Effect Of Prior Cancer History on The Survival of Gallbladder Cancer Patients: A Propensity Score Matching Study Based on The SEER Database

Jie Ren

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Wei Liu

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Qinglin Li

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Ruixia Cui

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Yingmu Tong

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Kai Qu

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Chang Liu

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery

Jingyao Zhang (✉ you12ouy@163.com)

Xi'an Jiaotong University Medical College First Affiliated Hospital Department of Hepatobiliary Surgery
<https://orcid.org/0000-0002-8227-9396>

Research article

Keywords: Gallbladder cancer, Second primary cancer, Overall survival (OS), PSM (propensity score matching), Gallbladder cancer-specific survival (GCSS).

Posted Date: December 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-115865/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: The effect of previous malignancy history on the survival of individuals with a second primary gallbladder cancer remains unclear. Therefore, this study was conducted to analyze the impact of previous malignancy history on the survival of individuals with gallbladder cancer and to compare the prognostic differences between gallbladder cancer patients with and without previous cancer.

Methods: Extract the United States Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2015 for cases diagnosed with gallbladder cancer. The Kaplan-Meier curves and log-rank test were used to compare the survival difference between gallbladder cancer individuals with and without previous malignancy. Cox proportional hazards regression model was used to explore the risk factors of gallbladder cancer.

Results: A total of 5861 patients with gallbladder cancer were enrolled, including 5622 (95.9%) patients without prior primary cancer and 239 (4.1%) patients with prior primary cancer. Patients with gallbladder cancer with prior primary malignancy were older, and the tumors were at localized and regional stages more frequently and more early stages. The Kaplan-Meier curves showed that gallbladder cancer patients with prior cancer had better overall survival (OS) ($P=0.027$) and gallbladder cancer-specific survival (GCSS) ($P<0.001$) before propensity score matching (PSM), and gallbladder cancer patients with prior cancer had better GCSS ($P<0.001$), and there was no difference in OS ($P=0.113$) between gallbladder cancer patients with and without prior cancer after PSM. Multivariable cox regression analysis revealed that prior malignancy history was not a risk factor for OS ($HR=0.875$, 95%CI: 0.752-1.018, $P=0.084$), but it was beneficial to GCSS ($HR=0.404$, 95%CI: 0.318-0.513, $P<0.001$).

Conclusions: Gallbladder cancer individuals with previous primary malignancy have different clinical characteristics from those without previous primary malignancy. Gallbladder cancer patients with previous primary malignancy have better progress than those without previous malignancy.

Background

Gallbladder cancer is a malignant tumor with a high mortality rate. According to Global Cancer Statistics 2018, based on 185 countries, there were 210,000 new patients of gallbladder cancer in the world in 2018, accounting for 1.2% of all new cancer cases. However, global deaths from gallbladder cancer reached 160,000, accounting for 1.7% of deaths in 2018. ^[1]

Due to the aging population, early diagnosis, treatment and improvements in life support, there are more and more cancer patients. By 2040, the number of cancer patients is expected to reach 26 million. ^[2-4] With the increase in the number of cancer survivors and the extension of lifespan, it is very likely that they will suffer from a second type of primary malignant cancer during their survival, but at present, little is known about the clinical features of the second primary gallbladder cancer. Currently, the level of diagnosis and treatment of gallbladder cancer continues to increase. Because gallbladder cancer

individuals with previous cancer history are usually excluded from gallbladder cancer research, the impact of previous malignancy history on the survival of individuals with gallbladder cancer is not clear.

Therefore, the main purposes of this study are to describe the clinical features of the second primary gallbladder cancer and explore the impact of previous malignancy history on the survival of individuals with gallbladder cancer.

Methods

Statistics collection

Extract the general data, clinical data, pathological data and follow-up data of all gallbladder cancer individuals in the United States Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2015, including age, sex, race, marital status, histology, cancer stage, cancer grade, therapy, survival status, cause of death, survival months, sequence number. Combining the sequence number can determine the types of prior cancer.

Inclusion and exclusion criteria

Include patients older than 18 years of age; select "positive histology" to ensure correct diagnosis; select data with complete survival time in the survival month flag; select "active follow-up" to ensure the effectiveness of follow-up; and remove cases obtained from autopsies and only death reports.

Statistical analysis

In the baseline data comparison between gallbladder cancer patients with and without prior cancer, the t test or Mann-Whitney U test was used for measurement of data; the chi-square test or Mann-Whitney U test was used for count data; and the Mann-Whitney U test was used for grade data. After that, the 1-year and 5-year Overall mortality (OM) and 95% confidence intervals of patients with gallbladder cancer with and without prior cancer and gallbladder cancer with prior different primary cancers were calculated. OM was defined as death for any reason. With a matching tolerance of 0.00005, age, sex, race, cancer stage, cancer grade, surgery, radiation, and chemotherapy and et.al were used as covariates to conduct 1:1 propensity score matching on the baseline data of patients with gallbladder cancer with and without prior cancer. The Kaplan-Meier curves and log-rank test were used to compare the survival difference between gallbladder cancer individuals with and without previous malignancy before and after PSM. The Cox proportional hazards regression model was also used to compare the OS and GCSS to reveal the impact of the previous primary malignancy on the survival of gallbladder cancer individuals. OS was defined as the time from diagnosis of gallbladder cancer to death from any cause; GCSS was defined as the time from diagnosis of gallbladder cancer to death from gallbladder cancer. Finally, a subgroup analysis was performed, and then the Cox proportional hazards regression model was used to compare OS and GCSS to explore the effect of prior different primary cancer on the survival of patients with gallbladder cancer.

SPSS22.0 (IBM Corp., Armonk, NY) was used for statistical analysis, and bilateral P values <0.05 were considered statistically significant.

Results

Patient baseline statistics

A total of 5861 cases with gallbladder cancer were enrolled, including 5622 (95.9%) patients without prior primary cancer and 239 (4.1%) patients with prior primary cancer. Table 1 shows the comparison of baseline statistics between the two groups. Patients with gallbladder cancer with prior primary cancer were older, with a greater proportion of people aged ≥ 65 years (76.6% VS 64.0%, $P<0.001$). The tumors were more localized and regional according to the SEER stage, and the AJCC(American Joint Committee on Cancer) stage was at more early stages. In terms of treatment, gallbladder cancer patients with prior primary cancer received less chemotherapy (29.3% VS 36.2%, $P=0.028$).

Fig. 1 shows the SEER stage and AJCC stage of the gallbladder cancer patients with and without prior primary cancer. Fig. a and Fig. b show the SEER stages of the patients with gallbladder cancer with and without prior primary cancer. Localized, regional, and distant stages accounted for 16.7%, 59.8%, and 23.4% and 11.6%, 53.0%, and 35.4%, respectively. Fig. c and Fig. d shows the AJCC stages of patients with gallbladder cancer with and without prior primary cancer. AJCC stages I, II, III, and IV accounted for 44.8%, 33.1%, 1.7%, and 20.5% and 32.6%, 34.3%, 2.7%, and 30.4%, respectively.

Prior primary cancer and interval time

As Table 2 shows, among those with prior primary cancer, 59 had gastrointestinal cancer, 51 had prostate cancer, 49 had breast cancer, 42 had urogenital cancer, 11 had lung cancer, and 27 had other types of cancer. The median time from the prior prostate malignancy diagnosis to the subsequent diagnosis of gallbladder cancer was the longest (45.04 months), while the median time from the prior gastrointestinal malignancy diagnosis to the subsequent diagnosis of gallbladder cancer was the shortest (21.47 months), with the rest ranging from 25.00 to 37.80 months (Fig. 2).

Comparison of mortality in gallbladder cancer patients with and without prior cancer

The 1-year overall mortality and 5-year overall mortality of gallbladder cancer individuals without prior primary cancer was 64.6% and 97.1%, respectively, and 58.0% and 95.5%, respectively, of gallbladder cancer individuals with previous malignancy. The gallbladder cancer individuals without previous primary malignancy had higher 1-year overall mortality and 5-year overall mortality.

The 1-year OM of gallbladder cancer individuals with previous primary lung malignancy was the highest (77.8%), while the 1-year OM of gallbladder cancer individuals with previous gastrointestinal malignancy was the lowest (46.3%). The gallbladder cancer individuals with previous lung malignancy and genitourinary malignancy had the highest 5-year OM (100%), while the individuals with gallbladder cancer with previous gastrointestinal malignancy had the lowest 5-year OM (87.8%) (Table 3).

Propensity Score Matching (PSM)

Table 4 shows the results of 1:1 PSM for patients with gallbladder cancer with and without prior primary cancer. After PSM, the characteristics were no longer significantly different.

Comparison of OS and GCSS in gallbladder cancer individuals with and without previous malignancy

The Kaplan-Meier curves showed that gallbladder cancer individuals with prior cancer had greater OS than those without prior cancer ($P=0.027$, Fig. a) before PSM, although the Kaplan-Meier curves had a cross after 100 months. Individuals with gallbladder cancer with previous malignancy also had a greater GCSS ($P<0.001$, Fig. b) before PSM.

After PSM, the OS and GCSS of the two groups were compared again. The Kaplan-Meier curves showed that there were no significant differences in OS between patients with gallbladder cancer with and without prior cancer ($P=0.113$, Fig. c), and patients with gallbladder cancer with prior cancer also had a greater GCSS ($P<0.001$, Fig. d).

Multivariate analyses of OS and GCSS

To analyze the risk factors of OS and GCSS of the second primary gallbladder cancer, we also conducted a multivariable Cox regression analysis. After incorporating various variables into the model, it was found that the prior history of cancer did not affect OS ($HR=0.875$, 95%CI: 0.752-1.108, $P=0.084$). A history of cancer before gallbladder cancer was a protective factor with regard to GCSS ($HR=0.404$, 95%CI: 0.318-0.513, $P<0.001$) (Table 5).

Subgroup analysis stratified by types of prior cancer

To explore the effects of prior different cancers on the OS and GCSS of patients with gallbladder cancer, we also conducted a subgroup analysis: prior gastrointestinal cancer was a favorable factor for OS ($HR=0.675$, 95%CI: 0.496-0.918, $P=0.012$) and GCSS ($HR=0.158$, 95%CI: 0.079-0.316, $P<0.001$); prior prostate cancer was a favorable factor for GCSS ($HR=0.486$, 95%CI: 0.301-0.785, $P=0.003$); prior breast cancer was a favorable factor for GCSS ($HR=0.579$, 95%CI: 0.376-0.889, $P=0.013$); prior genitourinary cancer was a favorable factor for GCSS ($HR=0.579$, 95%CI: 0.376-0.889, $P=0.013$); and prior lung cancer was an adverse factor for overall survival ($HR=2.248$, 95%CI: 1.167-4.331, $P=0.015$) (Table 6).

Discussion

Previously, few studies have included individuals with a prior history of malignancy within the scope of oncology research^[5-9]. With the increasing malignancy survivors and the extension of lifespan, it is very likely that they will suffer from a second primary cancer during their lifetime. The study by Sheng-Hsuan Chien et al. found that compared with normal people, the risk of patients with non-Hodgkin's lymphoma suffering from a second primary cancer was 10 times higher than that of normal people^[10]. The study by Chang-Hsien Lu et al. found that a prior history of thyroid cancer was related to a 33% increase in the risk

of a second primary cancer^[11]. Therefore, excluding cancer survivors from the scope of oncology research, these excessively strict inclusion and exclusion criteria have decreased the number of cancer patients who were originally eligible to participate in clinical trials, prolonged the research time, and affected the promotion of research results. At the same time, the number of cancer survivors is increasing, and the exclusion of this population in oncology research also makes the monitoring and treatment of cancer survivors a problem. To our knowledge, there is no research focused on the second primary gallbladder cancer. Therefore, this study intended to explore the effect of the previous primary malignancy on the second gallbladder cancer, providing a reference for solving this problem.

Our study found that the incidence of second gallbladder cancer was 2.7% at age ≥ 65 years, and the incidence was 4.8% at age ≥ 65 years, indicating that a second primary gallbladder cancer is more common in the elderly, which suggests that this group should receive more attention; this result is consistent with previous studies^[5, 12-16]. As far as prior types of primary cancer, the three most common were gastrointestinal cancer, prostate cancer, and breast cancer, and the interval time of diagnosis was also different. This is because on the one hand, patients with prior cancer receive more frequent examinations of the large intestine, prostate, and breast^[17]; on the other hand, it may be related to the good prognosis of prostate cancer and breast cancer, and their survival time is longer and more likely to suffer from SPM^[18-19]. More research is needed to provide a reference for the interval time surveillance of the second primary gallbladder cancer.

Patients with gallbladder cancer with previous malignancy had lower 1-year overall mortality and 5-year overall mortality than individuals with gallbladder cancer without previous malignancy. Except for lung cancer, the individual with gallbladder cancer with a different previous malignancy had a lower 1-year mortality than those without prior cancer. This may be related to the high mortality of lung cancer^[15,20]. There was no significant difference in 5-year mortality.

The Kaplan-Meier curves showed that gallbladder cancer individuals with previous cancer had better OS and GCSS. After PSM, there was no difference in OS, but individuals with gallbladder cancer with prior cancer had better GCSS. This result was consistent with previous studies. Research by Lanjuan Li et al. showed that the prior history of cancer did not cause worse OS and liver cancer-specific survival in individuals with second primary HCC^[12]. The same was true in studies of pancreatic cancer^[13-14], stage IV lung cancer^[15], and nasopharyngeal cancer^[16]. However, in the study of other cancers, the opposite results were found. Angel López-Encuentra et al. found that the prior cancer history was a risk factor for survival of stage I non-small cell lung cancer^[18]. A study by Fei Ji et al. found that breast cancer individuals with previous malignancy had worse OS and cancer-specific survival^[19]. A study by Kathryn T. Dinh et al. found that a previous cancer history made the OS of individuals with second primary prostate cancer worse^[20]. Adi Nosrati et al. found that a history of previous malignancy promoted the conversion of a single melanoma to multiple melanomas^[21]. Subsequent multivariable Cox regression analysis also proved our hypothesis. After incorporating each variable into the model, it was found that the previous history of malignancy was not a risk factor for OS in the individuals with a second primary

gallbladder cancer, but it was beneficial to GCSS. A reasonable explanation is that the cancer is at a localized or regional stage and the AJCC stage is early in more than 80% of gallbladder cancer patients with prior cancer, which is also consistent with previous studies ^[12-16]. Because of a prior history of cancer, patients will be reviewed more frequently, which will help with the early detection of a second primary gallbladder cancer and will reduce smoking and alcohol intake. Studies have shown that smoking and drinking are risk factors for the second primary cancer ^[22-24]. Tobacco is an inducer, and alcohol is an accelerator. The two have a synergistic effect and jointly promote the progress of a second primary malignancy ^[24].

To explore the impact of prior different types of primary malignancy on the survival of individuals with a second gallbladder cancer, we also conducted a subgroup analysis. Our study found that the history of gastrointestinal cancer is more beneficial to OS and GCSS in patients with a second primary gallbladder cancer. A history of prostate cancer, breast cancer or genitourinary cancer is a protective factor for GCSS in patients with a second primary gallbladder cancer; a history of lung cancer is the risk factor for OS in patients with a second primary gallbladder cancer. This result is consistent with the results of the previous multivariate analysis. The combination of the previous primary cancer will promote patient follow-up and re-examination, which is conducive to the early detection and early treatment of the second primary gallbladder cancer; therefore, it is conducive to OS or GCSS ^[12-16]. However, due to the high mortality rate of lung cancer, it is not conducive to OS ^[15,18].

This study has some limitations. First, because data from a database were used, the data obtained were limited to the data available in the database. The SEER database cannot obtain the laboratory tests, imaging, etiology information, and comorbid diseases of patients, which are essential for survival analysis. Second, although the total number of patients with gallbladder cancer is large, the number of individuals with some types of previous malignancy is very small, which may affect the corresponding subgroup analysis. Therefore, more sample sizes are needed to verify the accuracy of the conclusions.

Conclusions

In short, patients with gallbladder cancer with prior primary cancer have different clinical characteristics from those without prior primary malignancy. Individuals with a second primary gallbladder cancer have no significant difference in OS compared to those without previous malignancy, but they have a better GCSS. Further research is needed to verify our study and explore the molecular principles involved. Thus, gallbladder cancer patients with prior cancer exhibit better progress than those without prior cancer.

Abbreviations

SEER, Surveillance, Epidemiology, and End Results database; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; OM, Overall mortality; OS, Overall survival; GCSS, Gallbladder cancer specific survival; PSM, Propensity score matching; HR, Hazard ratio; CI, Confidence interval; GradeⅠ, well differentiated; GradeⅡ, moderately differentiated; GradeⅢ, poorly differentiated; GradeⅣ, undifferentiated.

Declarations

Ethics approval and consent to participate: This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University prior to commencing this study . The research data comes from a database, informed consent to participate in the study was not deemed necessary.

Consent for publication: Not applicable.

Availability of data and material: The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests: We declare that there is no conflict of interest regarding the publication of this article.

Funding: None

Authors' contributions:

Ren J participated in the research design, data analysis and writing of the paper; Liu W participated in the data analysis; Li QL participated in the data analysis; Ren J, Liu W and Li QL contributed equally to this work. Cui RX and Tong YM participated in revising of the paper; Qu K participated in research design and revising of the paper. Liu C and Zhang JY provided substantial advice in designing the study and assisting in the division of labor, writing and revising the paper.

Acknowledgements: We are indebted to all individuals who participated in or helped with this research project.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492Cancer Treatment and Survivorship Statistics, 2019
2. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* 2019;69(5):363-385. doi:10.3322/caac.21565
3. Shapiro CL. Cancer Survivorship. *N Engl J Med.* 2018;379(25):2438-2450. doi:10.1056/NEJMr1712502
4. Yabroff KR, Zheng Z, Han X. Cancer Survivorship. *N Engl J Med.* 2019;380(14):1380-1381. doi:10.1056/NEJMc1900709
5. Murphy CC, Gerber DE, Pruitt SL. Prevalence of Prior Cancer Among Persons Newly Diagnosed With Cancer: An Initial Report From the Surveillance, Epidemiology, and End Results Program. *JAMA Oncol.* 2018;4(6):832-836. doi:10.1001/jamaoncol.2017.3605
6. Zhou H, Huang Y, Qiu Z, et al. Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: A pan-cancer analysis of the SEER database. *Int J Cancer.* 2018;143(7):1569-

1577. doi:10.1002/ijc.31543
7. Smyth EC, Tarazona N, Peckitt C, et al. Exclusion of Gastrointestinal Cancer Patients With Prior Cancer From Clinical Trials: Is This Justified? . *Clin Colorectal Cancer*. 2016;15(2):e53-e59. doi:10.1016/j.clcc.2015.11.003
 8. Kim ES, Bruinooge SS, Roberts S, et al. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *J Clin Oncol*. 2017;35(33):3737-3744. doi:10.1200/JCO.2017.73.7916
 9. Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. Impact of prior cancer on eligibility for lung cancer clinical trials. *J Natl Cancer Inst*. 2014;106(11):dju302. Published 2014 Sep 24. doi:10.1093/jnci/dju302
 10. Chien SH, Liu CJ, Hong YC, et al. Development of second primary malignancy in patients with non-Hodgkin lymphoma: a nationwide population-based study. *J Cancer Res Clin Oncol*. 2015;141(11):1995-2004. doi:10.1007/s00432-015-1979-1
 11. Lu CH, Lee KD, Chen PT, et al. Second primary malignancies following thyroid cancer: a population-based study in Taiwan. *Eur J Endocrinol*. 2013;169(5):577-585. Published 2013 Oct 1. doi:10.1530/EJE-13-0309
 12. Bian X, He X, Yang L, Wu W, Li L. Prognosis of Hepatocellular Carcinoma Among Cancer Survivors with Other Types of Primary Tumors. *Dig Dis Sci*. 2020;65(7):2140-2147. doi:10.1007/s10620-019-05917-8
 13. He C, Zhang Y, Cai Z, Lin X. Effect of prior cancer on survival outcomes for patients with pancreatic adenocarcinoma: a propensity score analysis. *BMC Cancer*. 2019;19(1):509. Published 2019 May 29. doi:10.1186/s12885-019-5744-8
 14. He X, Li Y, Su T, et al. The impact of a history of cancer on pancreatic ductal adenocarcinoma survival. *United European Gastroenterol J*. 2018;6(6):888-894. doi:10.1177/2050640618765505
 15. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. *J Natl Cancer Inst*. 2015;107(4):djv002. Published 2015 Feb 9. doi:10.1093/jnci/djv002
 16. Zhou H, Zhang Y, Liu J, et al. Impact of prior cancer on outcomes in nasopharyngeal carcinoma. *Ann Transl Med*. 2019;7(14):299. doi:10.21037/atm.2019.05.78
 17. Corkum M, Hayden JA, Kephart G, Urquhart R, Schlievert C, Porter G. Screening for new primary cancers in cancer survivors compared to non-cancer controls: a systematic review and meta-analysis. *J Cancer Surviv*. 2013;7(3):455-463. doi:10.1007/s11764-013-0278-6
 18. Dinh KT, Mahal BA, Ziehr DR, et al. Risk of prostate cancer mortality in men with a history of prior cancer. *BJU Int*. 2016;117(6B):E20-E28. doi:10.1111/bju.13144
 19. Ji F, Yang CQ, Li XL, et al. Risk of breast cancer-related death in women with a prior cancer. *Aging (Albany NY)*. 2020;12(7):5894-5906. doi:10.18632/aging.102984
 20. López-Encuentra A, Gómez de la Cámara A, Rami-Porta R, et al. Previous tumour as a prognostic factor in stage I non-small cell lung cancer. *Thorax*. 2007;62(5):386-390.

doi:10.1136/thx.2005.051615

21. Nosrati A, Yu WY, McGuire J, et al. Outcomes and Risk Factors in Patients with Multiple Primary Melanomas. *J Invest Dermatol.* 2019;139(1):195-201. doi:10.1016/j.jid.2018.07.009
22. Tabuchi T, Ito Y, Ioka A, Nakayama T, Miyashiro I, Tsukuma H. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. *Ann Oncol.* 2013;24(10):2699-2704. doi:10.1093/annonc/mdt279
23. Druesne-Pecollo N, Keita Y, Touvier M, et al. Alcohol drinking and second primary cancer risk in patients with upper aerodigestive tract cancers: a systematic review and meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2014;23(2):324-331. doi:10.1158/1055-9965.EPI-13-0779
24. Do KA, Johnson MM, Doherty DA, et al. Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control.* 2003;14(2):131-138. doi:10.1023/a:1023060315781

Tables

Table 1 Baseline characteristics of included patients of gallbladder cancer				
Characteristics	Total	No prior cancer	With prior cancer	P
	N=5861	N=5622(95.9%)	N=239(4.1%)	
Age				<0.001
<65	2082	2026(36.0%)	56(23.4%)	
≥65	3779	3596(64.0%)	183(76.6%)	
Sex				0.001
Male	1726	1632(29.0%)	94(39.3%)	
Female	4135	3990(71.0%)	145(60.7%)	
Race				0.167
White	4466	4272(76.0%)	194(81.2%)	
Black	726	701(12.5%)	25(10.5%)	
Other	669	649(11.5%)	20(8.4%)	
Marital status				0.449
No married	2789	2681(47.7%)	108(45.2%)	
Married	3072	2941(52.3%)	131(54.8%)	
SEER stage				<0.001
Localized	691	651(11.6%)	40(16.7%)	
Regional	3124	2981(53.0%)	143(59.8%)	
Distant	2046	1990(35.4%)	56(23.4%)	
AJCC Stage				<0.001
I	1941	1834(32.6%)	107(44.8%)	
II	2008	1929(34.3%)	79(33.1%)	
III	154	150(2.7%)	4(1.7%)	
IV	1758	1709(30.4%)	49(20.5%)	
Grade				0.424
I	804	769(13.7%)	35(14.6%)	
II	2430	2327(41.4%)	103(43.1%)	
III	2474	2379(42.3%)	95(39.7%)	

		153	147(2.6%)	6(2.5%)	
Surgery					0.095
	No	774	751(13.4%)	23(9.6%)	
	Yes	5087	4871(86.6%)	216(90.4%)	
Radiation					0.998
	No	4905	4705(83.7%)	200(83.7%)	
	Yes	956	917(16.3%)	39(16.3%)	
Chemotherapy					0.028
	No	3754	3585(63.8%)	169(70.7%)	
	Yes	2107	2037(36.2%)	70(29.3%)	

AJCC, American Joint Committee on Cancer; GradeⅠ, well differentiated; GradeⅡ, moderately differentiated; GradeⅢ, poorly differentiated; GradeⅣ, undifferentiated

Table 2 Interval months from the diagnosis of prior cancer to the subsequent diagnosis of gallbladder cancer		
Prior cancer type	Number	Interval months(Median)
Gastrointestinal cancer	59	21.47
Prostate	51	45.04
Breast	49	37.80
Genitourinary cancer	42	30.98
Other	27	25.00
Lung	11	26.18

Table 3 1-year and 5-year cumulative incidences of mortality of gallbladder cancer patients		
Prior cancer type	Overall mortality	
	1-year (95%CI)	5-year (95%CI)
No prior cancer	64.6(63.1,66.0)	97.1(96.6,97.6)
With prior cancer	58.0(50.3,65.3)	95.5(91.2,98.0)
Gastrointestinal cancer	46.3(40.7,62.6)	87.8(73.8,95.9)
Prostate	64.1(47.2,78.8)	97.4(86.5,99.9)
Breast	61.1(43.5,76.9)	97.2(85.5,99.9)
Genitourinary cancer	58.1(39.1,75.5)	100.0(88.8,100.0)
Other	55.0(31.5,76.9)	95.0(75.1,99.9)
Lung	77.8(40.0,97.2)	100.0(66.4,100.0)

CI, Confidence interval

Table 4 Baseline characteristics of included patients of gallbladder cancer after PSM				
Characteristics	Total	No prior cancer	With prior cancer	P
	N=476	N=237(49.8%)	N=239(50.2%)	
Age				0.468
<65	105	49(20.7%)	56(23.4%)	
≥65	371	188(79.3%)	183(76.6%)	
Sex				0.909
Male	186	92(38.8%)	94(39.3%)	
Female	290	145(61.2%)	145(60.7%)	
Race				0.163
White	386	192(81.0%)	194(81.2%)	
Black	41	16(6.8%)	25(10.5%)	
Other	49	29(12.2%)	20(8.4%)	
Marital status				0.789
No married	218	110(46.4%)	108(45.2%)	
Married	258	127(53.6%)	131(54.8%)	
AJCC Stage				0.719
I	208	101(42.6%)	107(44.8%)	
II	162	83(35.0%)	79(33.1%)	
III	8	4(1.7%)	4(1.7%)	
IV	98	49(20.7%)	49(20.5%)	
Grade				0.547
I	76	41(17.3%)	35(14.6%)	
II	205	102(43.0%)	103(43.1%)	
III	179	84(35.4%)	95(39.7%)	
IV	16	10(4.2%)	6(2.5%)	
Surgery				0.234
No	54	31(13.1%)	23(9.6%)	

	Yes	422	206(86.9%)	216(90.4%)	
Radiation					0.641
	No	402	202(85.2%)	200(83.7%)	
	Yes	74	35(14.8%)	39(16.3%)	
Chemotherapy					0.728
	No	340	171(72.2%)	169(70.7%)	
	Yes	136	66(27.8%)	70(51.5%)	

PSM, Propensity score matching; AJCC, American Joint Committee on Cancer; GradeⅠ,well differentiated; GradeⅡ, moderately differentiated; GradeⅢ, poorly differentiated; GradeⅣ, undifferentiated

Table 5 Multivariable Cox regression analysis of OS and GCSS in patients of gallbladder cancer					
Characteristics		All-Cause adjusted HR (95%CI)	P	GCSS adjusted HR (95%CI)	P
Age					
	≤65	Reference		Reference	
	≥65	1.389(1.302,1.482)	<0.001	1.298(1.212,1.390)	<0.001
Sex					
	Male	Reference		Reference	
	Female	0.897(0.840,0.959)	0.001	0.926(0.862,0.994)	0.035
Race					
	White	Reference		Reference	
	Black	1.024(0.936,1.119)	0.607	1.031(0.937,1.134)	0.529
	Other	0.889(0.808,0.979)	0.016	0.888(0.801,0.985)	0.025
Marital status					
	No married	Reference		Reference	
	Married	0.853(0.802,0.907)	<0.001	0.885(0.828,0.946)	<0.001
AJCC Stage					
	I	Reference		Reference	
	II	2.557(2.356,2.776)	<0.001	3.112(2.833,3.419)	<0.001
	III	4.239(3.542,5.073)	<0.001	5.182(4.275,6.280)	<0.001
	IV	5.154(4.699,5.653)	<0.001	6.574(5.931,7.287)	<0.001
Grade					
	I	Reference		Reference	
	II	1.323(1.195,1.465)	<0.001	1.390(1.237,1.561)	<0.001
	III	1.864(1.682,2.066)	<0.001	2.005(1.785,2.253)	<0.001
	IV	1.896(1.560,2.305)	<0.001	2.056(1.666,2.539)	<0.001
Surgery					
	No	Reference		Reference	

	Yes	0.594(0.544,0.648)	<0.001	0.600(0.548,0.658)	<0.001
Radiation					
	No	Reference		Reference	
	Yes	0.841(0.769,0.920)	<0.001	0.861(0.784,0.946)	0.002
Chemotherapy					
	No	Reference		Reference	
	Yes	0.590(0.549,0.634)	<0.001	0.601(0.557,0.648)	<0.001
Prior Cancer					
	No	Reference		Reference	
	Yes	0.875(0.752,1.018)	0.084	0.404(0.318,0.513)	<0.001

OS, Overall Survival; GCSS, Gallbladder cancer specific survival; HR, Hazard ratio; CI, Confidence interval; AJCC, American Joint Committee on Cancer; GradeⅠ, well differentiated; GradeⅡ, moderately differentiated; GradeⅢ, poorly differentiated; GradeⅣ, undifferentiated.

Table 6 Multivariable cox regression analysis in gallbladder cancer patients stratified by prior cancer site					
Prior cancer typeⅠVS none)	All-Cause adjusted HR (95%CI)	P	GCSS adjusted HR (95%CI)	P	
Gastrointestinal cancer	0.675Ⅰ0.496,0.918Ⅰ	0.012	0.158Ⅰ0.079,0.316Ⅰ	<0.001	
Prostate cancer	0.964Ⅰ0.701,1.327Ⅰ	0.824	0.486Ⅰ0.301,0.785Ⅰ	0.003	
Breast cancer	0.854Ⅰ0.615,1.17Ⅰ	0.348	0.579Ⅰ0.376,0.889Ⅰ	0.013	
Genitourinary cancer	0.903Ⅰ0.634,1.286Ⅰ	0.571	0.545Ⅰ0.334,0.892Ⅰ	0.016	
Other cancer	1.074Ⅰ0.692,1.669Ⅰ	0.749	0.248Ⅰ0.093,0.662Ⅰ	0.005	
Lung cancer	2.248Ⅰ1.167,4.331Ⅰ	0.015	1.001Ⅰ0.322,3.110Ⅰ	0.998	

GCSS, Gallbladder cancer specific survival; HR, Hazard ratio; CI, Confidence interval.

Figures

Fig. a

Fig. b

Fig. c

Fig. d

Figure 1

a and b show the SEER stages of patients with gallbladder cancer with and without prior primary cancer, respectively. c and d show the AJCC stages of patients with gallbladder cancer with and without prior primary cancer, respectively.

Fig. a

Localized Regional Distant

Fig. b

Localized Regional Distant

Fig. c

AJCC I AJCC II AJCC III AJCC IV

Fig. d

AJCC I AJCC II AJCC III AJCC IV

Figure 1

a and b show the SEER stages of patients with gallbladder cancer with and without prior primary cancer, respectively. c and d show the AJCC stages of patients with gallbladder cancer with and without prior primary cancer, respectively.

Figure 2

Prior primary cancer types and interval months from the diagnosis of prior cancer to the subsequent diagnosis of gallbladder cancer.

Figure 2

Prior primary cancer types and interval months from the diagnosis of prior cancer to the subsequent diagnosis of gallbladder cancer.

Figure 3

OS a and GCSS b for patients with and without prior cancer before PSM; OS c and GCSS d for patients with and without prior cancer after PSM

Figure 3

OS a and GCSS b for patients with and without prior cancer before PSM; OS c and GCSS d for patients with and without prior cancer after PSM