INTRODUCTION

Carcinoma of the gallbladder is an uncommon but lethal malignancy. Collective tumor-registry data of over 2500 cases in the United States between 1985 and 1995 showed 5 years survivals of 15%, 5% and 1% for Stages II, III and IV patients, respectively. Approximately 70% of patients resent with Stage III or Stage IV disease. In tumors confined to the gallbladder wall, 5 years survival rates after resection only range from 10% to 30%. Most patients with gallbladder carcinoma will present with more advanced disease (i.e., adjacent-organ or metastatic involvement). Local invasion into surrounding tissue and liver is facilitated by the thin muscular gallbladder wall as well as continuum of the perimuscular connective tissue with the interlobular connective tissue of the liver. Hepatic infiltration by gallbladder cancer (GBC) has been observed in 60-70% of patients on collective review and autopsy series. Lymphatic spread by GBC is also common. Overall regional nodal involvement has been reported in 40-80% of patients. For patients with T2 lesions (confined to the gallbladder wall), the incidence of nodal metastases ranges from 40% to 62% respectively. When disease invades the covering serosa or adjacent organs, nodal metastases rates rise to 70-80% respectively. The primary draining nodal groups are along the cystic and common bile ducts. Retrograde spread to hilar nodes can occur, particularly in more advanced disease. Secondary spread occurs to the pancreaticoduodenal nodes and later to the periaortic nodes, both of which usually go undisected, even in more radical procedures. With either lymph node involvement or hepatic infiltration (Stage III/IV), prognosis is poor, with reported 5 years survivals of 5% or less.

SURGERY

In advert simple cholecystectomy is the most common surgical procedure for resection of primary carcinoma of the gallbladder, as the diagnosis is not usually suspected pre-operatively. Even in early stage disease, positive margins after resection are common, given that the plane of dissection at simple cholecystectomy is sub serosal. Therefore, many hepatobiliary surgeons advocate radical resection or re-resection (wedge resection of the gallbladder wall) and lymphadenectomy. This is particularly important for patients with advanced disease, where the incidence of nodal metastases is high.
bed/hepatic resection, excision of regional nodes) in the
treatment of Stage T2 or higher disease, although less than
10% of patients undergo such procedures. Although limited by small patient numbers, our data suggests
radical resection of gallbladder carcinoma affords a better survival (5 years survival 51 vs. 15%, P = 0.10). Differing surgical series have also reported that survival may be improved in patients with Stage T2N0 or higher disease by more radical operations. Nonetheless, the role of more radical resection versus simple cholecystectomy remains controversial. Patients with microscopically positive margins after gross total resection have a statistically worse outcome compared with those with negative margins. Margin negative resection had a superior survival versus patients with positive margins. However, we consider achieving margin-negative resection an important end point. The role of persistent local-regional disease contributing to the development of distant metastases is controversial, although in other disease sites, uncontrolled local disease appears to be a source of distant metastases. Reports that describe patterns of failure after surgery are limited. Available data suggests that local-regional recurrence is common and ultimately leads to death, usually from complications of biliary obstruction and liver failure. Literature review indicates local recurrence occurs in up to 86% of patients after cholecystectomy. In long-term survivors after surgery, local recurrence rates remain high, even beyond 5 years. A likely explanation for this finding is that occult nodal involvement is common and localized invasion of the liver is not recognized and respected. This high incidence of residual microscopic disease has been reported in autopsy series. Even in patients treated with radical cholecystectomy local regional recurrence has been reported to be as high as 75%. A recent large study from Memorial Sloan-Kettering Cancer Center showed that in patients who undergo radical resection of GBC, 45% of relapse loco regionally.

**POST-OPERATIVE RADIOTHERAPY**

The patterns of failure and poor overall prognosis in GBC, consideration of adjuvant treatments is appropriate. Only an estimated 20% of patients receive radiotherapy or chemotherapy after resection and fewer than 10% of all presenting patients undergo surgery, radiotherapy and chemotherapy. Therefore, reports that described the use of adjuvant radiochemotherapy in the setting of resected gallbladder carcinoma are limited. Recent series have suggested that local-regional control and possibly ultimate outcome can be improved by the use of adjuvant therapy. Kresl in their study have reported on 21 patient who underwent resection followed by adjuvant chemo-radiotherapy with 5-FU. They reported a 5 years survival rate of 33% and a 5 years survival of 64% in patients treated with margin-negative resection followed by adjuvant chemo-radiotherapy in a cohort that consisted primarily of Stage III/IV patients. A National Cancer Database collective report has suggested that patients who undergo trimodality therapy may have a superior survival when compared with patients who undergo surgery alone. The largest single-institution adjuvant radiation therapy series reported previously was performed by Houry et al., who described results of 20 patients treated post-operatively for GBC between 1977 and 1987. Of the 20 patients, 7 received 5-FU-based chemotherapy in addition to radiation therapy. No conclusions regarding adjuvant chemotherapy were made; however, the authors concluded that adjuvant external beam radiation therapy (EBRT) was associated with increased survival in palliative, but not curative, surgical resection cases. In contrast, Hanna and Rider reported from the Princess Margaret Hospital series that, upon retrospective comparison of GBC patients treated either with surgery alone or adjuvant therapy, there was a survival advantage for adjuvant EBRT compared to surgical resection alone. Based upon the findings of this study and those of the literature, it can be concluded that gallbladder carcinoma is associated with a generally poor prognosis. It is possible that the previous dismal outcome could be improved by noting the factors associated with favorable outcomes and applying these findings to patient care strategies. Surgical resection alone has resulted in relatively poor survival rates. However, performing a complete resection with negative margins seems critical to achieving a favorable outcome. After a negative margin resection, the administration of post-operative adjuvant 5-FU-based chemotherapy and EBRT seems to result in favorable local control and survival rates. Although a greater dose of EBRT (54 Gy) provided a non-statistically significant advantage in local control, the greater dose did not translate into a survival advantage. This is most likely a result of the confounding variable associated with patients with residual tumor (corresponding to poor survival prognosis), who more frequently received EBRT doses 54 Gy. Patients who had complete resection with negative margins followed by adjuvant chemotherapy plus radiation did reasonably well in the current series, with 64% surviving 5 year. However, maintenance chemotherapy should be considered, due to the high risk of distant failure, which is 67% in this study. In the future, methods of achieving earlier diagnoses may help improve outcomes. For patients who present with more locally advanced lesions and whose pre-operative imaging or surgical exploration suggests that a complete resection with negative margins would be unlikely, altered sequencing of treatment options should be evaluated. In these instances, pre-operative chemo-irradiation could precede an attempt at gross total resection. In these cases, intra-operative electron radiation therapy (IOERT) could be given to the area of marginal resection before surgical reconstruction, or a post-operative boost with either dose intensity modulated radiation therapy (IMRT) or three-dimensional conformal techniques to the area of marginal resection could be
considered. Todoroki et al. in their study have demonstrated the potential advantage of combining EBRT and IOERT with gross total marginal resection for Stage IV patients with GBC. Wu et al. and Eisbruch et al. have proposed the potential use of IMRT for dose escalation to improve tumor control and spare surrounding structure/organisms from receiving irradiation tolerance doses. Prospective Phase III studies testing the addition of neoadjuvant pre-operative or post-operative adjuvant radiochemotherapy would be of interest for patients with Stages II-IV GBCs. However, the low incidence of GBC may make it difficult to successfully complete accrual to such trials, unless they are designed as intergroup studies within the United States or as international studies. Advancement in radiation delivery technique like IMRT, image guided radiation therapy etc., and with availability of better chemotherapy drug the practice of adjuvant chemotherapy is likely benefit patients with high risk features.

**ADJUVANT CHEMOTHERAPY**

Chemotherapy has also been used in gallbladder malignancies with little or no survival benefit demonstrated. The only prospective randomized study of chemotherapy in the treatment of gallbladder malignancies was reported by the Eastern Cooperative Oncology Group for inoperable patients. This study failed to demonstrate a survival benefit and reported an objective response rate of only 10%. Other non-randomized trials using 5-FU chemotherapy alone or in combination with other chemotherapy agents infused systemically or locally have reported non-statistically significant improvements compared with surgery alone. Park et al. in retrospective study reported that overall survival (OS) was not significantly different among the adjuvant therapies (P = 0.180), but disease-free survival (DFS) was (P = 0.033). The 3 years OS and DFS from surgery alone, adjuvant chemotherapy and adjuvant radiotherapy and adjuvant concurrent chemo-radiotherapy were 64, 78, 36 and 36% and 56, 69, 14 and 47%, respectively. Overall, the chemotherapy group had a better prognosis, although there were no significant differences. He concluded from this study that adjuvant therapy is an effective treatment option for curative resected GBC. A large randomized controlled study is necessary to confirm the efficacy of adjuvant therapy. Newer adjuvant studies should be focused on gemcitabine-based chemotherapy or chemo-radiotherapy with molecular-based target agents.

**CONCLUSION**

Carcinoma of the gallbladder remains a lethal malignancy. In the minority of patients that are resectable for cure, local-regional recurrence remains a major cause of morbidity and mortality. Adjuvant treatment with radiotherapy and chemotherapy is effective adjuvant therapy is necessary to improve treatment outcome of GBC following resection. Studies suggest that adjuvant chemoradiation therapy may be effective in the treatment of lymph node-positive T2/T3 GBC after surgical resection. Further randomized controlled studies with a larger sample size and with a new chemotherapy regimen are needed to confirm similar therapeutic effects on other stage tumors.

**REFERENCES**


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