Review Article

Post-operative adjuvant treatment in carcinoma gall bladder: A brief review

Pramod Kumar Singh, Rakesh Kapoor, Ritesh Kumar, Amit Bahl, Narendra Kumar, Rajesh Gupta[1], Suresh Chandra Sharma

Departments of Radiotherapy and Oncology, and [1]Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Gallbladder cancer (GBC) represents the most common malignancy among the biliary tree cancers representing 3% of such tumors. Complete surgical resection offers the best chance for cure. Adjuvant chemotherapy and radiotherapy are less well-defined and need to be further evaluated to increase local and systemic control. Local recurrences as high as 75% have been reported after radical cholecystectomy in GBC. The patterns of failure and poor overall prognosis in GBC, justify administration of adjuvant treatments. 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. Recent series have suggested that local-regional control and possibly ultimate outcome can be improved by the use of adjuvant therapy.

Key words: Carcinoma gallbladder, chemotherapy, radiotherapy, surgery

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.[1] In tumors confined to the gallbladder wall, 5 years survival rates after resection only range from 10% to 30%.[2-5] 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.[6] Hepatic infiltration by gallbladder cancer (GBC) has been observed in 60-70% of patients on collective review and autopsy series.[2,7] Lymphatic spread by GBC is also common. Overall regional nodal involvement has been reported in 40-80% of patients.[2,7] For patients with T2 lesions (confined to the gallbladder wall), the incidence of nodal metastases ranges from 40% to 62% respectively.[8-11] When disease invades the covering serosa or adjacent organs, nodal metastases rates rise to 70-80% respectively.[10,11] 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.[12] 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.[3]

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.132108

SURGERY

In advert simple cholecystectomy is the most common surgical procedure for resection of primary carcinoma of the gallbladder,[1] 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.[13] Therefore, many hepatobiliary surgeons advocate radical resection or re-resection (wedge resection of the gallbladder

Address for correspondence: Dr. Pramod Kumar Singh, Department of Radiotherapy and Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drpramodsingh16@gmail.com

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.[1,14,15] 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.[15-19] 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.[20] 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.[21] 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.[22-24] 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.[25] Even in patients treated with radical cholecystectomy local regional recurrence has been reported to be as high as 75%.[22] 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.[1] Therefore, reports that described the use of adjuvant radio chemotherapy 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[20] 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.[20] 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.[1] 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.[4] 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.[26] 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.[27,28] Wu *et al*.[29] and Eisbruch *et al*.[30] have proposed the potential use of IMRT for dose escalation to improve tumor control and spare surrounding structure/organs 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%.[31] 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.[15,32] Park *et al*.[33] 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

1. Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. Surg Gynecol Obstet 1978;147:929-42.
2. Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989-1995. Cancer 1998;83:2618-28.
3. Arnaud JP, Casa C, Georgeac C, Serra-Maudet V, Jacob JP, Ronceray J, *et al*. Primary carcinoma of the gallbladder – Review of 143 cases. Hepatogastroenterology 1995;42:811-5.
4. Houry S, Schlienger M, Huguier M, Lacaine F, Penne F, Laugier A. Gallbladder carcinoma: Role of radiation therapy. Br J Surg 1989;76:448-50.
5. Shani M, Hart J, Modan B. Cancer of the biliary system: A study of 445 cases. Br J Surg 1974;61:98-100.
6. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer 1992;70:1493-7.
7. Sons HU, Borchard F, Joel BS. Carcinoma of the gallbladder: Autopsy findings in 287 cases and review of the literature. J Surg Oncol 1985;28:199-206.
8. Fong Y, Kemeny N, Lawrence T. Cancer of the liver and biliary tree. In: DeVita V, Hellman S, Rosenberg S, editors. Cancer of the Liver and Biliary Tree. 6th ed. Philadelphia: Lippincott, Williams and Wilkins; 2001. p. 1162-203.
9. Shimada H, Endo I, Togo S, Nakano A, Izumi T, Nakagawara G. The role of lymph node dissection in the treatment of gallbladder carcinoma. Cancer 1997;79:892-9.
10. Tsukada K, Kurosaki I, Uchida K, Shirai Y, Oohashi Y, Yokoyama N, *et al*. Lymph node spread from carcinoma of the gallbladder. Cancer 1997;80:661-7.
11. Ogura Y, Mizumoto R, Isaji S, Kusuda T, Matsuda S, Tabata M. Radical operations for carcinoma of the gallbladder: Present status in Japan. World J Surg 1991;15:337-43.
12. Fahim RB, McDonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: A study of its modes of spread. Ann Surg 1962;156:114-24.
13. Shoup M, Fong Y. Surgical indications and extent of resection in gallbladder cancer. Surg Oncol Clin N Am 2002;11:985-94.
14. Gall FP, Köckerling F, Scheele J, Schneider C, Hohenberger W. Radical operations for carcinoma of the gallbladder: Present status in Germany. World J Surg 1991;15:328-36.
15. Morrow CE, Sutherland DE, Florack G, Eisenberg MM, Grage TB. Primary gallbladder carcinoma: Significance of subserosal lesions and results of aggressive surgical treatment and adjuvant chemotherapy. Surgery 1983;94:709-14.
16. Shirai Y, Yoshida K, Tsukada K, Muto T. Inapparent carcinoma of the gallbladder. An appraisal of a radical second operation after simple cholecystectomy. Ann Surg 1992;215:326-31.
17. de Aretxabala XA, Roa IS, Burgos LA, Araya JC, Villaseca MA, Silva JA. Curative resection in potentially resectable tumours of the gallbladder. Eur J Surg 1997;163:419-26.

18. Muratore A, Polastri R, Bouzari H, Vergara V, Capussotti L. Radical surgery for gallbladder cancer: A worthwhile operation? Eur J Surg Oncol 2000;26:160-3.
19. Donohue JH, Nagorney DM, Grant CS, Tsushima K, Ilstrup DM, Adson MA. Carcinoma of the gallbladder. Does radical resection improve outcome? Arch Surg 1990;125:237-41.
20. Kresl JJ, Schild SE, Henning GT, Gunderson LL, Donohue J, Pitot H, *et al*. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002;52:167-75.
21. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949-55.
22. Kopelson G, Galdabini J, Warshaw AL, Gunderson LL. Patterns of failure after curative surgery for extra-hepatic biliary tract carcinoma: Implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1981;7:413-7.
23. Kopelson G, Harisiadis L, Tretter P, Chang CH. The role of radiation therapy in cancer of the extra-hepatic biliary system: An analysis of thirteen patients and a review of the literature of the effectiveness of surgery, chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1977;2:883-94.
24. Cady B, McDonald J, Gunderson L. Cancer of the hepatobiliary system. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and Practice of Oncology. Philadelphia: Lippincott; 1985. p. 741.
25. Vaittinen E. Carcinoma of the gall-bladder. A study of 390 cases diagnosed in Finland 1953-1967. Ann Chir Gynaecol Fenn Suppl 1970;168:1-81.
26. Hanna SS, Rider WD. Carcinoma of the gallbladder or extrahepatic bile ducts: The role of radiotherapy. Can Med Assoc J 1978;118:59-61.
27. Todoroki T, Iwasaki Y, Orii K, Otsuka M, Ohara K, Kawamoto T, *et al*. Resection combined with intraoperative radiation therapy (IORT) for stage IV (TNM) gallbladder carcinoma. World J Surg 1991;15:357-66.
28. Todoroki T, Gunderson LL, Nagorney D. Biliary tract IORT: Bile duct and gallbladder. In: Gunderson LL, editor. Intraoperative Irradiation Techniques and Results. Totowa, NJ: Humana Press; 1999. p. 223-49.
29. Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: A treatment design study. Int J Radiat Oncol Biol Phys 2000;46:195-205.
30. Eisbruch A, Dawson LA, Kim HM, Bradford CR, Terrell JE, Chepeha DB, *et al*. Conformal and intensity modulated irradiation of head and neck cancer: The potential for improved target irradiation, salivary gland function, and quality of life. Acta Otorhinolaryngol Belg 1999;53:271-5.
31. Falkson G, MacIntyre JM, Moertel CG. Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. Cancer 1984;54:965-9.
32. Macdonald JS, Smalley S, Benedetti J. Postoperative combined radiation and chemotherapy improves disease-freesurvival (DFS) and overall survival (OS) in resected adeno carcinoma of the stomach and G.E. junction. Results of Intergroup Study INT-0116 (SWOG 9008). Proceedings of American Society of Clinical Oncology, Plenary 1a; 2000. p. 19.
33. Park HS, Lim JY, Yoon DS, Park JS, Lee DK, Lee SJ, *et al*. Outcome of adjuvant therapy for gallbladder cancer. Oncology 2010;79:168-73.

Cite this article as: Singh PK, Kapoor R, Kumar R, Bahl A, Kumar N, Gupta R, *et al*. Post-operative adjuvant treatment in carcinoma gall bladder: A brief review. Clin Cancer Investig J 2014;3:196-9.

Source of Support: Nil, **Conflict of Interest:** None declared.