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RESEARCH ARTICLE

EARLY RECURRENCE OF CARCINOMA GALL BLADDER AFTER R0 RESECTION OF STAGE T1B-T3

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Abstract

Objective: The time to tumour recurrence after curative intent excision can predict the prognosis of hepatobiliary malignancies. As a result, we studied the risk factors for early recurrence of gallbladder cancer and related prognosis in patients with T1b–T3 gallbladder carcinoma who had received R0 resection.

Material and Methods: Total of 18 patients who underwent R0 resection for gall bladder carcinoma of stage T1b–T3 between March 2009 and Feb 2017 at Hayatabad Medical Complex Peshawar Pakistan were included in the study. The exclusion and inclusion criteria were strictly followed. Logistic regression models were used to identify the risk factors for early recurrence.

Results: At the time of radical surgery the type of resection consisted primarily of cholecystectomy with partial hepatic resection was (n=15, 83.3%). Resection of regional lymph nodes was performed routinely in all patients. Pathologically most patients had tumors at stage I&II (n=13, 72.2%). Postoperatively 5 (27.7%) patients had at least one complication & almost 2 (11.1%) individuals developed major complications, the overall morbidity was 4 (22.2%). Overall survival rate at 1, 3, and 5 years was 15 (83.3%), 11 (61.1%) and 6 (33.3%) respectively. Total of 7 (38.8%) patients experienced tumor recurrence after treatment, among them 4 (57.1%) developed a local recurrence, while 1 (14.2%) developed distant recurrence and 2 (28.5%) experienced both local and distant recurrence. The liver parenchyma 3 (42.8%) was the most prevalent site of relapse.

Conclusion: T3 stage, N1–N2 stage, poor differentiation and lymphovascular invasion were independent risk factors associated with early recurrence for patients with gall bladder carcinoma with stage T1b–T3 disease after R0 resection.

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Introduction:-

Gall bladder carcinoma is the fifth most common gastro-intestinal neoplasm and the most common biliary tract malignancy in the world.¹ Since the clinical symptoms can be non-specific, the diagnosis is often late, resulting in a poor prognosis. The spread of gall bladder carcinoma to the liver parenchyma and the adjacent internal organs is due to lack of serosa in gall bladder wall, proximity, cholecystic veins draining into liver portal vein, lymphatics from gall bladder draining into the liver.²

Gallbladder carcinoma accounts for 80–95 % of all biliary-tract cancers worldwide and is the most common biliarytract malignancy.¹ Gallbladder Ca was identified coincidentally in several patients during or after cholecystectomy for a presumed benign disease [i.e. incidental gallbladder cancer IGBC] due to a lack of efficient screening and early symptoms.³⁻⁴ Radical resection with a R0 margin is the mainstay of curative intent treatment for gallbladder Ca. This technique included a long hepatectomy paired with an adequate lymphadenectomy.⁵ Gallbladder carcinoma however is a highly malignant tumour characterised by early lymph node involvement and distant metastases. Even after R0 resection, such aggressiveness leads in a high rate of postoperative recurrence and a terrible prognosis.⁶⁻⁷ The time of recurrence is related to the long-term survival of gallbladder Ca patients. Several studies have indicated the effect of early recurrence on the prognosis of a variety of hepatobiliary malignancies, including hepatocellular carcinoma, cholangiocarcinoma, and pancreatic carcinoma.⁸

In comparison, only gall bladder Ca at stages T1b–T3 requiring hepatectomy were included in this study, since T1a tumours can be treated well with cholecystectomy alone, and the amount of primary resection for T4 lesions is debatable.⁹⁻¹⁰ Furthermore patients with gall bladder carcinoma who underwent R1 resection were excluded from the present cohort since the R0 margin is of the highest importance in curative intent surgery.¹¹

The goal of this study is to find the optimal cutoff time for identifying early recurrence in patients with GBC with T1b–T3 disease who had received R0 resection. In addition, the clinicopathological factors associated with early recurrence were investigated. We also looked at whether the period between re-resections for IGBC affected the prognosis of patients who had risk factors for early recurrence.

Material & Methods:-

Total of 18 patients who underwent R0 resection for gall bladder carcinoma of stage T1b–T3 between March 2009 and Feb 2017 at the Hayatabad Medical Complex Peshawar Pakistan were analyzed. The exclusion criteria comprised patients:

1. With macroscopically/microscopically positive margins
2. With T1 disease or metastatic disease
3. Who died <30 days after surgery

Details of the demographic features, imaging findings, surgical records, pathology data, and survival outcome of patients after radical surgery were collected and reviewed retrospectively. Tumor stage was classified. Upon pathology, complete removal of any tumor lesions with microscopically negative margins was defined as a curative resection (R0). Overall survival was defined as the time from the date of radical surgery to the date of death or the date of the last follow-up. Disease-free survival was measured from the date of curative resection to the date of recurrence or last follow-up. Sample t-test was used for comparison of continuous variables. Chi-square test was applied for categorical factors. P value ≤ 0.05 was considered significant. Data analyses were carried out using SPSS 27.0 software for windows 10.

Results:-

Total 18 patients 7 males and 11 females, age ranged between 45–70 years with a median age of ± 57.5 years who underwent R0 resection for gall bladder Ca of grade T1b–T3 were included in the study. At the time of radical surgery the type of resection consisted primarily of cholecystectomy with partial hepatic resection was (n=15, 83.3%). Resection of regional lymph nodes was performed routinely in all patients. Pathologically most patients had tumors at stage I&II (n=13, 72.2%). Postoperatively 5 (27.7%) patients had at least one complication & almost 2 (11.1%) individuals developed major complications, the overall morbidity was 4 (22.2%). Overall survival rate at 1, 3, and 5 years was 15 (83.3%), 11 (61.1%) and 6 (33.3%) respectively (Fig-I). Total of 7 (38.8%) patients experienced tumor recurrence after treatment, among them 4 (57.1%) developed a local recurrence, while 1 (14.2%) developed distant recurrence and

2(28.5%) experienced both local and distant recurrence (Fig-II). The liver parenchyma 3(42.8%) was the most prevalent site of relapse. To determine the optimal cutoff point for early recurrence and late recurrence, recurrence prevalence was calculated at 6 months intervals. The majority 5(71.5%) of recurrence occurred within 25 months after surgery (early recurrence), with the remaining 2(28.5%) cases were discovered beyond 25 months (late recurrence) Fig-III. Overall survival of patients with gall bladder Ca who experienced early recurrence was markedly lower than that of patients who experienced late recurrence ($P < 0.002$) i.e. 2(40%) vs 0(0%). Moreover, patients who experienced early recurrence were more likely to have distant metastasis than those who had late recurrence ($P = 0.004$). Univariate analysis revealed the positive predictors of early recurrence to be cancer antigen 19-9 > 40 U/mL, high T category, high N category, poor differentiation, lymphovascular invasion (LI) and perineural invasion. Multivariate analyses of the logistic regression model revealed T3 stage, N1-N2 stage, poor differentiation, and LI as independent risk factors associated with early recurrence following R0 resection of gall bladder carcinoma.

Fig-I:- Overall Survival rate in terms of years.



Fig-II:- Tumour Recurrence rate.

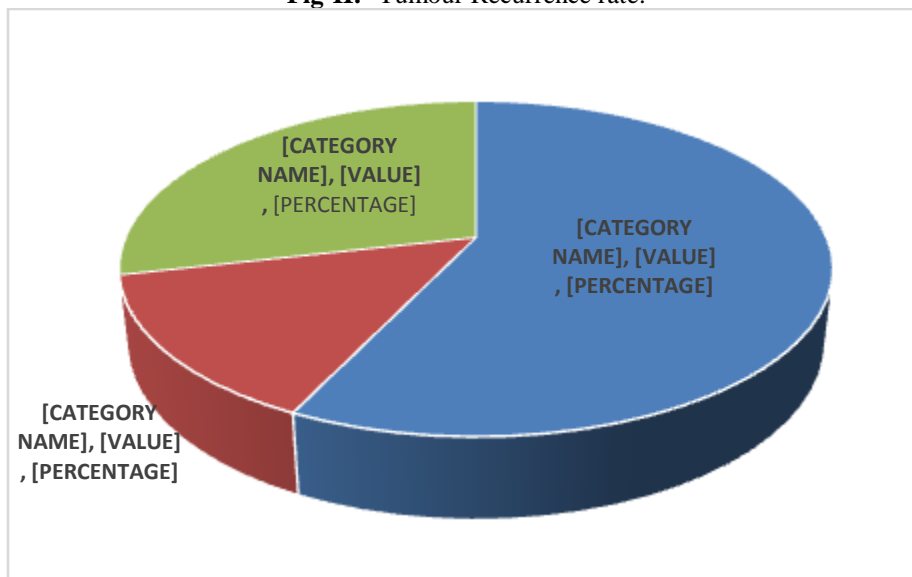
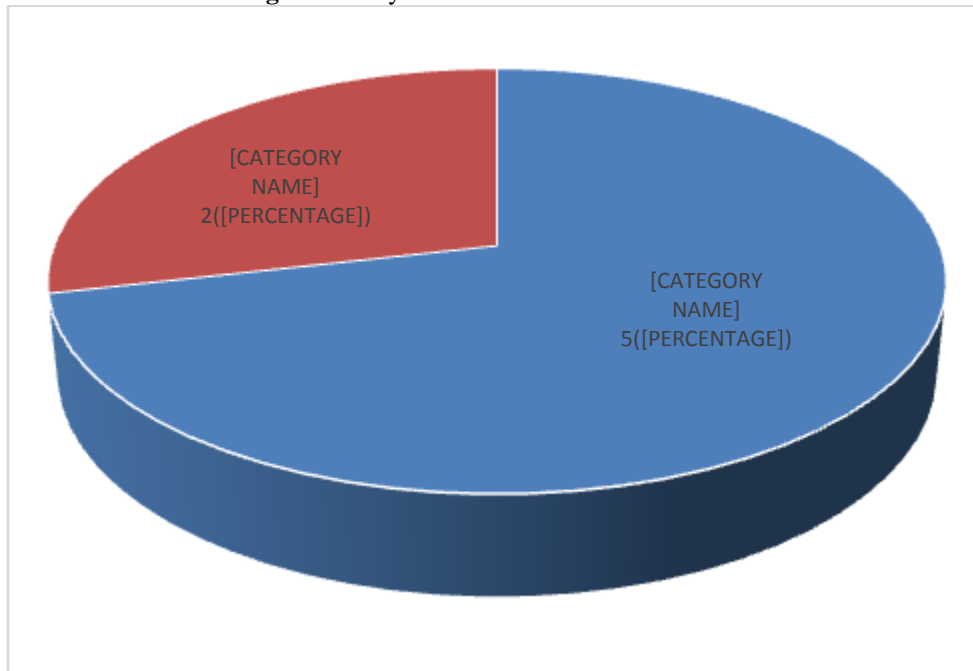


Fig-III:- Early & Late recurrence stratification.**Discussion:-**

Radical surgery aiming to achieve R0 resection is the only curative treatment for gall bladder Ca. However, because of its aggressive local infiltration and early metastasis, the prevalence of postoperative recurrence of gall bladder Ca has been reported to be 25–65%.¹² Several studies have demonstrated the association between early recurrence and poor prognosis for patients with hepatobiliary carcinoma. Although the recurrence patterns of patients with gall bladder Ca after R0 resection have been revealed in some studies, little is known about the predictive factors of early recurrence.¹³

Our cohort comprised patients with gall bladder Ca with T1b–T3 disease who had undergone R0 resection. We calculated 25 months as being the optimal cutoff to distinguish early recurrence from late recurrence. Perhaps unsurprisingly, the 5-year overall survival of patients in the early recurrence group was significantly shorter than that of patients in the late recurrence group. In addition, early recurrence tended to occur in a location distal to the primary tumor, whereas regional recurrence was more prevalent in the late recurrence group. This phenomenon has been demonstrated in other cancer types, but until now, it has not been reported for gall bladder Ca.^{14,15}

Sahara et al evaluated patients with gall bladder Ca with T1–T4 disease and found that major hepatectomy was a prognostic factor for early recurrence when compared with minor hepatectomy involving segments IVB/V.¹⁶ In our cohort, however, major hepatectomy failed to remain a risk factor of early recurrence for patients with gall bladder Ca with T1b–T3 disease. This inconsistency could reflect the variation in patient selection. As mentioned above, cholecystectomy alone is sufficient for gall bladder Ca of stage T1a, whereas radical resection for a T4 lesion is controversial, thus neither of these two stages were included in our cohort.

The scope of liver resection for gall bladder Ca should be performed according to the T stage. We hypothesized that it is the T stage, rather than the scope of liver resection, that affects the risk of early recurrence in patients with gall bladder carcinoma. We also discovered that the tumors in the early recurrence group had more advanced T categories than those in the non-early recurrence group. This result emphasized the importance of an adequate scope of resection to achieve long-term survival of patients with gall bladder Ca. The present study demonstrated that more than 80% of recurrence occurred within 25 months after resection (early recurrence), typically in a location distant from the primary tumor site. Therefore, a more intense follow-up schedule in the first 2–3 years might be required for patients with T1–T3 stage gall bladder Ca with early recurrence related risk factors.

Gall bladder carcinoma that is diagnosed by pathology during or after resection for a presumed benign disease is defined as IGBC and accounts for about 50–70% of all cases of gall bladder carcinoma.^{17,18} Avoidance of a secondary

surgical procedure requires frozen-section histopathology during cholecystectomy; however, this is not feasible for all hospitals in view of the increased medical expenditure and operative time.¹⁹

According to Sahara et al, early recurrence worsened the prognosis of patients with gall bladder carcinoma with stage T1–T4 following R0/R1 resection.²⁰ Kohn N et al established a scoring system for predicting recurrence based on the T-stage, margin status, differentiation, and type of liver resection.²¹

Our study comprising data from a single center tertiary care hospital. Therefore, a larger scale study is needed to identify the variables that determine the optimal timing of a secondary surgical procedure.

Conclusions:-

T3 stage, N1–N2 stage, poor differentiation, and lymphovascular invasion were identified as independent risk factors associated with early recurrence in patients with gall bladder carcinoma with stage T1b–T3 disease after R0 resection. Moreover, intense follow-up schedule might be recommended for those with early recurrence related risk factors in the first 2–3 years.

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