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Survival Analysis of 250 Gallbladder Cancer Patients: A Prospective Study over a period of 2 Year

Authors
Pandey Punam[1], Singh K.K.[2], Pandey M.[3] Shukla V.K.[1]
[1]Department of General Surgery, [2]Departments of Statistics [3]Department of Surgical Oncology
IMS, BHU, Varanasi, UP, India
Corresponding Author
Pandey Punam
Department of General Surgery, IMS, BHU, Varanasi, UP, India
Email: *punampandey38@gmail.com*

Abstract

Background and Aims: *The cancer of the Gallbladder are the tumors with a poor prognosis and a lower quality of life (QoL). The aim of this study was to evaluate the survival rate in Cancer of the gallbladder patients.*

Method: *We prospectively enrolled 250 patients diagnosed with the cancer of the gallbladder in the cancer units of university hospital Varanasi, UP, each patient was reviewed, over a 9-month or till death within the period of (2011-2013).*

Results: *The mean age of the patients was 53 ± 10 years: 22.4% were male and 77.6% of the patients were female. Total number of patients in study were 250 at nine month only 23 patient was alive. The univariate analysis showed Age of the patients, tumor cell differentiation, Grade, preoperative lymph node metastasis, response of the patients and the surgical approach significantly correlated with median survival time, the prognosis of the patients was found to be negatively significant ($p < 0.05$). The results of the multivariate analysis (Cox regression) showed age, grade and the surgical approach, lymph node involvement, patients response were independent predicators with relative risks of .74, .52, .47, and .66, respectively found to be significant ($p=0.00, 0.01, 0.02, 0.00$).*

Conclusion: *The highest 9 month survival rate was 9.2%. Slightly longer survival was recorded when surgery and chemotherapy was added as treatment surgery improved the QOL faster than other treatment. Age, grade and the surgical approach, lymph node involvement, patients response were independent predicators of patient's survival respectively found to be significant.*

Key words: *– survival – quality of life- adjuvant chemotherapy – curative surgery –prognosis- resectable*

INTRODUCTION

Carcinoma of the biliary tract is a rare tumour.[1] To date, there is no therapeutic measure with curative potential apart from surgical intervention. Thus, patients with advanced, i.e. unresectable or metastatic disease, face a dismal prognosis.[2] They present a difficult problem to clinicians to choose a strictly supportive approach and to prevent the patients from the side-effects of a potentially ineffective treatment.[3] The objective of this article is to assess the survival of patients with Survival analysis with life time table with in 9 month duration. Further univariate and multivariate analysis is done to identify prognostic factors effecting survival of the gallbladder cancer patient. This study shows high mortality rate in the gallbladder cancer patients with moderate and poor QOL.

METHODOLOGY

This study plan was approved by Institute Ethics Committee of Banaras Hindu University Varanasi. Well informed written consent was obtained from each of the participants/guardians.

We prospectively enrolled 250 patients diagnosed with the cancer of the gallbladder in the cancer units of university hospital Varanasi, UP, each patient was reviewed, over a 9-month or till death, within the period of (2011-2013). Self develop questionnaire regarding symptoms, stage, grade, treatment, patient's responce and other demographic variables were recorded with the patients record.

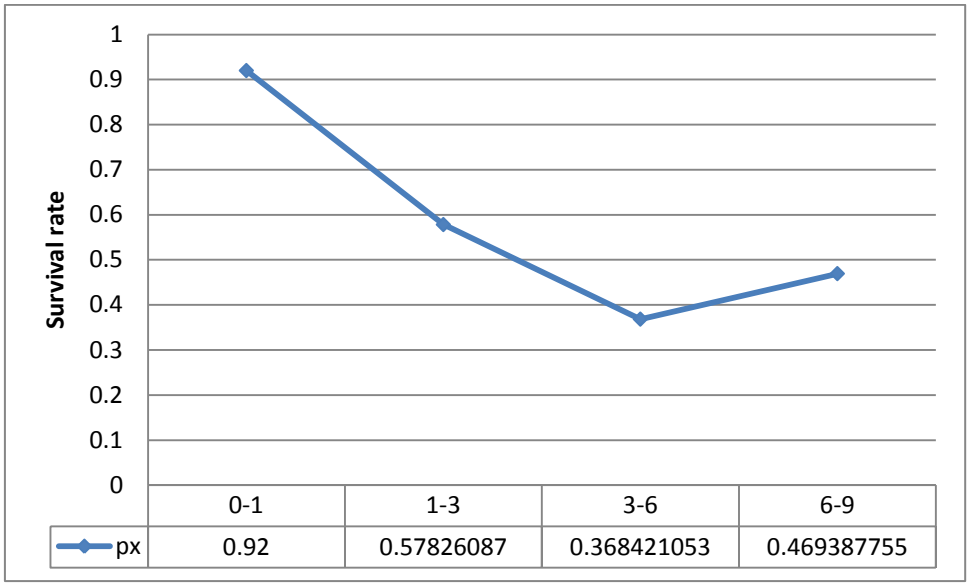
ANALYSIS

Table1 Survival analysis with life table showing time duration, no of patients, death rate, survival rate and proportion death and mean survival in study population.

Time	**No of patient**	**No of death**	**Death rate**	**Survival Rate**	**Proportion death**	**Mean Survival**
0-1	250	20	0.08	0.92	0.08	240
1-3	230	97	0.421739	0.578261	0.421739	181.5
3-6	133	84	0.631579	0.368421	0.631579	91
6-9	49	26	0.530612	0.469388	0.530612	36
9 and above	23					

Table2 Survival analysis with life graph table.

This table shows qx is servival rate, and px is death rate, with time duration in month.



[3]Univariate Analysis of the Prognosis

Factors	No (%)	Median survival time in (month)	Wilcoxon Gehan P value
Gender			
Male	56	3.00	0.50
Female	194	3.11	
Age			
≤50	121	3.28	0.00
≥50	129	1.73	
Cell differen -tiation			
Well	27	3.25	
Moderate	103	3.18	0.02
Poorly	120	1-98	
Stage			
1	29	3.27	
2	65	3.32	0.28
3	109	1.95	
4	47	1.93	
Grade			
1	22	3.37	0.01
2	54	3.40	
3	99	3.05	
4	75	1.85	
Lymphatic Invation			
Yes	60	3.277	0.02
No	47	3.264	
Venous Invation			
Yes	120	3.07	

No	23	1.65	
Treatment			.001
Surgery	53	3.54	
Chemo	136	3.00	.98
Chemosurg	27	1.95	.79
Radiosurg	34	1.76	.050
Marital st.			
Married	221	3.16	0.68
Widow/widowed	29	1.60	
Area			
Rural	181	3.02	0.45
Urban	69	3.22	
Diet			
Vegetarian	115	3.16	0.25
Nonveg.	135	3.03	
Addiction			
No addic	161	3.19	0.37
Tobacco	80	3.94	
Smoking	7	1.58	
Alcoholic	2	3.00	
Patient response in (1month)			
Improving	66	3.60	
Same as before	110	3.15	0.00
Not impro.	74	1.62	

Table[3] The univariate analysis showed Age of the patients, tumor cell differentiation, Grade, preoperative lymph node metastasis, response of the patients and the surgical approach significantly correlated with median survival time, the prognosis of the patients was found to be significant ($p < 0.05$).

[4] Multivariate Cox Regression Analysis for survival and their relative Significant

Variables	**B(Estimate)**	**Wald statistics(W) at 1 df**	**Sig. P Value**	**Exp(B) (relative risk)**
Age ≥50	-.293	4.601	.032	.746
Grade(3)	-.207	.757	.384	.813
Grade(4)	-.385	4.045	.044	.680
Cell-differan (poorly)	-.654	6.010	.014	.520
Celldifferent(moderately)	-.378	2.681	.102	.685
Lymphatic invest.	-.649	3.695	.055	.523
Patient response Not improving	-.744	15.119	.000	.475
Patient response Same as above	-.408	6.314	.012	.665

Gender male	.451	.018	.894	1.022
Stage(2)	.052	.041	.840	1.054
Stage(3)	.081	.173	.678	1.084
Area (rural)	-.699	.957	.328	.497
Diet (Nonveg)	.301	.996	.318	1.351
Surgery	-.507	4.871	.027	.602
Chemo	-.098	.993	.319	.907
Chemsur	-.108	1.379	.240	.898

[4]Result of Cox Regression Analysis for survival: The results of the multivariate analysis (Cox regression) showed age, grade and the surgical approach, lymphnode involvement, patients responce were independent predicators with relative risks of .74, .52, .47, and .66, respectively significant (p=0.00, 0.01, 0.02, 0.00). However, factors like gender, treatment chemotherapy, stage, area and diet lost their relationship when subjected to logistic regression analysis.

DISCUSSION

Overall five-year survival for patients with advanced carcinoma of the gallbladder is dismal [4,5,6] Following complete surgical resection of early stage disease, the actuarial survival rate had been reported to be as high as 100% [7,8,9] However, only a small proportion of patients have resectable disease at the time of diagnosis. Early detection of disease is therefore crucial to improve overall prognosis.

In this study, the patients with stage 1was29, stage II carcinoma gallbladder was 65 , 109 with stage III , and 47 with stage IV. .This study also found that 53,136,27,34 number of the patients were selected for curative surgery, chemotherapy, adjuvant chemotherapy and surgery with radiotherapy respectively, for gallbladder cancer did not have resectable disease despite a rigorous preoperative assessment and staging process. The median survival for the surgically operable group is significantly higher than that of the radiologically inoperable group, suggesting that exploratory surgery has a positive impact on survival. Other studies have also reported a reduced survival in patients who underwent non-curative chemotherapy and radiotherapy treatment[10,11]due to side effect of drugs as patients was having poor general wellbeing and low immunity in their advance stage.

Table[1]The table shows time duration of 0-1 month total no of patients were 250 with in 1month 20 patients expired rest remaining patient 230 was reviewed at 3 month 97 patients were expired, rest alive patient was 133 this patient was seen at 6 month 84 patient was expired. remaining 49 patient was examined at nine month only 23 patient was alive and 26 was dead. And this table also shows death rate, Survival rate, proportion death (death of the gallbladder cancer in a particular time period), and mean Survival of the gallbladder cancer patients. The incidence is comparatively high and contributes to a social

disaster as a result of its associated poor outcome. Even among patients who undergo surgery, chemotherapy, adjuvant chemotherapy and radical surgical resections

[2] Survival analysis with life time graph: This table shows qx servival rate, and px death rate, with time duration in month 0-9 months.0 to 1 month total no of patients are 250 no of death 20 death rate is .08, Survival rate is .92, proportion death .08 mean survival is 240. In 1-3 month total no of patients are 230 no of death 97 death rate is .42, Survival rate is .57, proportion death .42 mean survival is 181. In month of 3-6 total no of patients are 133 no of death 84 death rate is .84, Survival rate is .63, proportion death .63 mean survival is 91. In month 6to9 month total no of patients are 49 no of death 26 death rate is .53, Survival rate is .46, proportion death .53 mean survival is 56. After 9 month total 23 patient was found alive. This table indicate that death rate was highest within 6 moth duration 133 patients were alive, and after 6 month the survival was slightly improved with treatment modalities. GCS Smith et.al.2003 observed 44 patients (33 women, 11 men) had a mean age of 66 years (range 42–90 years). The diagnosis was established preoperatively in 25 patients (57%), intraoperatively in 5 patients (11%) and incidentally following pathological examination of cholecystectomy specimens in 14 patients (32%). None of the 25 patients diagnosed preoperatively underwent curative operations (median survival was 4 months). All five patients diagnosed at the time of attempted cholecystectomy had advanced irresectable disease (median survival 1 month). The overall median survival in 14 patients with an incidental diagnosis of gallbladder cancer was 16 months; however, in eight of these patients who were considered to have had a potentially curative resection, the median survival was 38 months. [12]

[3]Univariate Analysis of the Prognosis To evaluate the prognostic factors for survival in 250 carcinoma of the gallbladder patients were examined who underwent gallbladder surgery, chemotherapy, chemosurgery and radiosurgery in our unit during 2011-2013, and follow-up results were obtained from every patient for univariate survival analysis. The univariate analysis showed Age of the patients, tumor cell differentiation, Grade, preoperative lymph node metastasis, response of the patients and the surgical approach significantly correlated with median survival time, the prognosis of the patients was found to be significant ($p < 0.05$).

Chijiiwa K et. al.1995 in their study included 65 patients with gallbladder carcinoma who had undergone surgical resection from 1983 to 1999, 28 had T2 carcinoma histologically proved. The significance of variables for survival was examined by the Kaplan-Meier method and log-rank test followed by multivariate analyses using Cox's proportional hazard model. There were 17 patients with stage II carcinoma , 6 with stage III , and 5 with stage IV. Lymph node metastasis was present in 11 patients (39%) and it reached to the peripancreatic head region (N2) in 5 of them. Lymphatic, venous, and perineural invasions were found in 68%, 57%, and 43%, respectively. significant factors in the univariate analysis.

Cancer-free surgical margins provided a significantly better survival (5-year survival rate, 62%); none with cancer-positive surgical margins survived for more than 27 months. In the multivariate analysis, surgical procedure was significant (OR 25.49, 95% CI 1.62-400.72, p = 0.021). Radical surgery, including extended cholecystectomy (resection of the gallbladder together with the gallbladder bed of the liver) and anatomic resection of liver segment 5 and of the lower part of segment 4, gave a significantly better 5-year survival rate than cholecystectomy (59% versus 17%). The 5-year survival rate after radical resection in patients with stage II was 75%; that in patients with stage III and IVB was 33%. Results suggest that radical surgery is the treatment of choice for patients with T2 carcinoma of the gallbladder. The presence of lymph node metastasis, perineural invasion, or both suggests the necessity of additional treatment after radical surgery.[13] Malik IA et al, 2003 However , on multivariate analysis tumor node metastasis (TNM) stage was the only factor influencing survival of the patients was 44 months for patients with stage 1 disease, 23 months for stage 2, 17 months for stage 3 and 6 months for stage 4. Data were analyzed to evaluate variables that influenced survival. Kaplan-Meier analysis was used to calculate survival.[14] Claire L. Donohoe et al.2011 stated in their study the Background Gallbladder cancer is associated with a dismal prognosis with a 5-year survival rate of 5% for those patients with disease not amenable to surgery., the reported median survival across all stages is 35% to 38%. the surgical management of gallbladder cancer has always been controversial. Surgeons across the world have repeatedly stressed the need for a complete surgical resection and have demonstrated improved survival in patients who underwent radical resection. Guidelines for the surgical management of gallbladder cancer have been formulated on the basis of the available evidence. Despite this, it now appears that one of the biggest problems in gallbladder cancer is the lack of performance of the correct surgery in the first place. An offshoot of the problem of inadequate surgery for gallbladder cancer is the misuse of the term incidental gallbladder cancer and the resulting mismanagement of the patients included in this group.[15]

Table [4] In this table age more than > 50 is found to be negatively significant .03 than age less than< 50 with relative risk .74 (1-.74=.25) having 25% more risk for survival. The patient of grade 3 and grade 4 have relative risk .81 and .68 having 19%, 32% more risk of survival than patients with grade 1 simultaneously. Cell differentiation poorly and moderately, are having more risk of survival than well differentiated with relative risk .520 and .685 respectively. Patient with Lymphatic involvement have more relative risk .523 48% of survival than patient having no lymphatic involvement. Patients response of improving from previous condition have better survival than not improving and same as above with relative risk .475, .665. respectively. Area rural have more relative risk .497 of survival than urban population. Treatment Surgicalradiation chemotherapy, chemosurgery have more relative risk of survival than surgery

is .602, .907, .898. i.e 40%, 10%, 11% respectively. .Rui-Tao Wang, et.al. 2012 In their study evaluated the prognostic factors of gallbladder carcinoma. Survival outcome were examined for 132 gallbladder carcinoma patients who underwent gallbladder surgery in their unit during 2002-2007, and follow-up results were obtained from every patient for univariate and multivariate survival analysis. The univariate analysis showed that gallbladder lesion history, tumor cell differentiation, Nevin staging, preoperative lymph node metastasis and the surgical approach significantly correlated with the prognosis of the patients ($p < 0.05$). The results of the multivariate analysis (Cox regression) showed that gallbladder lesion history, Nevin staging and the surgical approach were independent predicators with relative risks of 6.9, 4.4, 2.8, respectively ($p=0.002$, 0.003, 0.008). The study indicate that Gallbladder Cancer is a rapidly fatal disease. Therefore, early diagnosis, anti-infective therapy and radical surgery are greatly needed to improve the prognosis of gallbladder carcinoma.[16] Eugenia E. Calle et.al.(2003)in their study depict The heaviest members of this cohort (those with a body-mass index [the weight in kilograms divided by the square of the height in meters] of at least 40) had death rates from all cancers combined that were 52 percent higher (for men) and 62 percent higher (for women) than the rates in men and women of normal weight. For men, the relative risk of death was 1.52 (95 percent confidence interval, 1.13 to 2.05); for women, the relative risk was 1.62 (95 percent confidence interval, 1.40 to 1.87). In both men and women, body-mass index was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher body-mass-index values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast, uterus, cervix, and ovary in women. On the basis of associations observed in this study[17]

CONCLUSION

Surgical resection provides a better chance of cure for the cancer of the gallbladder when it is early detection and in indicial and first stage. The gallbladder cancer and Surgery offers the best probability of long-term survival but is associated with an increased morbidity and mortality. Surgical exploration where unresectable disease is encountered reduces survival significantly. Hence, diligent preoperative evaluation of all gallbladder cancers is essential to optimize the survival and quality of life in these patients. A more standardized approach in the surgical management of gallbladder cancer would in addition facilitate the future comparisons between different treatment groups.

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