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# The Effect of Adjuvant Radiotherapy in Patients Undergoing Complete Resection for Gallbladder Cancer with Lymph Node Metastasis

**Purpose:** We evaluated the effect of adjuvant radiotherapy on survival in patients who underwent curative resection for gallbladder cancer with lymph node metastasis.
**Methods:** Among the patients underwent curative resection even though there was lymph node metastasis; fifteen patients underwent adjuvant radiotherapy with over 40 Gy (RTx group) and 10 patients did not (no RTx group). We compared these two groups retrospectively.
**Results:** The median disease free survival (DFS) of the RTx group (21.6 months) was longer than for the no RTx group (6.6 months, $p$=0.451). The median overall survival (OS) of the RTx group (30.5 months) was also longer than the no RTx group (14.2 months). One-, 2-, and 5-yr OS rates were 60.0%, 40.0% and 40.0% in the no RTx group, and 86.7%, 70.9% and 26.6% in the RTx group, respectively ($p$=0.507). Five patients developed recurrence within 1 year (50.0%) in the no RTx group; there were 3 (20.0%) in the RTx group.
**Conclusion:** Our study was limited by its retrospective nature and small numbers of patients. However, it suggests that adjuvant radiotherapy might improve DFS and OS for patients with completely resected but lymph node metastasized gallbladder cancer. Also this therapy seems to delay time to postoperative recurrence.

Key Words : Gallbladder cancer, Postoperative radiotherapy, Survival

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## Introduction

The prognosis of gallbladder (GB) cancer is extremely poor due to the high proportion of tumor that is advanced at the time of presentation.[1,2] The major therapeutic modality and the only curative treatment is surgical resection. However, despite of the aggressive surgical approach, 40～86 % of patients who undergo a potentially curative resection will develop recurrent metastatic disease.[3,4] Therefore, radiotherapy or chemotherapy has been considered as an adjuvant therapy to improve loco-regional control and overall survival rate (OS). Some reports have suggested a benefit of concurrent

chemo-radiation therapy for GB cancer.[5,6] However, the effect of adjuvant radiotherapy for the GB cancer is not well established.[7,8] In general, the decision to administer adjuvant therapy is dependent upon the type of surgery and the pathologic risk factors and is based on physician and patient preference after discussion about the possible risks and benefits.

To evaluate the effect of adjuvant radiotherapy, we reviewed only for the patients who underwent curative resection for gallbladder cancer with pathologically confirmed lymph node metastasis.

## Methods

One hundred forty-seven patients had been performed the surgical treatment for GB cancer at Ajou University Hospital between October 1994 and March 2008. Among them, 30 patients underwent curative resection though there was lymph node metastasis. We excluded 5 patients received radiotherapy of less than 18 Gy from this study. Fifteen patients underwent adjuvant radiotherapy with ≥40 Gy (hereafter, RTx group) and 10 patients did not (hereafter, no RTx group). Altogether, the two groups had 10 male patients and 15 female patients with median age of 59.0±12.1 years, ranging from 34～79 years.

The adjuvant radiotherapy was administered using a 10～15 MV linear accelerator with a median total dose of 46.8±28.6 Gy (range, 43.4～50.4 Gy in 22～28 fractions). Initial radiation fields encompassed the tumor bed and regional lymph nodes (porta hepatis, pericholedocal, celiac, and pancreaticoduodenal nodes). After 45 Gy, boost radiation to the tumor bed was delivered in some patients based on physcian's decision. Patients were treated at 1.8～2 Gy per fraction, once a day, 5 days a week. Three- or four- field techniques were used in most patients.

Among the 15 patients of the RTx group, 7 patients (46.7%) were treated with radiation alone and 8 patients (53.3%) received chemoradiotherapy. Chemotherapy was given as a radiosensitizer in 5 patients and concurrently with radiotherapy as a part of systemic chemotherapy in 3 patients. Chemotherapy regimens were varied; daily cisplatin in 3 patients and 5-Fluorouracil based regimens in 5 patients. Maintenance chemotherapy after completion of radiotherapy was used in 2 patients.

GB cancers were staged according to the 6th edition of the AJCC.UICC TNM classification.[2] The clinical characteristics of GB cancer included gender, age, tumor size and operation method. The pathologic characteristics included stage, pathology, differentiation, and lymphovascular or perineural invasion.

Survival was calculated from the date of surgery. We examined the exact survival status and date of death of patients by calling to the patients' family or checking the medical records. Continuous variables were written as the median±standard deviation (range). Crosstabs, such as Pearson's chi-square test and Fisher's exact test, independent t-test, nonparametric test such as Mann-Whitney test and Kaplan-Meier survival analysis were used for statistical analyses using SPSS (version 15.0; SPSS, Inc., Chicago, IL, USA). Difference was considered statistically significant when the $p$-value was $<0.05$.

## Results

There were no statistical differences between the two groups in clinical characteristics (Table 1) and pathological characteristics (Table 2). The median age of the RTx group was younger than the no RTx group (56.0±9.4 vs. 63.0±15.2, $p$=0.183).

The median follow-up duration was 25.6 months (range, 4.0～165.9 months). We analyzed the patterns of failure and overall (OS) and disease-free survivals (DFS) for comparing the RTx group (N=15) and the no RTx (N=10) group. The median DFS of the RTx group (21.6±9.1 months) was longer than the no RTx group (6.6±5.2 months), however, there was no statistically significant difference ($p$=0.451; Table 3). The patient number who developed recurrence within 1 year was 3 (20.0%) in RTx

**Table 1.** Comparison of the clinical characteristics between no RTx group and RTx group

| No. (%) | No RTx (N=10) | RTx (N=15) | *p*-value |
|---|---|---|---|
| Gender | | | |
| Male | 3 (30.0%) | 7 (46.7%) | 0.678* |
| Female | 7 (70.0%) | 8 (53.3%) | |
| Age (years) | 63.0±15.2 | 56.0±9.4 | 0.183† |
| Tumor size (cm) | 3.0±1.5 | 5.0±2.4 | 0.262† |
| Operations | | | |
| LC‡ | 1 (10.0%) | 1 (6.7%) | 0.211 |
| OC§ | 0 (0.0%) | 1 (6.7%) | |
| OC+LN dissection | 0 (0.0%) | 3 (20.0%) | |
| Extended chole¶ | 4 (40.0%) | 7 (46.7%) | |
| OC+hepatectomy | 4 (40.0%) | 1 (6.7%) | |
| Extended chole+Whipple's | 1 (10.0%) | 1 (6.7%) | |
| OC+colon resection | 0 (0.0%) | 1 (6.7%) | |

*Fisher's exact test; †Mann-Whitney test; ‡LC=laparoscopic cholecystectomy; § OC=open cholecystectomy; ¶Extended chole=open cholecystectomy+liver wedge resection+LN dissection

**Table 2.** Comparison of the pathological characteristics between no RTx group and RTx group

| No. (%) | No RTx (N=10) | RTx (N=15) | *p*-value |
|---|---|---|---|
| T stage | | | |
| T2 | 3 (30.0%) | 9 (60.0%) | 0.226* |
| T3 | 7 (70.0%) | 6 (40.0%) | |
| Pathology | | | |
| Adenocarcinoma | 7 (70.0%) | 12 (85.7%) | 0.412 |
| Adenocarcinoma+signet ring cell | 0 (0.0%) | 1 (6.7%) | |
| Adenosquamous | 1 (10.0%) | 1 (6.7%) | |
| Adenocarcinoma+Mucinous | 1 (10.0%) | 0 (0.0%) | |
| Mixed endocrine+exocrine carcinoma | 1 (10.0%) | 0 (0.0%) | |
| Differentiations | | | |
| Well | 1 (10.0%) | 3 (20.0%) | 0.178 |
| Moderate | 2 (20.0%) | 8 (53.3%) | |
| Poorly | 2 (20.0%) | 2 (13.3%) | |
| Undifferentiated | 0 (0.0%) | 1 (6.7%) | |
| Not determined | 5 (50.0%) | 1 (6.7%) | |
| Lymphovascular invasion | | | |
| − | 4 (40.0%) | 8 (53.3%) | 0.688* |
| + | 6 (60.0%) | 7 (46.7%) | |
| Perineural invasion | | | |
| − | 7 (70.0%) | 11 (73.3%) | 1.000 |
| + | 3 (30.0%) | 4 (26.7%) | |

*Fisher's exact test

group and 5 (50.0%) in no RTx group.

The median OS of the RTx group (30.5±3.7 months) was also longer than the no RTx group (14.2±4.0 months). One-, 2-, and 5-yr OS were 86.7%, 70.9% and 26.6% in the

**Table 3.** Comparisons of the disease free survival and overall survival between no RTx group and RTx group

| Group | No RTx (N=10) | RTx (N=15) | *p*-value |
|---|---|---|---|
| Median disease free survival (mo) | 6.6±5.2 | 21.6±9.1 | 0.451 |
| Disease free survival (%) | | | |
| 1-year | 50.0% | 79.0% | |
| 2-year | 40.0% | 49.2% | |
| 5-year | 40.0% | 41.0% | |
| Median overall survival (mo) | 14.2±4.0 | 30.5±3.7 | 0.507 |
| Overall survival rates (%) | | | |
| 1-year | 60.0% | 86.7% | |
| 2-year | 40.0% | 70.9% | |
| 5-year | 40.0% | 26.6% | |

**Table 4.** Comparison of the pattern of failure between no RTx group and RTx group

| No. (%) | No RTx | RTx | *p*-value |
|---|---|---|---|
| Development of recurrence | (N=10) | (N=15) | |
| No recurrence | 3 (30.0%) | 6 (40.0%) | 0.497 |
| Recurrence | 6 (60.0%) | 8 (53.3%) | |
| Other cancer | 1 (10.0%) | 0 (0.0%) | |
| Unknown | 0 (0.0%) | 1 (6.7%) | |
| Recurrence patterns | (N=6) | (N=8) | |
| Loco-regional | 2 (33.3%) | 4 (50.0%) | 0.627* |
| Systemic | 4 (66.7%) | 4 (50.0%) | |
| Sites of systemic recurrence | (N=4) | (N=4) | |
| Liver | 1 (25.0%) | 2 (50.0%) | 0.175 |
| Loco-regional+liver | 1 (25.0%) | 0 (0.0%) | |
| PS† | 1 (25.0%) | 1 (25.0%) | |
| Bone | 0 (0.0%) | 0 (0.0%) | |
| Para-aortic LN‡ | 0 (0.0%) | 1 (25.0%) | |
| PS+lung+neck LN | 1 (25.0%) | 0 (0.0%) | |

*Fisher's exact test; †PS=peritoneal seeding; ‡LN=lymph node

RTx group and 60.0%, 40.0% and 40.0% in the no RTx group, respectively. There were no statistical differences in OS between the two groups ($p$=0.507). Subgroup analysis was performed to identify the benefit from adding chemotherapy to radiotherapy. Patients who received chemoradiotherapy had shorter median OS than patients treated with radiotherapy alone (25.9±26.0 months vs. 30.5±4.4 months, $p$=0.923).

The recurrence pattern was described in Table 4. In the no RTx group, 6 patients (60.0%) showed postoperative recurrences; the first site of failure was loco-regional in 2 patients (33.3%) and systemic in 4 (66.7%). In the RTx group, 8 of 14 evaluable patients (53.3%) experienced recurrences; loco-regional failure in 4 (50.0%) and systemic metastasis in 4 (50.0%). In subgroup analysis, recurrence was developed in 3 of 7 patients treated with chemoradiotherapy and in 5 of 7 radiotherapy alone patients.

In the RTx group, 12 out of 15 patients (80.0%) experienced acute complications. Most of the side effects were tolerable. Most common side effect was gastrointestinal trouble such as nausea (5 patients, 38.5%) and anorexia (2 patients, 15.4%). Leukopenia was observed in 1 patient

(7.7%); this patient restarted the radiotherapy after rest for some period and the other patient should stop the concurrent chemotherapy but maintained the radiotherapy.

## Discussion

Surgical treatment is the only potentially curable modality for GB cancer, currently. However, unfortunately, the majority of patients present advanced lesions and have no chance of a curative resection.[9] And moreover, even if patients undergo a curative resection they harbor frequently poor prognosis factors like as positive lymph node, higher T stage, old age and non-papillary histology those increase the chance of failure.[10,11] Because of this aggressive nature of GB cancer, individualized multimodality approach is required to be optimized.

The rationale for postoperative radiation therapy is to sterilize tumor cell areas surrounding the tumor that could be left after surgery.[9,12] Radiosensitive nature of gallbladder cancer is evidenced by numerous studies reporting tumor size reduction after radiotherapy for unresectable disease.[13,14] However, because of the rarity of GB cancer, actual benefit of adjuvant therapy has not been well established.[7,8]

There are some reports about the efficacy of adjuvant radiotherapy for GB cancer. Kresl et al. reported an improved 5-year survival (33%) of GB cancer patients underwent adjuvant radiation therapy following optimal surgical resection. They included 21 patients who received 50.4～60.8 Gy of radiation with concurrent chemotherapy after surgery.[5] Czito et al. reported 22 patients with GB cancer who received adjuvant therapy consisting of 5-FU chemotherapy and a median radiation dose of 45 Gy with an overall 5-year survival of 37%.[6]

Reports announced the benefit of adjuvant radiotherapy in node positive GB cancer is few. Wang et al.[11] suggested greatest net benefit from adjuvant radiotherapy in patients with higher stage (T2 or greater) and lymph node-positive disease. Balachandran et al.[15] reported adjuvant chemoradiotherapy made significant survival improvement in node positive patients. In their study, patients who underwent adjuvant chemoradiotherapy (N=31) showed 18 months median survival and 25% 5-year survival, whereas, patients who did not undergo chemoradiotherapy (N=25) showed 7 months median survival and 0% 5-year survival ($p$=0.005). However, their data included non-curative resection, and node positive patients had more R1 resection and it could reflect the efficacy of chemoradiotherapy in non-curable surgical patients. Mogica et al.[16] reported adjuvant radiation therapy for patients who presented with regional disease (positive lymph nodes) and demonstrated an improved overall median survival from 5 to 16 months with the use of radiation therapy (no RTx (n=277) vs. RTx (n=127), $p$ <0.0001). Gold et al.[7] also reported the median OS for patients receiving adjuvant chemoradiotherapy vs. surgery only was 4.8 years and 4.2 years, respectively (log-rank test, $p$=0.56). After adjusting for prognostic factors in the multivariate analysis, the administration of adjuvant chemoradiotherapy resulted in significantly improved OS (hazard ratio for death, 0.30; 95% confidence interval, 0.13 ～0.69; $p$=0.004).

We restricted the study group to patients with positive lymph node metastasis after curative resection. In our study, the median DFS and median OS were longer in RTx group than no RTx group. Five-year OS of RTx group was similar with no RTx group, whereas, 1- and 2 - year OS were superior in RTx group (1-year OS, 86.7% vs. 60.0% and 2-year OS, 70.9% vs. 40.0%). The recurrence rate within 1 year after surgery was lower in RTx group than no RTx group (20.0% vs. 50.0%). From this result, we guessed the effect of radiotherapy in terms of delay time to recurrence and this effect improved the short term DFS and OS of GB cancer until 2 years after surgery.

In our study, RTx group has slightly younger age compared with no RTx group ($p$=0.183). This is maybe due to more aggressive application of treatment modality to young patients than old aged patients. Some reports suggested age was important independent prognostic factor of GB cancer and the survival rates decreased with

increasing age.[17-19] Therefore, the effect of younger age to superior survival in RTx group cannot be ruled out.

There is no uniform agreement regarding radiation dose, modality and timing of therapy.[16] About the timing of radiation therapy, Kraybill et al.[20] noted a trend towards long - term survival in the patients who received radiation therapy within 2 months after surgery compared with delayed radiation with an absolute improvement of about 30% in 5 years. Several reports have suggested the relation between radiation dose higher than 40 Gy and improved survival.[21,22] In our study, radiation therapy was started within 2 months after surgery and all patients received radiation of 40 Gy and greater.

Based on the recurrence patterns, it is difficult to advocate the use of radiotherapy alone. Jarnagin et al.[23] observed that GB cancer had a higher incidence of distant metastases as a first site of failure compared with hilar cholangiocarcinoma. Therefore, the addition of chemotherapy would be essential for improving results.[6,9,14] However, in our study, the patients who underwent adjuvant chemoradiotherapy (N=8) showed short median OS than the patients who underwent only radiotherapy (25.9±26.0 months vs. 30.5±4.4 months, $p$=0.923) despite the two groups showed no statistical differences in the stages. Because of small number of patients and variety of chemotherapy regimens, we supposed our results could not reflect the effect of chemoradiation, sufficiently.

Current National Comprehensive Cancer Network 2007 guidelines stated although there is limited clinical trial data to support a standard regimen, all patients with stage higher than T1N0 should be considered for adjuvant therapy.[11] Although, our study has a drawbacks such as the small number of patients in each group and retrospective study, our results support these suggestions. Therefore, we are continued to consider adjuvant radiotherapy for GB cancer with lymph node metastasis after curative resection.

## Conclusion

Our data showed adjuvant radiotherapy after curative resection for GB cancer with lymph node metastasis might have some beneficial effect on survival of patients. And adjuvant radiotherapy seemed to delay time to recurrence. The reason of no statistical significance in this study was regarded as small number of the patients. Therefore, further study with large number of patients can be helpful to evaluate the effect of radiotherapy for gallbladder cancer.

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