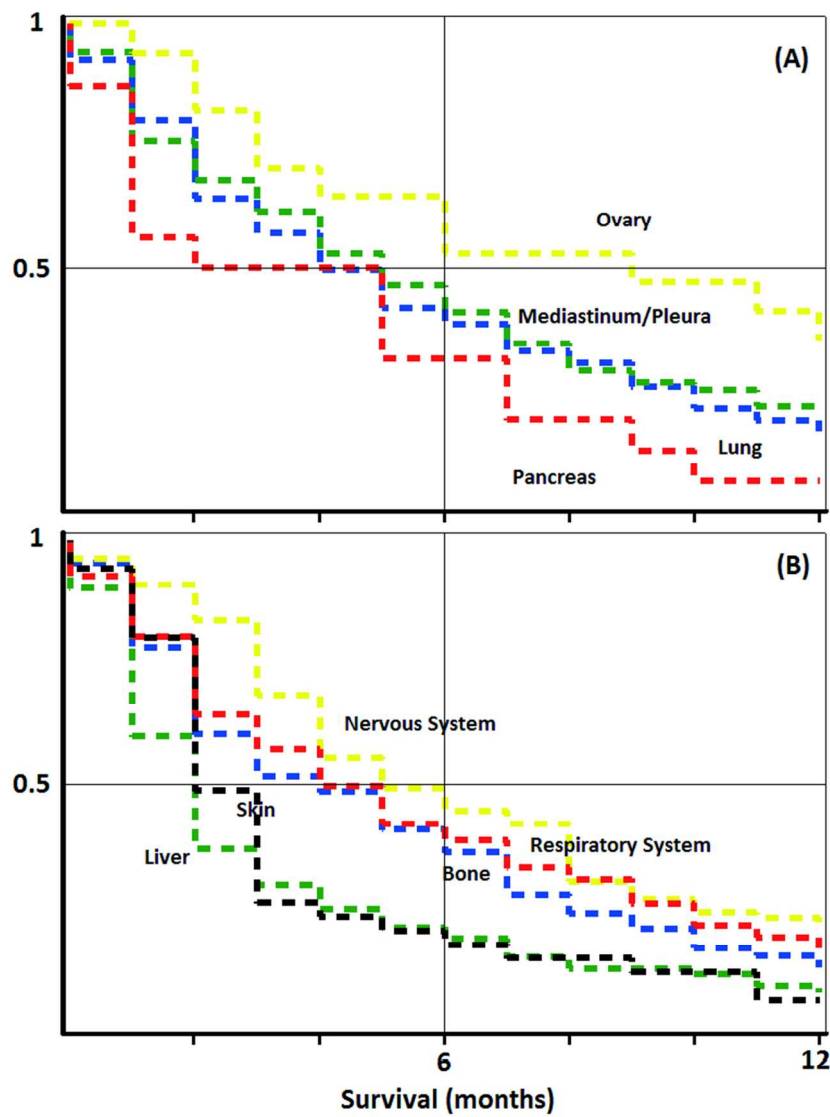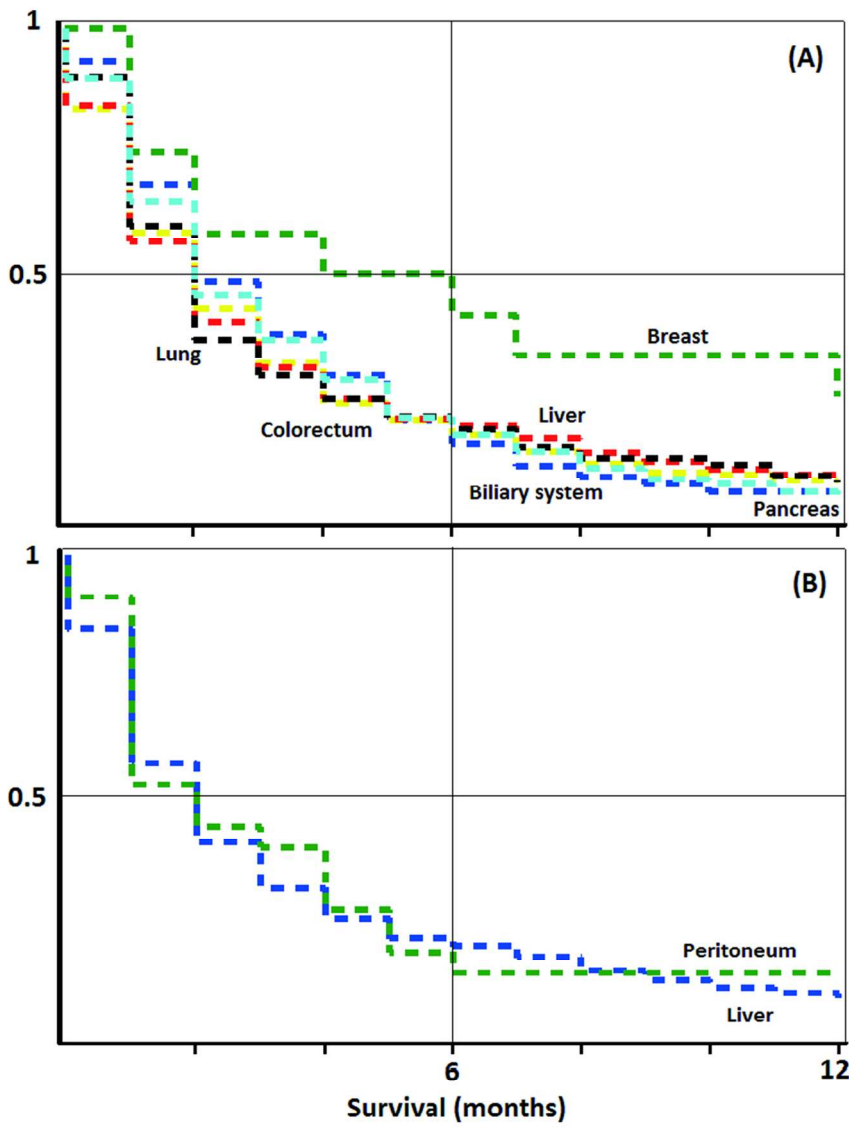
Figure 1
287x390mm (72 x 72 DPI)

Figure 2
279x378mm (72 x 72 DPI)