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A RESEARCH STUDY ON GENERAL SURVIVAL EXAMINATION OF HEPATOID ADENOCARCINOMA OF THE LUNG

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Abstract:
Background: *We conduct this SEER (surveillance epidemiology and end result) database to illuminate the characteristics overall survival (OS) and prognosis of HAL. Hepatoid Adenocarcinoma of lung (HAL) is very rare and aggressive malignant tumor originated in the lungs. The exact features of the disease are still unclear because very less data available about this disease.*
Materials and Method: *Propensity score matching (PSM) was performed using the package in R, version 3.3.1 (R Foundation). We obtained this data from the SEER database between the years 2011 - 2016. Patient demographic and disease information statistics was compared by using the pearson chi-square test and binary logistic regression.*
Results: *In matched data we have HAC 42 patients and AC 208 Patients and following are the results. In the unmatched data there are some imbalances in the certain characteristics such as age at diagnosis, year of diagnosis, grade and surgery, there is no imbalances in the matched data. In unmatched data we have hepatoid adenocarcinoma of the lung (HAC) 42 patients and adenocarcinoma of the lung (AC) 111426 patients. The estimated OS time before propensity score matching (PSM) in HAC of the lung is 4 months and AC of the lung is 13 months, and the estimated OS time after PSM in HAC of the lung is also 4 months while AC of the lung is 9 months.*
Conclusion: *The OS of the disease before PSM and after PSM is very poor, most of the HAC of the lung patients present in the advance age, the gender ratio is almost same.*
Key words: *Overall Survival, Lung Cancer; Hepatoid Adenocarcinoma;*

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INTRODUCTION:

The WHO defines Hepatoid Carcinoma as an Adenocarcinoma with morphologic characteristics similar to Hepato-cellular carcinoma, arising anatomic site other than liver. Hepatoid adenocarcinoma is the term for number of uncommon or rare neoplasms in humans, named for visual resemblance for under the microscope to those of Hepato-cellular Carcinoma (HCC), the most common form of liver cancer. They can arise in different parts of body, and thus form sub-types of diseases such as stomach cancer and pancreatic cancer.

The interesting characteristics of this tumor, it has very close resemblance to Typical Hepato-cellular carcinoma (HCC) under the light microscope visual. Hepatoid Adenocarcinoma of lung (HAC) is very rare and aggressive malignant tumor originate in lungs. For differentiating the HAC from metastatic HCC need immunohistochemistry staining. The HAC was first described by Ishikura in 1990 [1]. HAC usually present as a large bulky solitary mass in the upper lobe. Prevalence is higher in males most of the patient are smokers. High levels of serum AFP is a distinguishing feature of this tumor. Nodal and the distant metastasis are common at initial presentation. Some tumors had component of signet ring cells and NEC instead of adenocarcinoma. Tumors with typical hyper vascular radiologic features coupled with Histopathologic staining features allow us to distinguish HAC of the lung from HCC [2-5]. In hepatoid adencarcinoma (HAC) Hep_Par stains positive and CEA staining along with the Hep-Par staining would be positive in a canalicular pattern. In HCC while Hep-par would stain positive, CK7 would be negative and CEA would stain positive in a canalicular pattern. If HAC present as only localized mass, tumor resection can have long term survival tyrosine kinase inhibitor to be use in chemotherapy according to some studies. Two diagnostic criteria for HAC include typical acinar or papillary adenocarcinoma and a component resembling HCC and expressing alpha fetoprotien.

Moreover some studies that have relatively large sample but they have data about other organs e.g. Hepatoid Adenocarcinoma of Stomach, pancrease etc. So we conduct this SEER (surveillance epidemiology and end result) database to illuminate the characteristics and prognosis of HAC of the Lung, our study have largest data until to date. Because it is a rare disease, no large sample reported so exact features and prognosis of the disease is still unclear.

MATERIALS AND METHOD:

Patient Population and Database:

For the every patient, the whole SEER data set was merged.The study protocol was approved by the institutional review board of The Affiliated Hospital of The Qinghai University. We obtained this data from the SEER database from the year 1973- 2016. We have total of 111426 patients diagnosed with lung adenocarcinoma or hepatoid adenocarcinoma in the SEER 2010-2015 unknown survival time 210 patients with known survival time 111216 patients among them 42 HAC patients and 111174 AC patients between 2010 and 2015 were identified from the SEER database. HAC 42 patients and AC 111174 patients from randomize selected from the total patients of AC 111426 in SEER database. And we defined the patient characteristics according to the age, gender, race, year of diagnosis, primary site, grade, laterality, tumor stage, T stage, N stage, M stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis and surgery.

Tumor Biology:

The patient tumor features including, grade, T stage, N stage, M stage, were obtained from the SEER database.

Treatment Variables:

Based on the information from SEER database treatment given to the patients was unclear.

Statistical analysis:

The overall survival (OS) measured from the time of diagnosis to death. All survival analyses included patients diagnosed between 2010 and 2015 with survival information. Statistical analysis Patient demographic and disease information was compared using the Pearson chi-square test and binary logistic regression.

Propensity Score Matching:

In brief, the based on baseline characteristics (age, gender, race, year of diagnosis, primary site, grade, laterality, tumor stage, T stage, N stage, M stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis, surgery) was calculated using logistic regression, which generated a propensity score for HAC and AC of each patient. Propensity score weighting was performed to account for selection bias by creating a control cohort matched to have similar representation with regard to baseline features. Statistical analysis was performed using SPSS statistical software (version 21; IBM Corporation, Armonk, NY) and STATA SE 12.0 (Stata Corp LP, College Station, Tex). *P* values <0.05 were considered to be statistically significant. Propensity score matching was performed using the package in R, version 3.3.1 (R Foundation). Balance

in the baseline covariates after matching was examined using standardized differences. An absolute standardized difference less than 0.1 implies and adequate match. Balance in baseline variables as also evaluated match using likelihood ratio test following conditional logistic regression modeling of the management approach HAC and AC of lung in the matched data.

Survival Data Analysis:

A log-rank test stratified on matched patients was used to compare survival in both groups. We used the Kaplan-Meier curves to estimate the overall survival from the time of diagnosis in the HAC and AC of lung groups in the matched data. The OS was evaluated using a Cox proportional hazards model stratified on matched patients. We also estimated the treatment effect using a Cox regression model within each level of covariate. The following covariates were evaluated age, gender, race, year of diagnosis, primary site, grade, laterality, tumor stage, T stage, N stage, and M stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis, surgery.

RESULTS

Unmatched Data Characteristics:

Table 1. Clinicopathologic features of the study population beforepropensity score matching

Variable	HAC (n=42)	AC (n=111174)	*P value*
Age at diagnosis (years)			**0.002**
15-19	0 (0.0%)	3 (0.0%)	
20-39	2 (4.8%)	625 (0.6%)	
40-59	13 (31.0%)	22606 (20.3%)	
60-79	23 (54.8%)	67397 (60.6%)	
>80	4 (9.5%)	20543 (18.5%)	
Gender			**0.890**
Male	54129 (48.7%)	20 (47.6%)	
Female	57045 (51.3%)	22 (52.4%)	
Race			**0.769**
White	34 (81.0%)	87616 (78.8%)	
Black	6 (14.3%)	13326 (12.0%)	
Other	2 (4.8%)	9994 (9.0%)	
Unknown	0 (0.0%)	238 (0.2%)	
Year			**0.004**
2010	8 (19.0%)	16750 (15.1%)	
2011	3 (7.1%)	17873 (16.1%)	
2012	1 (2.4%)	18439 (16.6%)	

2013	5 (11.9%)	18955 (17.0%)	
2014	15 (35.7%)	19474 (17.5%)	
2015	10 (23.8%)	19683 (17.7%)	
Primary site			**0.606**
Upper lobe	21 (50.0%)	58192 (52.3%)	
Middle lobe	1 (2.4%)	4941 (4.4%)	
Lower lobe	9 (21.4%)	28708 (25.8%)	
Main bronchus	2 (4.8%)	2773 (2.5%)	
Overlapping lesion	0 (0.0%)	950 (0.9%)	
Unknown	9 (21.4%)	15610 (14.0%)	
Grade			**<0.001**
Unknown	29 (69.0%)	54146 (48.7%)	
Well differentiated	0 (0.0%)	8097 (7.3%)	
Moderately differentiated	0 (0.0%)	21394 (19.2%)	
Poorly differentiated	11 (26.2%)	26994 (24.3%)	
Undifferentiated	2 (4.8%)	543 (0.5%)	
Laterality			**0.055**
Left	16 (38.1%)	42691 (38.4%)	
Right	21 (50.0%)	62876 (56.6%)	
Paired site	4 (9.5%)	3774 (3.4%)	
Only one side - side unspecified	1 (2.4%)	368 (0.3%)	
Bilateral	0 (0.0%)	1429 (1.3%)	
Not a paired site	0 (0.0%	36 (0.0%)	
Tumor stage (AJCC 6th ed.)			0.073
Stage I	2 (4.8%)	24924 (22.4%)	
Stage II	2 (4.8%)	3849 (3.5%)	
Stage III	12 (28.6%)	24013 (21.6%)	
Stage IV	26 (61.9%)	54181 (48.7%)	

OCCULT	0 (0.0%)	997 (0.9%)	
UKN Stage	0 (0.0%)	3210 (2.9%)	
T-stage			**0.027**
T0	1 (2.4%)	648 (0.6%)	
T1	3 (7.1%)	26423 (23.8%)	
T2	8 (19.0%)	29245 (26.3%)	
T3	3 (7.1%)	4216 (3.8%)	
T4	22 (52.4%)	40367 (36.3%)	
TX	5 (11.9%)	10275 (9.2%)	
N-stage			**0.227**
N0	17 (40.5%)	45355 (40.8%)	
N1	1 (2.4%)	8537 (7.7%)	
N2	11 (26.2%)	35480 (31.9%)	
N3	10 (23.8%)	14592 (13.1%)	
NX	3 (7.1%)	7210 (6.5%)	
M-stage			**0.177**
M0	16 (38.1%)	54478 (49.0%)	
M1	26 (61.9%)	54181 (48.7%)	
M2	0 (0.0%)	2515 (2.3%)	
Bone metastasis			**0.834**
Yes	11 (26.2%)	23377 (21.0%)	
No	30 (71.4%)	83457 (75.1%)	
Unknown	1 (2.4%)	4266 (3.8%)	
N/A	0 (0.0%)	74 (0.1%)	
Brain metastasis			**0.559**
Yes	9 (21.4%)	15679 (14.1%)	
No	32 (76.2%)	90978 (81.8%)	
Unknown	1 (2.4%)	4433 (4.0%)	
N/A	0 (0.0%)	84 (0.1%)	

Liver metastasis			**0.872**
Yes	5 (11.9%)	9522 (8.6%)	
No	35 (83.3%)	97041 (87.3%)	
Unknown	2 (4.8%)	4523 (4.1%)	
N/A	0 (0.0%)	88 (0.1%)	
Lung metastasis			**0.816**
Yes	9 (21.4%)	18235 (16.4%)	
No	31 (73.8%)	87835 (79.0%)	
Unknown	2 (4.8%)	4771 (4.3%)	
N/A	0 (0.0%)	333 (0.3%)	
Surgery			**0.004**
Not recommended	38 (90.5%)	76821 (69.1%)	
Not recommended, contraindicated due to other cond	1 (2.4%)	4885 (4.4%)	
Not performed,patient died prior to recommended surgery	0 (0.0%)	197 (0.2%)	
Surgery performed	2 (4.8%)	25748 (23.2%)	
Recommended, unknown if performed	1 (2.4%)	256 (0.2%)	
Recommended but not performed	0 (0.0%)	2861 (2.6%)	
Recommended but not performed, unknown reason	0 (0.0%)	406 (0.4%)	

Abbreviations: AC=adenocarcinoma, HAC=hepatoid adenocarcinoma, AJCC=American Joint Committee on Cancer, N/A=not available.

Table 2. Clinicopathologic features of the study population after 1:5 propensity score matching

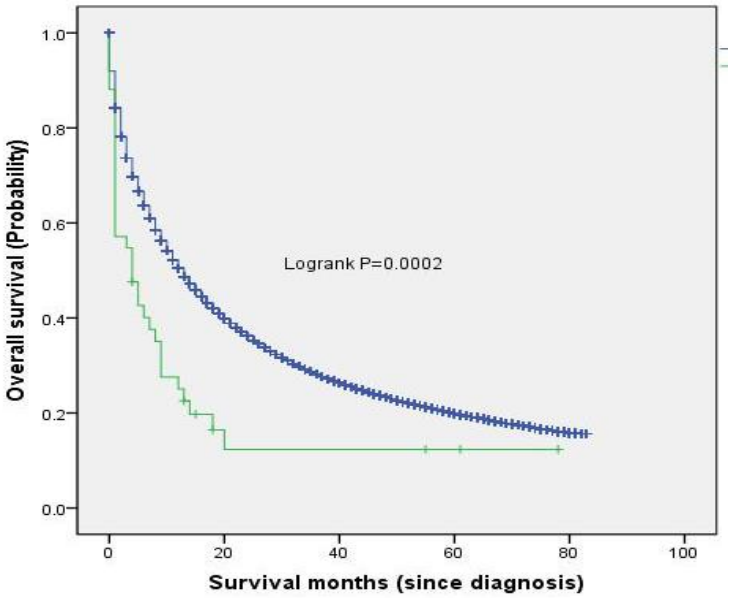
Variable	**HAC (n=42)**	**AC (n=210)**	***P value***
Age at diagnosis (years)			**0.3291**
20-39	2 (4.8%)	5 (2.4%)	
40-59	13 (31%)	76 (36.2%)	

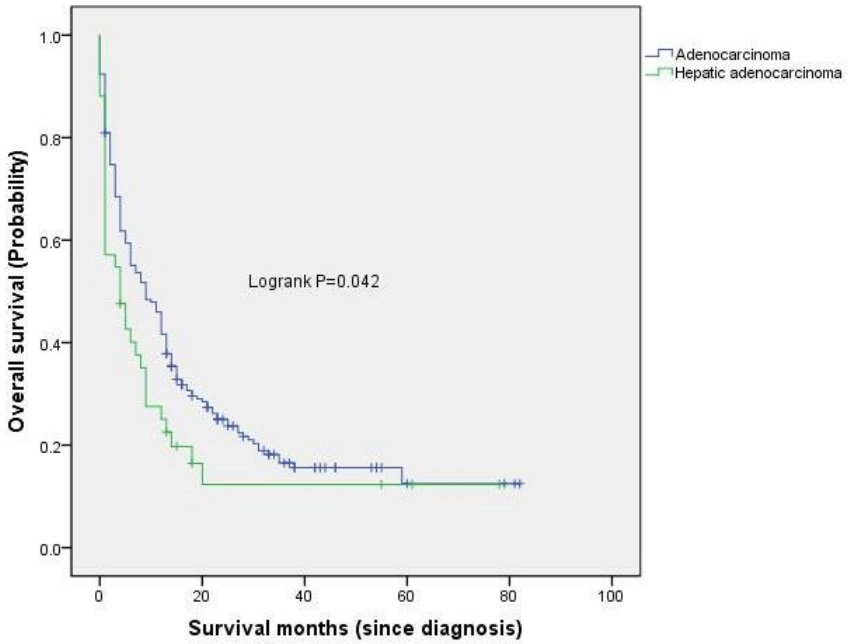
60-79	23 (54.8%)	121 (57.6%)	
>80	4 (9.5%)	8 (3.8%)	
Gender			**1.000**
Male	20 (47.6%)	99 (47.1%)	
Female	22 (52.4%)	111 (52.9%)	
Race			**0.9009**
White	34 (81%)	173 (82.4%)	
Black	6 (14.3%)	30 (14.3%)	
Other	2 (4.8%)	7 (3.3%)	
Year			**0.0899**
2010	8 (19%)	28 (13.3%)	
2011	3 (7.1%)	22 (10.5%)	
2012	1 (2.4%)	21 (10%)	
2013	5 (11.9%)	44 (21%)	
2014	15 (35.7%)	40 (19%)	
2015	10 (23.8%)	55 (26.2%)	
Primary site			**0.8703**
Upper lobe	21 (50%)	102 (48.6%)	
Middle lobe	1 (2.4%)	12 (5.7%)	
Lower lobe	9 (21.4%)	51 (24.3%)	
Main bronchus	2 (4.8%)	8 (3.8%)	
Unknown	9 (21.4%)	37 (17.6%)	
Grade			**0.0616**
Poorly differentiated	11 (26.2%)	63 (30%)	
Undifferentiated	2 (4.8%)	1 (0.5%)	
Unknown	29 (69%)	146 (69.5%)	

Laterality			**0.5029**
Left	16 (38.1%)	71 (33.8%)	
Right	21 (50%)	122 (58.1%)	
Paired site	4 (9.5%)	16 (7.6%)	
Only one side - side unspecified	1 (2.4%)	1 (0.5%)	
Tumor stage (AJCC 6th ed.)			**0.9295**
Stage I	2 (4.8%)	16 (7.6%)	
Stage II	2 (4.8%)	9 (4.3%)	
Stage III	12 (28.6%)	60 (28.6%)	
Stage IV	26 (61.9%)	125 (59.5%)	
T-stage			**0.2316**
T0	1 (2.4%)	0 (0%)	
T1	3 (7.1%)	29 (13.8%)	
T2	8 (19%)	31 (14.8%)	
T3	3 (7.1%)	12 (5.7%)	
T4	22 (52.4%)	109 (51.9%)	
TX	5 (11.9%)	29 (13.8%)	
N-stage			**0.3125**
N0	17 (40.5%)	68 (32.4%)	
N1	1 (2.4%)	21 (10%)	
N2	11 (26.2%)	73 (34.8%)	
N3	10 (23.8%)	38 (18.1%)	
NX	3 (7.1%)	10 (4.8%)	
M-stage			**0.9085**
M0	16 (38.1%)	85 (40.5%)	
M1	26 (61.9%)	125 (59.5%)	

Bone metastasis			**0.7978**
Yes	11 (26.2%)	62 (29.5%)	
No	30 (71.4%)	140 (66.7%)	
Unknown	1 (2.4%)	8 (3.8%)	
Brain metastasis			**0.5561**
Yes	9 (21.4%)	31 (14.8%)	
No	32 (76.2%)	173 (82.4%)	
Unknown	1 (2.4%)	6 (2.9%)	
Liver metastasis			**0.6864**
Yes	5 (11.9%)	17 (8.1%)	
No	35 (83.3%)	185 (88.1%)	
Unknown	2 (4.8%)	8 (3.8%)	
Lung metastasis			**0.7865**
Yes	9 (21.4%)	36 (17.1%)	
No	31 (73.8%)	165 (78.6%)	
Unknown	2 (4.8%)	9 (4.3%)	
Surgery			**0.3557**
Not recommended	38 (90.5%)	178 (84.8%)	
Not recommended, contraindicated due to other cond	1 (2.4%)	11 (5.2%)	
Surgery performed	2 (4.8) %	20 (9.5%)	
Recommended, unknown if performed	1 (2.4) %	1 (0.5%)	

Abbreviations: AC=adenocarcinoma, HAC=hepatoid adenocarcinoma, AJCC=American Joint Committee on Cancer, N/A=not available.





According tumor stage variable most of the patients presented in advance stage. According to laterality variable the right side is affected mostly HAC (50.0%) and AC (56.6%) see the (Table 1). We compared the patient characteristics between the two groups HAC (n=42) and AC (n=111174) of the lung. In the unmatched data of the HAC have more patients in younger age <60 than AC at the time of diagnosis HAC (35.8%) and while AC (20.9%) and the *(P =0.002)*. The poorly differentiated grade HAC (26.2%) and AC (24.3%) have more patients and the

（P <0.001）. The surgery did not performed in most of the patients HAC (92.9%) and AC (73.7%) and the *(P = 0.004)*. In the racial variable there is more white patients HAC (81.0%) and AC (78.8%). According to primary site involvement upper lobe is the most involved site HAC (50.0%) and AC (52.3%).

Survival of Unmatched Data:
The estimated OS time in HAC is 4 months and 13 months in AC of the lungs and in AC (95% CI 12.824 – 13.176) in HAC (95% CI 0.000 – 8.156). The OS curve showed no significant difference between two groups see the (fig1).

Matched Data CharacteristicsIn the matched data comparison we have HAC (n=42) and AC (n=210) of the lung, there is no imbalances in the characteristics such as age at diagnosis, gender, race, year, primary site, grade, laterality, tumor stage, T stage, N stage, M stage, bone metastasis, brain metastasis, lung metastasis, liver metastasis, surgery see (table 2).

Survival of Matched Data:
After the PSM analysis showed no significant difference in OS. The estimated time of the OS in HAC of lung is 4 months and 9 months in AC of lung. The OS curve showed no significant difference before and after PSM. The AC (95% CI 5.969 – 12.031) and HAC (95% CI 0.000 – 8.156) see figure (fig.2).

DISCUSSION:

In the previous studies there is little or no data available about the overall survival (OS) of the HAC of lung. No large studies discussed the OS because they did not have the large data, the largest case report study only have the data about 20 patients. The HAC of the lung is a rare disease so very less information available about this, there are only few case report studies present about the HAC of the lung, so there is a lot of ambiguity about the clinical signs, symptoms, diagnosis and treatment, also the disease process is unclear. In our study have relatively large data so we discuss the different characteristics and the OS of disease with the data obtained from the SEER database. The diagnostic criteria of the disease, include typical acinar or papillary adenocarcinoma, signet-ring cells or neuroendocrine carcinoma and expressing the alpha feto proteins[2-5]. Different studies proposed the different immunohistochemical markers for diagnosis. According to some studies the morphologic features of the HAC of lung are remarkably similar to HCC [6-8]. Exclusion of metastatic HCC was clinically relevant because both hepatitis B,C patients were at risk to develop HCC and lung is the most common site for extrahepatic metastasis. However, CT scans showed no liver masses in both hepatitis B,C patients and the immunophenotypic signature was inconsistent with HCC [9-11]

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In our study we try to assess the OS with the use of certain variable such as age, gender, race, year of diagnosis, primary site, grade, laterality, tumor stage, T stage, N stage, M stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis, and the surgical treatment. Our data showed HAC of the lung have younger patient than the AC of lung, and the upper lobe is the most affected part in both of the groups. Most of the patients have unknown grade, the right side of lung have significant population involvement in both groups. And data also showed the most of the patients present in advance stage, many patients did not had bone metastasis or brain metastasis in both of the groups and very less number of patients were presented with the liver metastasis and the lung metastasis in both groups, many did not performed the surgery due to different reason. With the comparison to the other studies we discussed the OS of HAC of the lung but the previous studies just talked about the general features of the disease and very less information of OS is available. In the world literature HAC of lung have 16 cases report, in which all the patients were only men with large tumor, the majority of patients were presented in advanced stage disease and progression of the stage was common with the poor prognosis [12]. Some studies also suggested that the poor prognosis of HAC of lung is due to the production of AFP, which bear the characteristics of immunosuppression.
However, various studies also suggested about the survival advantage of adjuvant chemotherapy for stage IB patients [13], and one study indicated that in early stage patients radical surgery may significantly increase the cure rate [14-16]. In HAC of various organs studies have shown following suggestions, the poor prognosis is associated with the predominant advance stage at the time of diagnosis, in the literature the survival data about 83 cases of different organs of HAC shown, 43 patients were died within the first 12 months, while the other 40 patients were alive for more than 12 months. The estimated 12 months survival rate was based on about 55% which was comparable with 40% presented by Hoshida et al [17,18]. In HAC of the ovary and endometrium the OS was slightly better, although due to less number of cases the differences were not significant statistically. In HAC of stomach after the surgery survival varied from days to 1.5 year [19-21]. So there is no such study available with the large data which had discussed about the OS of HAC of the

lung, only the current study have the relatively large data until to date.

Those patients who did not received any chemotherapy/Radiotherapy and those patients whose chemotherapy/Radiotherapy information did not recorded. The limitation of our study include, similar to the other retrospective study, lack of some information in SEER database no large, lack of some treatment information such as particular chemotherapy, the disease progression and relapse time, the pattern of treatment after the disease progression, gene mutation, and use of tobacco etc.

CONCLUSION:

Our study has the important information about the OS which will also help the future studies. Most of the HAC of the lung patients present in the advance age, the ratio of the both gender almost the same, the OS of the disease before PSM and after PSM is very poor.

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Conflict of interest:

There was no conflict of interest declared by the authors.

Informed consent:

The basics of this study and evaluation are on the data obtained from surveillance epidemiology end result so consent was taken.

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