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Survival from skin cancer and its associated factors in Kurdistan province of Iran

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Abstract

Background: We explored survival of skin cancer and its determinants in Kurdistan province of Iran.

Methods: In a retrospective cohort design, we identified all registered skin cancer patients in Kurdistan Cancer Registry from year 2000 to 2009. Information on time and cause of death were obtained from Registrar's office and information on type, stage and anatomic locations were extracted from patients' hospital records. Additional demographic information was collected via a telephone interview. We calculated the 3 and 5 years survival. Survival experiences in different groups were compared using log rank test. Cox proportional hazard model was built and hazard ratios and their 95% confidence intervals were calculated.

Results: Of a total of 1353, contact information for 667 patients were available, all of which were followed up. 472 telephone interviews were conducted. Mean follow-up time was 34 months. We identified 78 deaths in this group of patients and 44 of them were because of skin cancer. After controlling for confounding, tumour type, anatomical location, and diseases stage remained significantly associated with survival. Hazard ratios for death because of squamous cell carcinoma was 74.5 (95%CI: 4.8-1146) and for melanoma was 24.4 (95%CI: 1.3-485) compared with basal cell carcinomas. Hazard ratio for tumours in stage 4 was 16.7 (95%CI: 1.8-156.6) and for stage 3 was 16.8 (95%CI: 1.07-260) compared with stage 1 and 2.

Conclusion: Tumour stage is independently associated with survival. Relatively low survival rates suggest delayed diagnosis. Increasing public awareness through media about the warning signs of skin cancers could increase the chance of survival in these patients.

Keywords: Skin cancer, Survival analysis, Kaplan Meier, Cox model.

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Introduction

Prevalence of skin cancer has increased in recent decades and its public health burden has also grown alongside (1,2). Although mortality rate from skin cancer is relatively low, it can cause a great deal of morbidity instead, emphasising its public health importance (3). It has been suggested therefore that skin cancer will play an important part in the global burden of disease in the next decade (4).

There are three major types of skin cancer (2,3). Basal cell carcinoma is the most common type of skin cancer. Squamous cell carcinoma is in the second place. It is less prevalent than the basal cell type but it can cause more tissue damage as the tumour usually invades the adjacent tissue and therefore is more aggressive (3). Malignant melanoma is the third common skin

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cancer type. It was once very rare about 50 years ago but its prevalence has since increased considerably (3). Although it only comprises 3% of all skin cancer types, it is still responsible for 75% of deaths due to skin cancer (5).

Skin cancer is an important health problem in Iran. According to Iranian National Cancer Registry 2003-2007 reports it is the most common cancer type in men. In women it is the second most prevalent type of all cancers. When we put data for men and women together it still holds the first place among the most common cancer types in Iranian population (6-13).

Estimating survival rate and factors associated with it is an important first step in any effective program aimed at decreasing the overall burden of any type of cancer. Knowledge of 3 or 5 years survival rates could also help in provision of healthcare in these patients as understandably they will have particular needs during this period. We have therefore studied survival rates of skin cancer in Kurdistan province of Iran and its associated factors using data from Kurdistan cancer Registry.

Methods

In this retrospective cohort study that was conducted in 2010 we identified all patients registered with Kurdistan Cancer Registry as having any type of skin cancer between years 2000 and 2009 and extracted all their demographic and tumour related information. We then contacted all those who had a telephone number recorded in their files and willing to participate that comprised about half of the registered skin cancer population and entered them into the study. Characteristics of study subjects were compared with the rest of the registered skin cancers. Through linkage with Registrar's provincial office information on date and cause of death for study subjects were obtained and their vital status double checked when contacted. A telephone interview was carried out with the patient if s/he was alive or with a close relative in case the patient had passed away. Those we could not reach at our first try were contacted twice more at different times.

We used a two-part questionnaire for our data collection. The first part was completed using the available data at the cancer registry. The second part was filled during the telephone interview with the patients or their first degree relatives.

In addition to their vital status, questions were asked about a list of factors that are potentially associated with survival. These factors included age, sex, tumour type, anatomic location of the tumour, place of residence, any report of delay in diagnosis of cancer, tumour stage, and educational level of the patients. Delay in diagnosis was defined as the time between first appearance of symptoms and the definitive diagnosis of skin cancer. Anatomical locations of the tumours were categorised according to the Iranian National Registry guidelines.

Tumour stage was determined using the TNM system (according to the seventh edition of the American Joint Committee on Cancer (AJCC). AJCC-7 Cancer Staging Manual includes a major revision of the staging protocol for cutaneous carcinomas (14). T stands for tumour and defines the size of the lesion; N stands for lymph nodes and describes the degree of involvement of the adjacent lymph nodes; and M stands for metastasis and explains whether the tumour has reached other parts of body. Based on the above three dimensions tumours are divided into 5 stages (Table 1). When the staging information were absent in registry records, data were collected from hospitals' files where possible.

We collected data on time and cause of death from both the relatives and the Kurdistan Provincial Registrar Office. In case of any discrepancy between the two, the family of the patients was contacted directly in urban areas and indirectly via rural health center officers (Behvarz) in rural areas in order to obtain accurate information.

Statistical analysis was conducted using SPSS 18. Survival analysis methods including Kaplan Meier and log rank tests were used to compare the survival experience in

Table 1. Tumour and patient characteristics by tumour type

Variable		BCC	SCC	MM	Other	Total
Age(year)		N(%)	N(%)	N(%)	N(%)	N(%)
	<60	128(41.4%)	28(26%)	4(30.8%)	20(46.5%)	180(38%)
	60-79	134(43.4%)	59(55%)	7(53.8%)	17(39.5%)	217(46%)
	>=80	47(15.2%)	20(18.7%)	2(15.4%)	6(14%)	75(16%)
	Total	309(100%)	107(100%)	13(100%)	43(100%)	472(100%)
Sex	Male	190(61.5%)	82(76.6%)	6(46.2%)	25(58%)	303(64%)
	Female	119(38.5%)	25(23.4%)	7(53.8%)	18(42 %)	169(36%)
	total	309(100%)	107(100%)	13(100%)	43(100%)	472(100%)
Place of residence	Urban	223(72.2%)	61(57%)	12(92.3%)	29(67.5%)	325(69%)
	Rural	86(27.8%)	46(43%)	1(7.7%)	14(32.5%)	147(31%)
	Total	309(100%)	107(100%)	13(100%)	43(100%)	472(100%)
Tumour anatomic site	Face	257(83. 5%)	66(62.3%)	3(23%)	16(37%)	342(73%)
	scalp and neck	25(8%)	8(7.5%)	1(7.7%)	3(7%)	37(8%)
	Trunk	4(1.3%)	3(2.8%)	0	9(21%)	16(3.5%)
	Upper extremity and shoulder	2(0.7%)	6(5.7%)	0	3(7%)	11(2%)
	Lower extremity and hip	0	6(5.7%)	9(69.2%)	8(18.6%)	23(5%)
	Multiple sites	2(0. 7%)	5(4.7%)	0	2(4.7%)	9(2%)
	Face & scalp and neck	4(1.3%)	2(1.9%)	0	1(2.3%)	7(1.5%)
	External ear	14(4.5%)	10(9.4%)	0	1(2.3%)	25(5%)
	Total	308(100%)	106(100%)	13(100%)	43(100%)	470(100%)
Stage	StageI & Stage II	11(64.7%)	5(18.5%)	4(50%)	2(22.2%)	22(36%)
	Stage III	4(23.5%)	5(18.5%)	0	0	9(14.8%)
	Stage IV	2(11.8%)	17(63%)	4(50%)	7(77.8%)	30(49.2%)
	Total	17(100%)	27(100%)	8(100%)	9(100%)	61(100%)
Delay in diagnosis (month)	<=24	229(80.4%)	86(89.6%)	12(92.3%)	31(81.6%)	358(83%)
	25-48	32(11.2%)	5(5.2%)	1(7.7%)	5(13.2%)	43(10%)
	49-72	14(4.9%)	3(3%)	0	0	17(4%)
	>=73	10(3.5%)	2(2%)	0	2(5.2%)	14(3%)
	Total	285(100%)	96(100%)	13(100%)	38(100%)	432(100%)
Educational level	Illiterate	189(63.9%)	72(74%)	10(76.9%)	25(62.5%)	296(66.4%)
	Below diploma	76(25.7%)	23(23.7%)	2(15.4%)	9(22.5%)	110(24.6%)
	=>Diploma	31(10.5%)	2(2%)	1(7.7%)	6(15%)	40(9%)
	Total	296(100%)	97(100%)	13(100%)	40(100%)	446(100%)

different patient categories. Cox proportional hazard regression model was used to account of the potential confounding variables. Hazard ratios and their 95% confidence interval were calculated. Proportional hazard assumption was checked for every model using log minus log plot.

Results

There were 1353 registered patients of which, telephone contact details were available for 667. A total of 472 interviews were conducted and the remaining 195 patients could not be reached for a variety of reasons including change of address (24 cases), wrong number (84 cases), closure of line (28 cases), and finally 59 cases did not respond to the calls. Average follow up time was 34 months. A total of 78 deaths were detected of which 44 was due to skin cancer. Study subjects had similar characteristics to the rest of the registered skin cancers (Table 4).

Of 472 cases that were analysed, 64% were men and 62% were over 60 years old. Mean and median ages of the subjects were 64 and 65 years, respectively. According to tumour histological type, 66% had basal cell carcinoma, 23% had squamous cell carcinoma, 3% malignant melanoma, and the remaining 8% had other types of skin tumours. 36% of tumours had been diagnosed in stage I and II, 15% in stage III and 49% in stage IV (Table 1).

One, two and five years survival rates were 96%, 91.6, and 85%, respectively.

Table 2. Characteristics associated with survival in univariate analysis

Variables		No.	Event	Hazard Ratios and 95% CI
Age (year)	60>	180	7	Reference
	60-79	217	23	2.95 (1.3-6.8)
	>=80	75	14	6.29 (2.6-15.63)
	Total	472	44	Log Rank test, P<0.001
Sex	Male	303	29	Reference
	Female	169	15	1.03 (0.55-1.9)
	Total	472	44	Log Rank test, P=0.07
Place of residence,	Urban	325	24	Reference
	Rural	147	20	2.05 (1.21-3.71)
	Total	472	44	Log Rank test, P=0.01
Anatomic site	Face	342	24	Reference
	Scalp and neck	37	3	1.07 (0.32-3.5)
	Trunk	16	1	1.15 (0.15-8.5)
	Upper extremity and shoulder	11	1	1.64 (0.22-12)
	Lower extremity and hip	23	7	5.27 (2.3-12.3)
	Multiple sites	9	4	9.36 (3.3-24.3)
	Face & scalp and neck	7	1	1.55 (0.3-11.5)
	External ear	25	2	1.1 (0.3-4.7)
	Total	470	43	Log Rank test, P<0.001
Type of tumor	BCC	309	3	Reference
	SCC	107	29	33.66 (10.3-110.6)
	MM	13	3	27.2 (5.5-135.5)
	Others	43	9	25.8 (7-95.5)
	Total	472	44	Log Rank test, P<0.001
Stage	Stage I and II	22	2	Reference
	Stage III	9	3	3.1 (0.5-18.6)
	Stage IV	30	23	10.85 (2.6-46.2)
	Total	61	28	Log Rank test, P<0.001
Delay in diagnosis (month)	<=24	358	25	Reference
	25-48	43	5	1.74 (0.7-4.6)
	49-72	17	3	2.4 (0.8-7.9)
	>=73	14	2	2 (0.5-7.5)
	total	432	35	Log Rank test, P=0.300
Educational level	illiterate	296	30	Reference
	below diploma	110	4	0.33 (0.2-0.9)
	=>Diploma	40	1	0.22 (0.03-1.6)
	total	446	35	Log Rank test, P=0.02

There were only 3 cases of deaths in basal cell carcinoma patients that were attributable to their skin cancer. Three- year survival rate for squamous cell carcinoma was 67% and for malignant melanoma 50%.

In univariate analysis age, place of residence, education, tumour anatomical location, type and diseases stage were all significantly associated with survival. Risk of death increased with age and was higher in women than in men but the difference did not reach statistical significance. People living in rural areas died twice as faster as their urban counterparts. Regarding the anatomical location, facial lesions carried the lowest risk and involvement of multiple body site the highest risk of death. Squamous cell carcinoma and malignant melanoma patients died 33.6 (95% CI 10.3-110.6) and 27.2 (95% CI 5.5-135.5) faster than patients having basal cell carcinomas that carried the lowest risk. Stage of the tumour was also significantly associated with survival. Risk of death increased with the increase in the tumour stage. Stages I and II carried the lowest risk. Risk of death in stage III was 3 (95% CI 0.5-18.6) times and in stage IV 10.8 (95% CI 2.6-46.2) times higher compared to the stages I and II (Table 2).

Cox proportional hazard model was built to account for the possible confounding effects of existing variables. The three variables of tumour type, stage and anatomical location remained significant in the model and were independently associated with survival (Table 3). In model checking, there was not a serious violation of the propor-

Table 3. Variables predicting survival in the final Cox proportional hazard model

Variables	subgroups	p-value	Hazard Ratios	95% confidence interval	
Tumor stage	stage I and II	0.040	Reference	Lower	Higher
	stage III	0.044	16.8	1.07	260.2
	stage IV	0.014	16.7	1.8	156.6
Tumor type	Bcc	0.023	Reference		
	Scc	0.002	74.5	4.8	1146.7
	Mm	0.036	24.4	1.3	485
	Other	0.013	77	2.5	2412.8
Tumor	Face	0.170	Reference		
Anatomical site	scalp and neck	0.033	48.6	1.4	1714.5
	Trunk	0.098	0.000		0
	Upper extremity and shoulder	0.628	0.6	0.05	6.3
	Lower extremity and hip	0.676	0.7	0.2	3.7
	Multiple sites	0.437	0.6	0.09	2.8
	Face+scalp and neck	0.256	0.2	0.006	3.9
	External ear	0.017	0.09	0.011	0.7

Table 4. Comparing some characteristics of interviewed subjects with the rest of the skin cancers registered in Kurdistan Cancer Registry from year 2000 to 2009

		Rest of the registered skin cancers	Study subjects
Age		N(%)	N(%)
	below 60 years	295(33.6%)	180 (38%)
	60-79 years	482(54.8%)	217 (46%)
	80 years and over	102(11.6%)	75(16%)
	total	879(100%)	472(100%)
Sex			
	Male	522(59%)	303(64%)
	Female	359(41%)	169(36%)
	total	881(100%)	472(100%)
Tumor type			
	BCC	578(66%)	309(65%)
	SCC	220(25%)	107(23%)
	MM	21(2%)	13(3%)
	Others	62(7%)	43(9%)
	total	881(100%)	472(100%)
Anatomical site			
	Face	612(74%)	342(73%)
	Head and neck	81(10%)	37(8%)
	Trunk	41(5%)	16(3.5%)
	Upper extremities	22(3%)	11(2%)
	Lower extremities	37(4%)	23(5%)
	Multiple site	0(0%)	9(2%)
	Face and neck	4(1%)	7(1.5%)
	External ear	27(3%)	25(5%)
	total	824(100%)	470(100%)

tional hazard assumption.

Discussion

We found that the survival figures are relatively low in Kurdistan province compared to similar international studies. One, two and 5 years survival rates for all skin cancer were 96%, 91.6% and 85%. In squamous cell cancer the three-years survival rate was 67% and the corresponding figure for malignant melanoma was 50%. Age, place of residence, education, tumour anatomical location, type and stage were associated with survival in univariate analysis. However after controlling for the possible confounding factors, type, anatomical location and stage of the tumour were the significant predictors of survival.

Our findings regarding the survival rates for squamous cell carcinoma and malignant melanoma show that the survival rates in Kurdistan province is relatively low. In a prospective study on patients having squamous cell carcinoma in Texas, USA, three years survival rate was found to be 85% (15). This figure for most European coun-

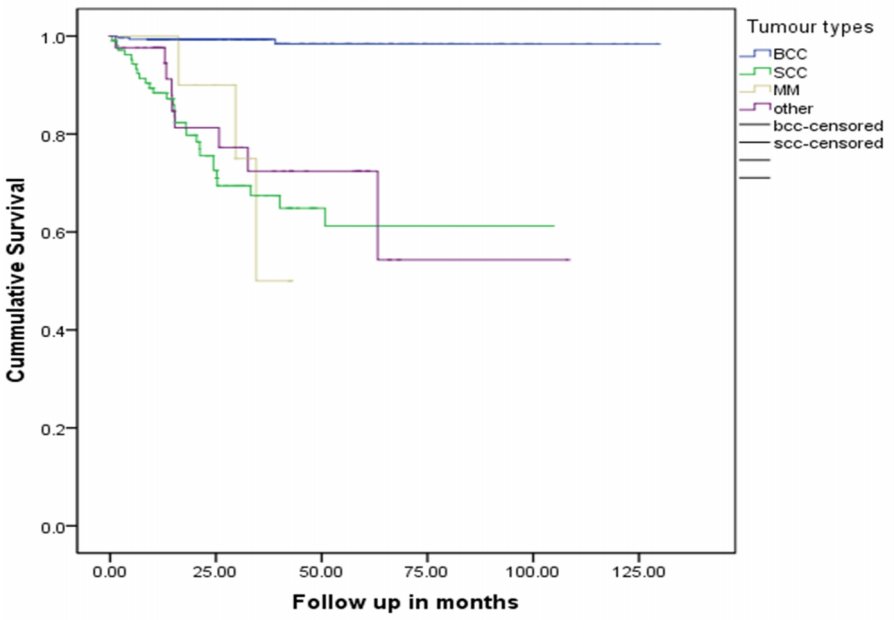

Fig. 1. Kaplan-Meier estimates of disease-specific survival in study cohort by tumour type

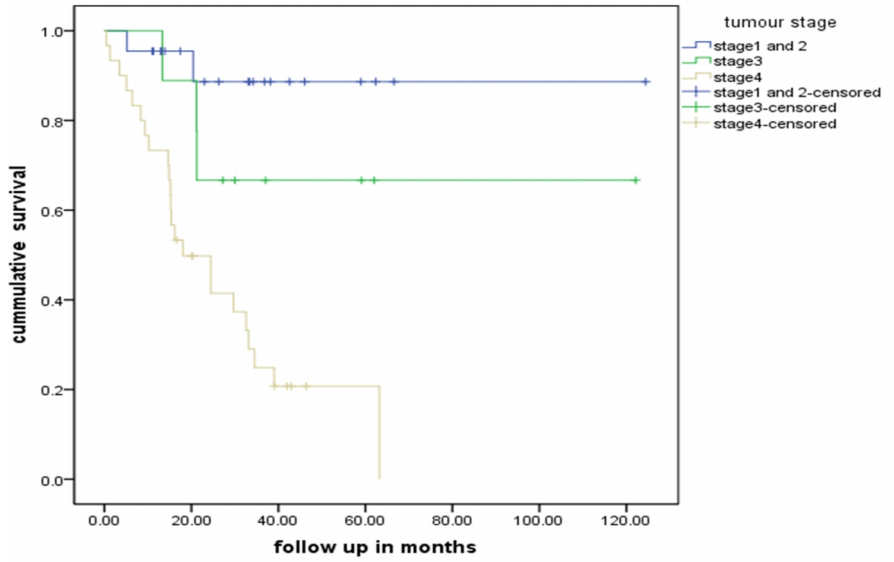

Fig. 2. Kaplan-Meier estimates of disease-specific survival in study cohort by tumor stage

tries is around 90% (16). Other reports from Europe estimates the 5-year survival rate of melanoma at around 70% (17) and in the United States the 5-year survival were 86.8% and 92.0 in men and women (18). In another review study, survival rates for malignant melanoma were 78% and 91% in men and women respectively (19). Our findings, therefore, of a 5 years survival of 50% for malignant melanoma indicate a significant gap with the international figures. A possible explanation for this finding is the late diagnosis (in stage III or IV) of the tumour that makes an effective treatment unlikely. Our finding that anatomical location of the tumour is an independent predictor of survival is in agreement with most of the literature on this subject. Studies from Netherlands (20), California USA (21), and United States (16) all showed that anatomical location of tumour is significantly associated with survival. Variation in survival according to the anatomical location of the tumour may result from a variation in tumour invasive behaviour in different body sites.

Our study showed that tumour type is an important predictor of survival (Fig.1). The difference originates from the tumour invasive behaviour and its ability to send distant metastasis. In our current study survival experience of patients with squamous cell carcinoma were worse than those having malignant melanoma while in other studies usually worst survival belongs to malignant melanoma. In a study from Denmark (22) and a retrospective cohort analysis (23) in general, relative survival after basal cell carcinoma was better than after squamous cell carcinoma.

In many countries mortality rates for non-melanoma skin cancer is very low (1). The possible explanation for our finding is the late diagnosis of patients having squamous cell carcinoma. While 50% of melanoma tumours were in stages I and II at the time of diagnosis, this figure was 18.5% for squamous cell carcinoma and the majority were diagnosed at stages III and IV (Table 1).

Tumour stage is a very important predictor of survival (Fig.2). The higher the stage of the tumour is at the time of diagnosis, the lower the survival. Our finding of the effect of stage on survival was in complete agreement with the existing literature (18,20,24).

Age was a significant predictor of survival in univariate analysis in our study. Similar findings have been reported by many researchers (18,20,25), although, some did not find any association between age, sex and survival (26). In the current study, men survived slightly longer than women although the association was not significant. There are other studies that have found similar results regarding gender, but the bulk of literature does not support this finding. In these studies, women have a longer survival than men (18-20,27-30).

Living in a rural area put people in a disadvantaged position regarding skin cancer survival. In the current study 44% of patients living in the urban areas were diagnosed in stage 1 and 2 while the corresponding figure for residents of rural areas was 27%. Access to the healthcare facilities and therefore delay in seeking medical attention could explain this difference. Risk of death was lower in literate people compared with illiterate that could also originate from delay in asking medical advice.

More than 24 months delay in diagnosis could double the risk although it did not reach statistical significance. Delay in diagnosis increases the stage of tumour at the time of diagnosis and therefore could be an important factor in survival. However we did not find any association between the two that might reflect the retrospective design of this study and subsequent limitations in collecting accurate information on the actual amount of delay time.

Our study has some strengths and limitations. Accurate recording of time and cause of death as we had access to registrar office in Kurdistan province and cross checked the information in our interviews. On the other hand, we were unable to ascertain stage in some patients as we could not access all necessary data. Furthermore we only followed those patients who had their contact details recorded in their registry file. This may result in exclusion of some disadvantaged people from our study. However, comparison between characteristics of interviewed subjects with the rest of the skin cancers registered in Kurdistan Cancer Registry (Table 4) showed no considerable difference between the two populations. Future studies with a prospective design could address this limitation and provide a more accurate estimate of survival.

Adopting some strategies towards prevention, and timely diagnosis and treatment could help reduce the burden of the disease particularly in rural areas. An important first step is a public education campaign about causes of skin cancer particularly in those who are exposed to sun light for long hours such as farmers. In any educational campaign in rural areas it is also helpful to get help from institutions which are not directly involved in heath matters but are an important point of access for farmers such

as those that provide agricultural advice and equipment. Educating women about ways of prevention and early signs of skin cancer is another important step particularly in rural areas. Finally, encouraging family physicians for timely referral of patients to specialist could help with effective treatment.

In summary our study showed that survival from skin cancer in Kurdistan province is worse than most global figures and therefore in need of urgent attention. We found that delay in diagnosis is an important contributor to this problem. Effective public health campaign about preventive measures particularly from sun exposure and early signs of disease for timely diagnosis and treatment could tackle the problem in long term and increase the survival indicators in Iranian patients.

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