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Epidemiology, Aetiology and Multimodal Therapy in Cancer Gallbladder

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Abstract

Carcinoma gallbladder is the most common malignancy of the biliary tract and the fifth most common gastrointestinal cancer. High incidence rates of gallbladder cancer have been described from North India. Despite the fact that the precise etiology of this disease is ill understood there is a strong association between carcinoma gallbladder and cholelithiasis. Majority of patients present as advanced disease with unfavorable prognosis and poor results of treatment. Radical surgery is the main stay of curative intent treatment for gallbladder cancer. Extended or radical cholecystectomy when feasible is the standard treatment for resectable carcinoma gallbladder. A small but increasing proportion of incidental cancers detected during or after cholecystectomy is being also seen. These patients are generally in an early stage of disease and potentially more curable by a completion radical cholecystectomy, especially indicated for patients whose disease is pT1b or beyond. Patients with advanced stage III or IV disease can be taken up for more complex and usually high risk and morbid extended resections like hepatopancreaticoduodenectomy. Patients not fit for such major resection or found unresectable on imaging or exploration are usually offered palliative treatment. This may be in the form of a surgical palliation (e.g. palliative bypass for gastric outlet, bowel or biliary

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tract obstruction) endoscopic biliary stenting (for obstructive jaundice) or palliative chemotherapy. Chemotherapy for gallbladder cancer is generally used in the palliative setting. Gemcitabine, cisplatin, 5-fluorouracil, mitomycin and capecitabine are some of the effective agents. We have reported overall response rates of 55% with the combination of gemcitabine and cisplatin in patients with advanced carcinoma gallbladder. Patients with advanced gallbladder cancer and jaundice who undergo stenting followed by chemotherapy show a response and survival similar to those who present without jaundice.

Keywords : Carcinoma gallbladder, Radical cholecystectomy, Chemotherapy for gallbladder cancer.

Introduction

Carcinoma of the gallbladder is a highly lethal disease. It is the most common malignant lesion of the biliary tract and holds fifth place among malignant neoplasms of the digestive tract. Even today, with multiple diagnostic tests available, gallbladder cancer is usually first recognized during a laparotomy performed for a presumptive diagnosis of benign gallbladder disease (1-3). 1-2% of patients undergoing operations for cholelithiasis have the diagnosis made incidentally at the time of surgical exploration. In India, however, the majority are discovered with advanced disease during ultrasonography for upper abdominal symptoms. The 5 years survival rate for all gallbladder cancers in most series is 0-1% (4). This poor prognosis of gallbladder carcinoma is due to the special anatomical situation of the gallbladder and the high proportion of advanced tumours at the time of presentation.

Epidemiology and Aetiology

Gallbladder carcinoma affects women two to six times more commonly than men and the incidence steadily increases with age. The incidence of cancer gallbladder varies greatly in different areas of the world (5, 6). Highest incidence rates (up to 7.5 per 100,000 for males and 23 per 100,000 for females) are seen in American Indians, people of Chile and other South American countries, Poland and North India. Intermediate incidence rates (up to 5 per 100,000) are seen in Japanese and Hispanic Americans. Low incidence is seen in Singapore, Nigeria and United States (2.5 per 100,000). Incidence also varies within a country. For instance in India, the incidence of carcinoma gallbladder is very high in North India (4.5 per 100,000 for males and 10.1 per 100,000 for females in Delhi) compared to that in South India, *viz.* Chennai, Mumbai, Trivandrum and Bangalore (1.2 per 100,000 for males and 0.9 per 100,000

for females) (7). The wide geographical, ethnic and cultural variation in the incidence of carcinoma gallbladder suggests major genetic and environmental influences, like diet and lifestyle in the development of the disease. The incidence of gallstone disease is also significantly higher in these regions for reasons, which are ill understood (5, 6).

The aetiology of carcinoma gallbladder is unknown. However, several risk factors are associated with the development of gallbladder carcinoma (1-3) (Table-1).

Table 1 : Risk factors for carcinoma gallbladder

Cholelithiasis
Calcified or Porcelain Gallbladder
Gallbladder polyp
Anomalous pancreatico biliary duct junction (APBDJ)
Carcinogens (Adulteration of mustard oil, methylcholanthrene, nitrosamines)
Typhoid infection
Obesity
Oestrogens

Gallbladder cancer progresses from dysplasia to carcinoma in-situ (CIS) to invasive carcinoma. Limited information is available about genetic changes occurring in gallbladder carcinogenesis. Mutations in k-RAS have been reported in 39-59% of patients with gallbladder cancer. Abnormalities in p53 tumor suppressor gene are seen in 35-92% of gallbladder cancer (5, 6, 8). We found abnormalities in p53 tumour suppresser gene in 14/20 patients (70%) of gallbladder cancer. In contrast, none of the patients with chronic cholecystitis with cholelithiasis expressed it. Over expression of p53 significantly ($p < .05$) correlated with grade, stage (T status) and presence of gallstones (8). We have done DNA ploidy and S'Phase fraction estimation in 20 patients of gallbladder cancer and 40% of these patients demonstrated aneuploidy and elevated S phase fraction. This high S phase fraction and aneuploidy of DNA is well correlated with aggressive gallbladder cancer (9).

Staging

TNM system put together by the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) is currently used. This system is based on the depth of tumour invasion and correlates well with prognosis. The recently revised UICC/AJCC TNM (2002) (10) and the 1997 TNM (11) is mentioned in Table-2. The 2002

classification has several major changes, which are highlighted in table. We have used the 1997 TNM classification (5th edition) for describing treatment options and prognosis as nearly all published data is based on this classification.

Table 2 : TNM (5th Edition, 1997) and TNM (6th Edition 2002) of Carcinoma Gallbladder and their stage grouping

UICC TNM 1997	TNM stage grouping		UICC TNM 2002
	1997	2002	
Tis Carcinoma *in situ* N0 No lymph node metastasis M0 No distant metastasis	0	0	Tis Carcinoma *in situ* N0 No lymph node metastasis M0 No distant metastasis
T1a Tumour invades lamina propria T1b Tumour invades muscle layer N0	I	IA	T1a Tumour invades lamina propria T1b Tumour invades muslce layer N0, M0
M0		IB	T2 Tumour invades perimuscular connective tissue, no extension beyond serosa or into liver, N0, M0
T2 Tumour invades perimuscular connective tissue; no extension beyond serosa or into liver N0 M0	II	IIA	T3 Tumour perforates serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, e.g. stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, N0, M0
		IIB	T1, T2, T3 N1*** Regional lymph node metastasis, M0
T3 tumour perforates serosa or directly invades into one adjacent organ or both (extension 2 cm or less into liver) N1 regional lymph node metastasis* M0 or T1 N1 M0 or T2 N1 M0 or T3 N0 M0	III	III	T4 Tumour invades main portal vein or hepatic artery, or invades two or more extrahepatic organs or structures Any N, M0
14 Tumor extends more than 2 cm into liver and/or into two or more adjacent organs (bile duct, stomach duodenum, colon, pancreas, omentum, any involvement of liver) N0 or N1, M0 or Any T, N2**, M0 or any T, any N, M1 (distant metastasis)	IVA IVB	IV	Any T, Any N, M1

* Cystic duct, pericholedochal and/hilar lymph nodes (i.e. in the hepatoduodenal ligament).
** Peripancreatic (head only), periduodenal, periportal, coelaic and/or superior mesenteric lymph nodes.
*** The regional lymp nodes are the cystic duct node and the pericholedochal, hilar, peripancreatic (head only), periduodenal, periportal, coeliac, and superior mesenteric nodes.

Clinical Presentation

As the symptoms and signs of gallbladder carcinoma are vague and nonspecific clinical diagnosis is difficult. Early gallbladder carcinoma does not have any specific symptoms. The non-specific symptoms due to gallbladder carcinoma have been grouped into five clinical presentations (4), presenting as (a) acute cholecystitis, (b) as chronic cholecystitis, (c) symptoms of biliary tract disease - jaundice, weight loss, general weakness, and pain in right upper quadrant of abdomen, (d) clinical features of malignant tumor outside the biliary tract (metastatic disease) which include anorexia, weight loss, general weakness and local complications of the tumor such as fistula or invasion of adjacent organs (e) symptoms of benign manifestations outside the biliary tract such as gastrointestinal bleeding and obstruction. Gallbladder cancer may be suspected in patients with a long history of chronic cholecystitis with gallstones who have had a recent change in symptoms and who have continuous pain (1, 2). Usually these patients present late with locally advanced or metastatic disease where definitive treatment is not possible. In the present study 654 histologically or cytologically proven cases were included. Majority of patients presented in advanced stage based on UICC classification; Stage I : 26 (4%), stage II : 41 (5.9%), stage III : 83 (11.7%), and stage IV: 504 (78.4%). The majority of patients were between 42-69 years; incidence was twice in females as compared to males. Total duration of symptoms ranged from 2-13 months. Pain, weight loss, anorexia, lump abdomen, hepatomegaly, ascites and jaundice were the common presenting features. Multiple metastasis was more frequent than solitary as described in western literature. Histologically and cytologically all lesions were adenocarcinoma except in 2 patients it was squamous cell carcinoma.

Treatment

Carcinoma of the gallbladder is a highly fatal disease with poor prognosis. In a collected review by Piehler and Crichlow (4) of all the 5836 cases of gallbladder carcinoma (GBC) reported in the English literature up to 1978, the 5-year survival was less than *5%* with a median survival of 5 to 8 months. Similar results were reported in French Surgical Association Surgery of 724 cases of GBC (12). They reported a median survival of 3 months, a 1-year survival rate of 14% and a 5-year survival rate of 5%. These poor results are responsible for the general pessimism that surrounds this disease. The poor prognosis of this disease is attributed to the anatomical position of the gallbladder and the high proportion of tumors that are advanced at the time of presentation. The poor results also partly reflect the inadequate surgical resections that are usually performed for this cancer. However, major progress has been made in the treatment of gallbladder cancer during the last decade. As a result

of better preoperative imaging, early gallbladder cancer is now being diagnosed more frequently and the use of radical aggressive surgery promises an improvement in survival (1-3, 13).

Surgery

Treatment of individual patients depends on the stage of the patient (T status). Age, nutritional status, performance status and cardiopulmonary hepatic and renal functions all influence choice of treatment. Surgery is the only potentially curative therapy for gallbladder carcinoma (1-3, 13). However, only 10-30% patients can be considered for surgery.

Radical or extended cholecystectomy is the standard surgical treatment for gallbladder cancer. It involves removal of gallbladder plus at least 2 cm or more of the liver (gallbladder bed only, Segment IV and V or extended right hepatectomy) and dissection of lymph nodes from the hepatoduodenal ligament, behind the second part of duodenum, head of pancreas and the celiac axis. Simple cholecystectomy is curative in disease confined to the mucosa only. Bile duct needs to be removed when involved or in patients with tumours involving the cystic duct where a negative margin is not possible. In patients initially treated by laparoscopic cholecystectomy additional resection of port sites is done. T1 tumors are usually pathological findings (incidental diagnosis) after laparoscopic or open cholecystectomy. T1 disease includes T1a (mucosa) and T1b (muscle) sub stages. For patients with Tis and T1a disease simple cholecystectomy is adequate treatment. The five-year survival is from 85-100% (2,3,14,15). T1b tumours have lymph node metastasis in 15% patients and these patients show an improvement in survival (to 72-100%) when complete radical cholecystectomy is done (2, 15-17).

Radical cholecystectomy is necessary for T2 and more advanced tumours. The rate of metastasis to lymph nodes ranges from 40-80%. Radical cholecystectomy offers a 40-50%, 5-year survival advantage for these tumours compared to simple cholecystectomy (2, 17, 18). T3 -- T4 tumours also benefit by radical surgery with a five-year survival ranging from 15-63% and 7-25% respectively (1-3, 17). The extent of hepatic resection is more for these tumours (Segment IV - V to extended right hepatectomy).

One hundred and fifty three patients underwent surgery. Radical cholecystectomy was performed in 52 patients, (stage 1-8, stage 11-20, stage III-15, stage IV-8 highly selective group). There were 2 post-operative deaths. 33 patients underwent cholecystectomy for cholecystitis and cholelithiasis and gallbladder carcinoma was an incidental finding in them (stage 1-13, stage II-14, stage III-6). In 57 patients only exploration and biopsy was possible, 6 patients underwent biliary bypass for jaundice and 12 patients had enteric

bypass for obstruction. Patients undergoing radical cholecystectomy had a better survival than patients undergoing only exploration and biopsy. For stage I (T1a) there was no difference in survival in patients, undergoing radical or simple cholecystectomy.

Surgery in patients with advanced gallbladder carcinoma should not be done for the purpose of debulking alone. Radical surgery should be attempted only if it is possible to achieve a complete resection (3). Criteria for resectability can vary. However, surgical resection is contraindicated if there are - multiple liver metastases, ascites, multiple peritoneal metastases distant metastases, extensive involvement of hepatoduodenal ligament, encasement or occlusion of major vessels and poor performance status (1-3).

Direct involvement of colon, duodenum or liver is not an absolute contraindication for surgery. Several Japanese surgeons have advocated more extensive surgery like hepato – pancreatico duodenectomy. However, these procedures are associated with high morbidity (48-54%) and mortality (15-18%) (19). If undertaken, these procedures are indicated in a very select group of patients. Most patients with advanced disease are offered palliative treatment (chemotherapy, supportive and symptomatic treatment).

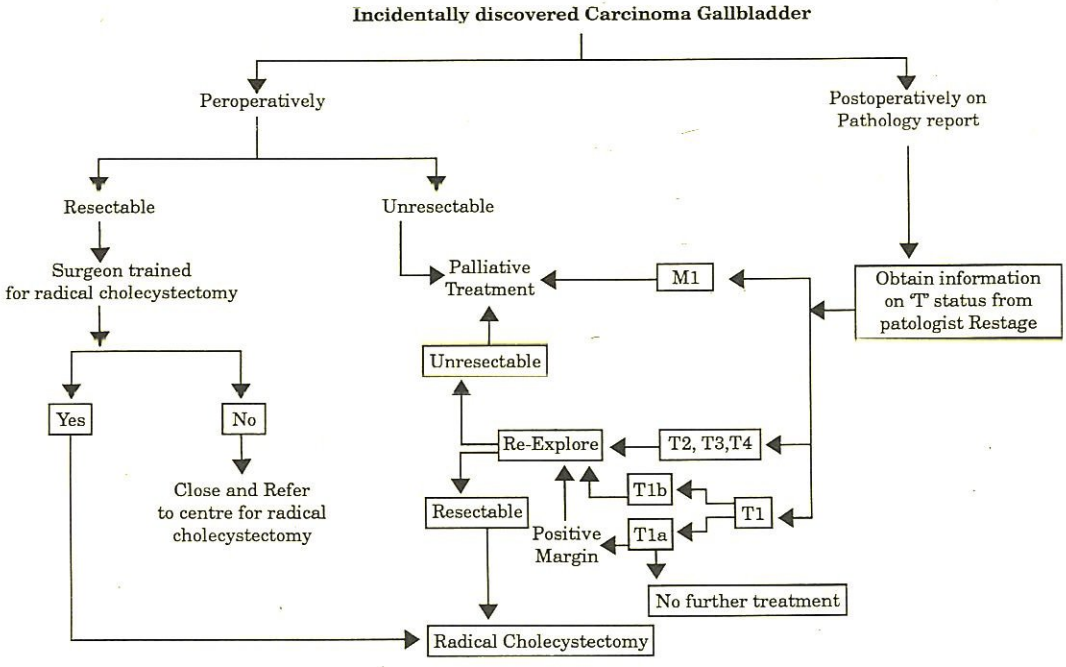
Incidental Gallbladder Carcinoma

Cholecystectomy for gallstones is one of the commonest surgeries performed by surgeons. Unsuspected gallbladder carcinoma may be discovered during open or laparoscopic cholecystectomy or as a histopathological finding in the cholecystectomy specimen. The surgeon should have a high index of suspicion in high incidence areas when he encounters a difficult cholecystectomy. All gallbladders removed for stone disease must always be opened and examined carefully for any suspicious lesions before the abdomen is closed. All suspicious specimens should be sent for frozen section examination. If the surgeon has the necessary training a radical cholecystectomy should be done, otherwise the patient should be referred to a center where radical cholecystectomy can be done and he must provide detailed description of the surgical findings. If the diagnosis of gallbladder carcinoma is made post operatively on histopathological examination, further management depends on T stage (Fig. 1). Patients with preoperative suspicion of gallbladder carcinoma should not undergo laparoscopic cholecystectomy.

Unresectable Gallbladder Carcinoma

Patients with advanced unresectable carcinoma of the gallbladder and obstructive jaundice may need palliation by a biliary enteric bypass or endoscopic / percutaneous stenting to relieve jaundice. Dramatic advances in the last decade in both endoscopic and radiologically guided percutaneous stenting of the biliary tract have made operative bypass in cases of unresectable cancers largely unnecessary.

Figure 1



Jaundice was palliated by either biliary bypass in 6 patients or by endoscopic stenting in 52 patients of gallbladder carcinoma. For advanced gallbladder carcinoma with obstructive jaundice endoscopic stenting is the preferred and effective method of palliation. Patients with biliary obstruction and good performance status whose jaundice is relieved by stenting are candidates for palliative chemotherapy. These patients have response rate and survival similar to non-jaundiced patients (20).

Duodenal or intestinal bypass may be performed as a palliative procedure if gastric outlet or intestinal obstruction is present. These patients may require palliation of pain, which is a major problem in advanced gallbladder carcinoma.

Chemotherapy

Chemotherapy has not been widely studied in the treatment of gallbladder cancer (9, 21). Gallbadder cancer patients typically present late in the course of their disease and often are not candidates for curative surgical resection. Mostly chemotherapy has been used as palliative chemotherapy with an aim to diminish symptoms and possibly to extend survival. Rarely it has been used as adjuvant therapy (22). Patients with advanced unresectable or metastatic disease with

good performance status should be considered for palliative chemotherapy.

Chemotherapy was administered in 7 salient groups to 206 patients. *Group I :* Intrahepatic arterial infusion of 5 fluorouracil (5 FU) and mitomycin-C (38 patients) (23,24), 36% patients showed response, median duration of response was 7 months (3-16 months). Poor prognosis was observed in patients having diffuse hepatic metastasis, as 12/20 patients did not show response. *Group II :* Adjuvant chemotherapy with 5FU and mitomycin-C was used till 1995 in 29 patients. The disease free survival in stage II was 14 months. Newer chemotherapy protocol of 5 to 6 cycle of cisplatin and 5 FU was used as adjuvant chemotherapy in 17 patients (stage II-12, III-5). Recurrence occurred in 7 patients, the median disease free survival was 21 months in contrast to 14 months with 5 FU and mitomycin-C in similarly staged patients (2, 25). *Group III :* Palliative chemotherapy: 5 FU+ mitomycin-C (MMC) in 28 patients, 7 patients (25%) showed objective response. The median duration of survival was 10.5 months (range 7-30 months) and median duration of response was 8 months (2, 25). *Group IV :* 5FU infusion + low dose leucovorin + MMC repeated at 3-4 weeks in 23 patients. 7 patients had PR with a median duration of response and survival of 9 months (range 7-15 + months) and 13 months (range 8-15 + months) respectively. 4 patients had SD with median duration of survival 4.7 months (2, 25). *Group V :* Cisplatin (C), 5FU infusion 21 patients 5 patients had PR, duration of response 8 to 24 months. 3 patients had SD and 6 patients had NR. The toxicity was tolerable - nausea and vomiting grade 1-1, grade 4-l, diarrhoea grade 3-2 and mucositis grade 3-l (2, 25). *Group VI :* Paclitaxel and 5FU was given to 10 patients, with poor response rate - 8 patients were non responder (2). *Group VII :* Recently we have studied the combination of cisplatin plus gemcitabine in 40 patients of advanced cancer gallbladder (Stage-IV). Criteria of selection of patients were histologically/ cytologically proven UICC stage IV disease, measurable/evaluable disease, ECOG PS $\leq$ 2, age $\leq$ 75 years, serum bilrubin <1.5mg/dl adequate hematologies and renal functions, no serious medical illness and affordability.

To monitor the response ultrasonography and CT scans were done after 2-3 courses. The breakup of cases is detailed here: carcinoma gallbladder without jaundice - 22, carcinoma gallbladder with jaundice - 18 (jaundice relieved by stenting). 18 patients with jaundice were provided stenting and jaundice regressed to normal - median time 2.6 months. The results were evaluated in 38 patients. Response occurred in 21 patients (CR-2, PR-19, RR-55.3%, 95CI, 32-56), stable disease-7 patients, no response - 10 patients. Median time to progression was 24 weeks (95% CI, 20-32 weeks). Median survival time was 32 weeks (95% CI, 18-36 weeks)

for the entire population. 44 weeks (95% CI, 32-56 weeks) for responders, 32 weeks (95% CI, 20-32) for SD and 12 weeks (95% CI, 4-16) for non responders. Significant favourable feature of this combination was subjective relief by disappearance of pain and improvement in appetite. Toxicity was minimal and the chemotherapy was well tolerated (20). Patients whose jaundice was relieved by stenting had survival similar to patients presenting initially without jaundice (20).

Conclusions

Based on this study it is concluded that carcinoma gallbladder is more common in North India, presenting frequently with advanced disease. Cholelithiasis emerges to be an important aetiological factor; p-53 gene plays a role in pathogenesis of carcinoma gallbladder. Surgery is the only potentially curative therapeutic option. Patients with advanced gallbladder cancer with good performance status should be offered chemotherapy. These different chemotherapeutic regimens are tolerable and active in patients with advanced gallbladder cancer and should be considered in patients with advanced inoperable disease. Relief of pain and improvement in appetite were other significant subjective achievements.

References :

1. Misra NC, Misra S, Chaturvedi A (1997). Carcinoma gallbladder. In : Johnson CD, Taylor I, Eds. *Recent Advances in Surgery,* London : Churchill Liingstone, **20:**69-87.
2. Misra S, Chaturvedi A, Misra NC, Sharma ID (2003). Carcinoma of the gallbladder. *Lancet Oncology* **4:**167-176.
3. Misra S, Chaturvedi A, Misra NC (2006). Gallbladder cancer. Current Treatment options. *Gastroenterology* **9:**95-106.
4. Piehler JM, Crichlow RW (1978). Primary carcinoma of the gallbladder. *Surg Gynaecol Obstet* **146:**929-942.
5. Lazcano-Ponce EC, Miquel JF, Munoz N, *et al* (2001). Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* **51:**349-364.
6. Wistuba II, Gazdar F (2004). Gallbladder cancer : Lessons from a rare tumour. *Nature Reviews Cancer* **4:**695-706.
7. Indian Council of Medical Research (ICMR). Annual Report of population based cancer registries of the National Cancer Registry Programme (1993), ICMR Publication, New Delhi; 1996; 18.
8. Misra S, Chaturvedi A, Goel MM, *et al* (2000). Overexpression of p53 protein in gallbladder carcinoma in North India. *Eur J Surg Oncol* **26:**164-167.
9. Misra NC, Misra S, Chaturvedi A, *et al* (2002). Epidemiology, aetiology and multimodal therapy in cancer gallbladder with special reference to radical surgery and newer chemotherapy protocols : A prospective study of 631 patients. *Proc American Society of*

Clinical Oncology PAN Asia Cancer conference (A-PACC) New Delhi, Feb. 24-26, 85-87.

10. Sobin LH, Wittekind CH (2002). Digestive system : Gallbladder. In : TNM Classification of Malignant Tumours, 6th edn. New York : Wiley - Liss, 84-86.
11. Sobin LH, Wittekind CH (1997). Digestive system : Gallbladder. In : TNM Classification of Malignant Tumours, 5th edn. New York : Wiley - Liss, 78-80.
12. Cubertafond P, Gainant A, Cucchiaro G (1994). Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. *Ann Surg* **219:**275-280.
13. Dixon E, Vollmer CM, Sahajpal A *et al* (2005). An aggressive surgical approach leads to improved survival in patients with gallbladder cancer. A 12-year study at North American Center. *Ann Surg* **241:**385-394.
14. Wakai T, Shirai Y, Yokoyama N *et al* (2001). Early gallbladder carcinoma does not warrant radical resection. *Br J Surg* **88:**675-678.
15. de-Aretxabala X, Rao IS, Burgos LA *et al* (1997). Curative resection in potentially resectable tumours of the gallbladder. *Eur J Surg* **163:**419-426.
16. Ogura Y, Mizumoto R, Isaji S *et al* (1991). Radical operations for carcinoma of the gallbladder : present status in Japan, *World J Surg* **15:**337-343.
17. Muratore A, Polastri R, Capussotti L (2000). Radical surgery for gallbladder cancer : current options. *Eur J Surg Oncol* **26:**438-443.
18. Bartlett DL (2000). Gallbladder cancer. *Semin Surg Oncol* **19:**145-155.
19. Kondo S, Numura Y, Hayakawa N *et al* (2002). Extensive surgery for carcinoma of the gallbladder. *Br J Surg* **89:**179-184.
20. Misra S, Chaturvedi A, Misra NC (2005). Gemcitabine (G) plus cisplatin (C) in advanced carcinoma gallbladder - A large single center experience (abstract 4136). *J Clin Oncol* **23:**341.
21. Todoroki T (2000). Chemotherapy for gallbladder carcinoma - a surgeon's perspective. *Hepatogastroenterology* **47:**948-955.
22. Takada T, Amano H, Yasuda H, et al (2000). Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreatico-biliary carcinoma. *Cancer* **95:**1685-1695.
23. Misra NC, Jaiswal MSD, Singh RV, Das B (1977). Intrahepatic arterial infusion with combination Mitomycin-C and 5-Fluorouracil for treatment of primary and metastatic carcinoma liver. *Cancer* **39:**1425-1429.
24. Misra NC, Chaturvedi A, Jaiswal MSD *et al* (1992). Intrahepatic arterial infusion with combination of Mitomycin C (MMC) and 5-Fluorouracil (5-FU) for treatment of primary and metastatic carcinoma liver. *Reg Cancer Treat* **5:**12-16.
25. Misra S, Misra NC, Sharma ID *et al* (1999). Newer Chemotherapy protocols in advanced cancer gallbladder. *Proc XV Asia Pacific Cancer Conference* 12-15, 94.