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Role of adjuvant radiotherapy in Gall bladder cancers: A review of literature

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Abstract
Gall bladder cancer (GBC) represents the most common biliary tract malignancy, it however it is a rare malignancy overall. Historical work has established complete resection as standard of care. Despite R0 resection the local recurrence (LR) rates remain high. High LR rates prompted interest in study of role of adjuvant therapy in form of radiotherapy and/ or chemotherapy after resection. We attempt to review the role of adjuvant radiotherapy in GBC and also to discuss prognostic factors and key problems in management of gall bladder cancers.
Keyword: *Gall Bladder Cancer, Adjuvant Radiotherapy.*

Introduction

Primary gall bladder cancer (GBC) is a disease with poor prognosis, 5 year overall survival of less than 10%.Incidence increases with age and women are affected more than men.

Carcinoma gall bladder is a relatively rare malignancy, accounting for less than 1% of all cancers, they rank amongst the first ten cancers in Indian Council of Medical Research (ICMR) registries in India.(1) It is common in northern and central regions of India.(2) Gall bladder has a thin muscular wall which lacksserosal layer adjacent to liver, GBCs therefore commonly present with invasion into liver and surrounding structures . They also present with early lymph node involvement. Majority of patients (>70%) present in advanced stages (stage III or stage IV with lymphatic and/or hepatic infilteration.(3) Complete resection of the tumour is the mainstay of treatment however due to late presentation, complete resection is possible in only 10-30% of patients.(4) 5 year survival rates according to SEER database of United states is: for localized stage (AJCC stage 1 and 2) is 61%, for regional stage (AJCC stage 3 and some stage 4 cancers) is 26% and for distant stage (AJCC stage 4) is 2%. These lethal outcomes are attributed to the loco-regional recurrences (LRR) and/ distant failures. To

overcome LRR, adjuvant therapy in form of radiotherapy, chemotherapy or chemoradiotherapy have been tried in multiple small studies and retrospective analysis. NCCN guidelines also recommend adjuvant therapy. As GBC is rare and has a poor prognosis, large prospective randomised trials have not been reported in literature, paucity of data makes it difficult to generate level 1 evidence of adjuvant therapy in GBC. Role of adjuvant radiotherapy remains a matter of debate in GBCs.

This review is aimed to evaluate the role of adjuvant radiotherapy in preventing loco-regional relapse in gall bladder cancers.

Standard of care: Surgery

Goal of R0 resection with initial cholecystectomy, en-bloc hepatic resection and lymphadenectomy (extended cholecystectomy) is the standard approach in GBC. Multiple studies have shown that survival may be improved with more radical resections in patients with stage T2N0 or more. [5][6][7] After gross total resection, positive surgical margins (R1) have a statistically worse outcome as compared to microscopically negative margins.[8] Locoregional recurrences are common and ultimately prove to be lethal due to complications arising from biliary tract obstruction and liver failure. Following radical surgery, the loco-regional recurrences due to occult nodal metastasis and hepatic invasion are seen in upto70-90% of cases. This has been reported in an autopsy series.[9] A large study from Memorial Sloan-Kettering Cancer Center showed that there were 45% of locoregional relapse in patients who underwent radical resection for GBC.

Adjuvant Radiotherapy

Role of adjuvant radiotherapy has been controversial in operated cases of GBC. Gall bladder cancers are considered radio-resistant and definite role of radiotherapy is uncertain. However, a number of small series have reported use of radiation in form of radical treatment, palliation, post-operative adjuvant treatment, intra-operative therapy etc. The major limiting factor in radiating GBC is the nearby critical structures like liver, pancreas, stomach, kidney and small bowel.

Studies reporting adjuvant radiotherapy with or without concurrent chemotherapy in operated cases of gall bladder carcinoma

Author	year	comparison	method	conclusion
Brian et al.[10]	2005	Resected, non-metastatic GBC : adjuvant radiation with or without concurrent chemotherapy (5-FU)	22 cases: treated with adjuvant RT, 18 cases received concurrent chemotherapy	Radical resection followed by adjuvant radiation with radio-sensitizing 5-FU may improve survival in locally advanced GBC.
Mahantshetty et al.[11]	2006	Resected GBC: adjuvant Chemotherapy/ adjuvant CT-RT/ adjuvant RT	60 cases: 13 cases- no adjuvant therapy, 32 received adjuvant RT alone, 8 received CT-RT and 7 received CT alone	Following curative surgery, pathological T stage and stage grouping are very important prognostic factors. Adjuvant chemotherapy and radiation favour local control in advanced cases.
Mojica et al.[12]	2007	Resected GBC: adjuvant RT vs no adjuvant RT	3,187 cases: 542 cases received adjuvant RT, median overall survival 14 months (with adjuvant RT) vs 8 months (without adj. RT) ($p<0.001$) Overall survival benefit limited to pT3-T4 or pN+ disease	Adjuvant RT is of benefit in pT3-T4 and pN+ cases with improved overall survival
Wang et al.[13]	2008	Resected GBC: adjuvant RT vs no adjuvant RT	4,180 cases: 752 cases received adjuvant RT	Significant OS benefit of varying degree with adjuvant RT for patients with pT2 or higher T stage and / or pN+.

Wang et al.[14]	2011	Resected GBC: adjuvant chemoradiotherapyvs adjuvant chemotherapy	1,137 cases: 125 cases received adjuvant CRT and 125 received adjuvant chemotherapy	Adjuvant chemoradiotherapy provided statistically significant OS benefit in patients pT2-T3 N0 and largest benefit in pT4 and pN+. Adjuvant chemotherapy also provided small benefit in pT4 and or pN+ disease but it was smaller than adjuvant chemoradiotherapy
Horgan et al.[15]	2012	Meta-analysis including studies with adjuvant chemotherapy, adjuvant radiotherapy and adjuvant chemoradiotherapy	6 studies were included	There was a strong trend towards benefit with adjuvant therapy, adjuvant chemoradiotherapy and adjuvant chemotherapy provided more significant benefit as compared to adjuvant RT alone, especially in R1 resection.
Ben-josef et al.[16]	2015	Single arm study in pT2-T4 or pN+ or R1 resection, 4 cycles of adjuvant Gemcitabine/Capecitabine followed by adjuvant RT 54-59.4 Gy with concurrent capecitabine	79 cases	Found to be effective and tolerable regimen compared to historical controls
Hassan et al.[17]	2018	Stage I-III resected GBC: adjuvant therapy vs surveillance only	251 cases: 78 received adjuvant therapy (CT/CT-RT) vs 173 were observed.	Adjuvant therapy had no statistically significant effect on overall survival or disease free survival in overall population, howeverstage IIIB patients had better survival with adjuvant therapy.

Hanna and rider reported results of 51 patients of resected GBC and concluded that survival in adjuvant radiotherapy arm was much more significant as compared to surgery alone arm. Another study reported median survival of 63 months in post-op RT arm as compared to 29 months in only surgery arm.[18] Todoroki et al. examined intra-operative radiotherapy in resected cases of stage IV GBC, with 3 year OS of 10% vs 0% in surgery alone arm.[19] The dose of adjuvant radiotherapy reported has been in range of 45 Gy to 54 Gy with a mean dose of 47 Gy and median dose of 50 Gy.

IMRT has been suggested for dose escalation by Eisbruch et al.[20] and Wu et al.[21] with benefit of maximal sparing of nearby normal structures.

All these studies suggest that use of adjuvant radiotherapy with or without concurrent chemotherapy in locally advanced operated cases of GBC have resulted in improvement in 5 year overall survival in the range of 33% to 45%. However, with development of safer radiation techniques and more effective chemotherapy drugs, a larger prospective trial is needed to pinpoint the exact role of radiation therapy in gall bladder cancer.

Adjuvant chemotherapy

Many studies have evaluated the role of adjuvant chemotherapy alone in resected GBC. However no statistically significant benefit has been reported. Most of the studies used 5-FU infusion while some studies used capecitabine and/or gemcitabine too. The major advantage was seen when chemotherapy was used concurrently with radiotherapy with maximal benefit seen in OS and DFS. To validate use of chemotherapy, a larger randomised trial is necessary before coming to any conclusion.

Conclusion

Gall bladder cancers are rare but potentially lethal. Because of lower number of cases reported, a definite guideline to treatment of these cancers has not been established. R0 resection is the primary aim of treatment and most important prognostic

factor too. Presently available literature suggests that adjuvant therapy should be considered in pT3-T4 cases, pN+ cases and in R1 resection as these are the cases which seem to be benefited the most. Adjuvant chemo-radiotherapy results are superior to the use of either of the single modality treatment in terms of local control, overall survival and disease free survival. However larger randomised study with adequate sample size needs to be done to see the role of newer chemotherapeutic agents and the high-end radiation technologies available in present era to establish the role of adjuvant therapy in gall bladder cancers.

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