Contemporary perspectives on the use of radiation therapy for locally advanced gallbladder cancer

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Abstract: Locally advanced gallbladder cancer poor prognosis due to a high distant metastatic rate and poor overall disease control. The impact of standard therapeutic options is unfortunately modest. Due to the rarity of the disease, evidence-based management continues to evolve. The goal of this review is to highlight the contemporary landscape of radiation therapy for gallbladder cancer. First, the rationale for radiation therapy is described. This includes the risk of locoregional recurrence following resection based on patterns-of-failure data, along with the high locoregional disease burden being a frequent cause morbidity and mortality in unresected cases. Additionally, improvements in systemic therapy over the next decade could shift contemporary patterns of failure more towards proportionally higher locoregional recurrence rates. Second, clinical data of radiation therapy for gallbladder cancer are discussed. These include consideration of postoperative chemoradiotherapy for margin- and/or node-positive cases. Patients with localized unresectable disease could benefit from ablative radiation therapy, based on promising data in non-gallbladder cancer pancreaticobiliary neoplasms. The use of advanced radiation therapy technologies such as proton beam therapy, as a means to deliver ablative radiation therapy in a potentially safer manner, is also mentioned. Lastly, the emerging concept of neoadjuvant therapy for gallbladder cancer is also described, in efforts to allow more patients to receive curative resection.

Keywords: Radiation therapy; gallbladder cancer; adjuvant; ablative; biliary cancer; radiotherapy


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Introduction

Although gallbladder cancer is relatively uncommon, it is the most common biliary tract cancer and is associated with a highly aggressive natural history. Owing to the low incidence of gallbladder cancer, well-powered randomized clinical trials have not been possible, and definitive evidence-based approaches to management are lacking in the literature. As a result, management decisions of gallbladder cancer continue to be centered on multidisciplinary discussion, carefully weighing the risks and benefits of various combinations of surgical resection, chemotherapy, and radiation therapy.

Although survival for gallbladder cancer remains poor, surgical resection remains the only recognized curative approach (1). However, many patients may not be candidates for resection owing to the extent and/or spread of disease. Chemotherapy is considered an integral portion of therapy in the post-operative or definitive setting, but does not substitute for definitive local therapy. The use of RT is controversial, yet is commonly used for selected cases in the adjuvant or definitive setting. The National Comprehensive Cancer Network (NCCN) currently...
recommends up-front resection when possible, followed by adjuvant chemotherapy or chemotherapy plus radiation therapy; if resection is not feasible, definitive chemotherapy plus radiation therapy or chemotherapy alone are also options (2).

The aim of this review is to critically examine the role of radiation therapy for gallbladder cancer, both in the adjuvant and definitive settings, as well as describe novel RT approaches and treatment paradigms of the contemporary era. The reader is cautioned that the overall quality and quantity of data are relatively limited, and hence this article does not substitute for careful, individualized judgment as part of a multidisciplinary team approach.

Rationale

Patterns-of-failure studies demonstrate the propensity for gallbladder cancer to metastasize, the high frequency locoregional recurrence after surgery alone, and a poor overall survival (OS) rates in patients with unresectable disease. Gallbladder cancer is a distinct entity from other biliary tract cancers. In comparison, patients with intrahepatic cholangiocarcinoma have a high distant metastatic rate; in spite of this, local disease progression leads to mortality in the vast majority of cases if a definitive local treatment is not possible (3,4). Patients with inoperable extrahepatic cholangiocarcinoma suffer significant morbidity and mortality from their primary disease and typically die from biliary sclerosis related to relentless bouts of cholangitis. There is also a very high locoregional recurrence rate after resection owing to the high incidence of close and positive margins and the propensity for isolated nodal spread (5,6), which supports the use of local therapy following resection.

In contrast, following resection of gallbladder cancer an estimated 15–25% of recurrences occur as locoregional recurrences if radiation therapy or chemotherapy plus radiation therapy is not used (7-12) (Table 1). Of note, these recurrence patterns have largely remained numerically similar in the modern era, suggesting that improved surgical techniques may not adequately make up for the high postoperative recurrence rates. In fact, studies show that, of incidental gallbladder cancer findings on non-oncologic cholecystectomy, 25–40% of patients harbor additional disease, largely in regional lymphatics (9,13). An even higher risk of locoregional occurs with margin positive resection, leading some to conclude that this population may particularly benefit from radiation therapy (11). The NCCN lists adjuvant CRT as a possible option in this circumstance as well (2).

Historically, treatment of patients with localized inoperable disease with definitive chemotherapy plus radiation therapy has been modestly effective (14). In-field local progression 1 to 2 years after treatment has been common because historically definitive doses have been limited to a bioequivalent dose of 50 Gy by the tolerance of the nearby duodenum, complicated by respiratory motion. These limitations of treatment provide a rationale for biologically effective dose (BED)-escalated radiation therapy (ablative radiation, discussed subsequently) made possible by the evolution of organ motion management and stereotactic treatment techniques. Moreover, administering ablative radiation following standard-of-care chemotherapy is probably the only definitive (non-palliative) therapy for inoperable patients. As such, improvements in systemic therapy over the current decade (15), and potentially extrapolating the successes of multi-agent regimens in pancreatic cancer (16,17) (randomized trials (e.g., clinicaltrials.gov NCT03768414 of gemcitabine plus Cisplatin with or without nab-paclitaxel) continue to accrue in biliary cancers), could shift contemporary patterns of failure more towards locoregional recurrences, which may be more conducive towards utilizing RT as a curative-intent modality.

Adjuvant radiotherapy

Table 2 summarizes relevant details of contemporary (published over the current decade) studies assessing adjuvant radiation therapy (18-27). Of note, the included studies comprised a majority of R0 resections, most commonly delivered radiation therapy at conventionally fractionated doses between 45–54 Gy, and utilized concurrent 5-fluorouracil (or capecitabine) based chemotherapy. A few noteworthy studies will be further highlighted below.

Two large national database studies analyzing over 4,500 patients each, were comparative analyses of adjuvant radiation therapy versus lack thereof. The first publication (21) demonstrated an OS benefit with adjuvant radiation therapy following propensity matching; however, the unadjusted cohorts showed that radiation therapy was associated with higher 1-year OS and lower 5-year OS. This implies a high degree of selection bias, possibly explained by the lack of chemotherapy information (or radiation therapy dose) in the database, thus potentially including subjects...
Table 1 Summary of patterns-of-failure studies of gallbladder carcinoma

<table>
<thead>
<tr>
<th>Study &amp; year</th>
<th>Sample size</th>
<th>Initial iLRR</th>
<th>Median time to recurrence</th>
<th>mOS after (any) recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopelson et al., 1981</td>
<td>28</td>
<td>25%</td>
<td>17 months</td>
<td>--</td>
</tr>
<tr>
<td>Jarnagin et al., 2003</td>
<td>97</td>
<td>15%</td>
<td>12 months</td>
<td>21 months</td>
</tr>
<tr>
<td>Barreto et al., 2014</td>
<td>127</td>
<td>25%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Margonis et al., 2016</td>
<td>217</td>
<td>16%</td>
<td>10 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Kim, 2017</td>
<td>70</td>
<td>19%</td>
<td>9 months</td>
<td>20 months</td>
</tr>
<tr>
<td>Choi et al., 2018</td>
<td>93</td>
<td>19%</td>
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<td>--</td>
</tr>
</tbody>
</table>

iLRR, isolated locoregional recurrence; mOS, median overall survival.

Table 2 Summary of contemporary studies of radiotherapy for resected gallbladder carcinoma

<table>
<thead>
<tr>
<th>Study &amp; year</th>
<th>Type</th>
<th>Sample size</th>
<th>Resection</th>
<th>Radiation dose</th>
<th>Chemotherapy</th>
<th>Outcomes/comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al., 2012</td>
<td>Retrospective single-institutional</td>
<td>47</td>
<td>R0 (79%), R+ (21%)</td>
<td>40–50 Gy</td>
<td>5-FU (n=41)</td>
<td>5 y OS 50%</td>
</tr>
<tr>
<td>Müller et al., 2013</td>
<td>Retrospective single-institutional</td>
<td>46</td>
<td>Unspecified</td>
<td>45–54 Gy</td>
<td>5-FU (n=34)</td>
<td>5 y OS 51%</td>
</tr>
<tr>
<td>Jeong et al., 2014</td>
<td>Retrospective single-institutional</td>
<td>86</td>
<td>R0 (84%), R1 (16%)</td>
<td>50 Gy (median)</td>
<td>5-FU based (n=61)</td>
<td>5 y LRC 73%, 5 y DFS 36%, 5 y OS 42%</td>
</tr>
<tr>
<td>Hyder et al., 2014</td>
<td>SEER database</td>
<td>5,011</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Higher OS with adjuvant RT</td>
</tr>
<tr>
<td>Wang et al., 2015</td>
<td>Retrospective multi-institutional</td>
<td>112</td>
<td>R0 (74%), R1 (26%)</td>
<td>45–54 Gy (n=68)</td>
<td>5-FU based (n=63)</td>
<td>RT reduces LF, similar OS</td>
</tr>
<tr>
<td>Ben-Josef et al., 2015</td>
<td>Prospective single-arm phase II</td>
<td>79 (25 GC)</td>
<td>R0 (68%), R1 (32%)</td>
<td>45–59.4 Gy</td>
<td>Gem/Cape, concurrent cape</td>
<td>No LF in GC group, 13/25 with DM, 2 y DFS 48%, 2 y OS 56%</td>
</tr>
<tr>
<td>Kim et al., 2016</td>
<td>Retrospective multi-institutional</td>
<td>291 (44 CRT)</td>
<td>R0 (86%), R1 (14%)</td>
<td>Unspecified</td>
<td>Gem-based</td>
<td>Higher DFS/OS with CT or CRT, especially T3–4, LN+, R1</td>
</tr>
<tr>
<td>Mantripragada et al., 2017</td>
<td>National Cancer Database</td>
<td>4,775</td>
<td>R0 (76%), R1 (34%)</td>
<td>50.4 (median)</td>
<td>Unspecified</td>
<td>No difference in OS with adjuvant RT</td>
</tr>
<tr>
<td>Gu et al., 2017</td>
<td>Retrospective single-institutional</td>
<td>94</td>
<td>R0 (100%)</td>
<td>50 Gy (median)</td>
<td>Cape/S-1 or 5-FU-based</td>
<td>CRT improves DFS/OS over observation</td>
</tr>
<tr>
<td>Kim et al., 2018</td>
<td>Meta-analysis</td>
<td>9,364</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Nonuniform</td>
<td>RT reduces LF, higher OS</td>
</tr>
</tbody>
</table>

Gy, Gray; 5-FU, 5-fluorouracil; OS, overall survival; LRC, locoregional control; DFS, disease-free survival; SEER, Surveillance, Epidemiology, and End Results; RT, radiotherapy; LF, local failure; GC, gallbladder cancer; Gem, gemcitabine; Cape, capecitabine; DM, distant metastasis; CRT, chemoradiotherapy; CT, chemotherapy; LN, lymph node.

without chemotherapy (or suboptimal receipt) and/or palliative radiation therapy. The second investigation (25) included information on radiation therapy dose but not chemotherapy agents/timing, and thus was an investigation of post-operative surveillance versus adjuvant chemotherapy plus radiation therapy. No differences in OS were found, even when statistically adjusting for several factors.

A meta-analysis (26) of 9,364 patients from 14 retrospective investigations also showed reduced recurrence and mortality with adjuvant radiation therapy, although
chemotherapy details were also discontinuous and non-uniform. Of note, subgroup analyses demonstrated that node-positive and/or incompletely resected patients benefited most from radiation therapy. This is consistent with established data displaying that aggressive management for these high-risk features may be most meaningfully beneficial to outcomes (28,29).

Lastly, the Southwest Oncology Group (SWOG) S0809 study (23), a single-arm phase II trial of adjuvant CRT for resected (pT2–4 or N1 or R1) extrahepatic cholangiocarcinoma (n=54) and GC (n=25), is the only prospective study that has been reported. Protocol therapy consisted of postoperative gemcitabine/capecitabine; if progression did not occur, chemotherapy plus radiation therapy (concurrent capecitabine and intensity-modulated radiation therapy in most cases) was delivered. Radiation therapy consisted of 45 Gy elective nodal irradiation and 54–59.4 Gy to the tumor bed depending on surgical margin status. At median follow-up of 35 months, 2-year OS (primary endpoint) was 65% (67% in R0 cases, 60% in R1 cases) and 2-year disease-free survival was 52%. Corresponding numbers for the gallbladder cancer subjects were 56% and 48%, respectively. The two-year local failure rate was 8% for gallbladder cancer and 11% overall. Of note, 14 subjects developed local failure (none of whom had gallbladder cancer), but most (n=9) had concomitant distant metastasis. Because the 2-year OS was higher than expected based on power calculations, together with the tolerability of the chemotherapy plus radiation therapy regimen, the authors concluded that the trial met its primary endpoint.

Recently, the American Society of Clinical Oncology (ASCO) published guidelines for gallbladder cancer and other biliary cancers, endorsing adjuvant capecitabine following resection and chemotherapy plus radiation therapy for R1 cases (30). Publication of the accruing Perioperative Therapy Preoperative Chemotherapy Versus Chemoradiotherapy in Locally Advanced Gall Bladder Cancers (POLCAGB) trial (NCT02867865), which randomizes patients with gallbladder cancer to perioperative gemcitabine plus cisplatin versus chemotherapy plus radiation therapy (50–55 Gy to gross disease and 45 Gy to subclinical infiltration, concurrent with gemcitabine), could further impact ASCO and NCCN guidelines.

### Definitive radiotherapy

Because unresected gallbladder cancer is near-universally fatal, most studies have utilized palliative chemotherapy for this circumstance; however, Table 3 displays contemporary (published over the current decade) investigations evaluating definitive radiation therapy (31-33). These are largely limited to big data studies and/or encompass a minority of gallbladder cancer cases. Both database studies observed a higher OS in patients having received chemotherapy plus radiation therapy over chemotherapy alone; this is notable because neither accounted for RT dose, implying that the effect of RT persisted despite the likely inclusion of palliative radiation therapy. However, owing to inherent limitations of national databases, these findings should be considered hypothesis-generating at the present time.

There is evidence for dose-response in gallbladder cancer. A study illustrated 5-year local control of 100% for

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### Table 3 Summary of contemporary studies of radiotherapy for unresected gallbladder carcinoma

<table>
<thead>
<tr>
<th>Study &amp; year</th>
<th>Type</th>
<th>Sample size</th>
<th>Radiation dose</th>
<th>Chemotherapy</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollom et al., 2017</td>
<td>SEER-Medicare database</td>
<td>2,343 (n=444 GC)</td>
<td>Unspecified</td>
<td>Received by 45%</td>
<td>Median OS 9 mo without RT, 10 with RT</td>
<td>Higher OS with RT only in patients who underwent CT</td>
</tr>
<tr>
<td>Verma et al., 2018</td>
<td>National Cancer Database</td>
<td>1,199</td>
<td>All doses</td>
<td>Unspecified</td>
<td>Median OS 8 mo with CT, 13 with CRT</td>
<td>Higher OS with addition of RT to CT</td>
</tr>
<tr>
<td>Bisello et al., 2019</td>
<td>Retrospective single-institutional</td>
<td>76 (any biliary)</td>
<td>Median 50 Gy EBRT + 14 Gy BT (51%)</td>
<td>5-FU- or Gem-based</td>
<td>2 y OS 26%, 2 y PFS 9%</td>
<td>CRT is feasible and tolerable</td>
</tr>
</tbody>
</table>

SEER, Surveillance, Epidemiology, and End Results; GC, gallbladder cancer; OS, overall survival; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy; Gy, Gray; EBRT, external beam radiotherapy; BT, brachytherapy; 5-FU, 5-fluorouracil; Gem, gemcitabine; PFS, progression-free survival.
patients having received >54 Gy, as compared to 65% for ≤54 Gy (34). Moreover, the initial site of progression for biliary neoplasms undergoing conventionally-fractionated radiation therapy is local (72%) rather than DM (15%) (6). As a result, with contemporary radiation therapy technology (e.g., high-quality image guidance, adaptive planning, and internal organ motion management), ablative radiation therapy has become an active area of further investigation. Ablation refers to high radiation therapy doses per fraction, thus allowing for much higher BEDs than afforded by conventional (1.8–2 Gy per fraction) fractionation. In addition to notable successes in pancreatic cancer (35), ablative radiation therapy was examined in an investigation of 79 unresected intrahepatic cholangiocarcinomas, most of which underwent chemotherapy prior to radiation therapy (36). This study compared two cohorts, one with BED ≤ 80.5 Gy (most common regimens 50.4 Gy/28 fractions or 58.1 Gy/15 fractions) and the other with BED >80.5 Gy (67.5 Gy/15 fractions or 75 Gy/25 fractions). Radiation therapy dose, when analyzed as a continuous variable in a multivariable model (also accounting for tumor size), independently predicted for higher local control and OS. For subjects having received >80.5 Gy BED, the 3-year local control and OS were impressively high (78% and 73%, respectively); this is noteworthy considering that the median tumor size in all-comers was 8 cm. Ablative radiation therapy was also tolerated well, with few high-grade events and no radiation therapy-induced liver disease.

An emerging modality with which to deliver ablative radiation therapy in a potentially safer manner is proton beam therapy. Proton beam therapy is a highly conformal modality that yields a sharp dose drop-off between the distal edge of the tumor and surrounding normal tissue, owing to the heavy size of the proton and its associated Bragg peak. Although there have been no dedicated series of proton beam therapy for gallbladder cancer, several studies of liver tumors and cholangiocarcinoma (37-39) along with a phase II trial (40) illustrate favorable safety profiles. The role of proton beam therapy for liver and biliary tumors will be better addressed with a number of ongoing randomized trials, including some that employ dose-escalation.

**Treatment sequencing**

Although management of gallbladder cancer (and other biliary neoplasms) has traditionally involved up-front resection, neoadjuvant therapy an emerging paradigm with a logical rationale in gallbladder cancer. Although there remain concerns regarding tumor progression during neoadjuvant therapy as well as postoperative complications thereafter, neoadjuvant chemotherapy or chemotherapy plus radiation therapy has several advantages. These include downstaging a proportion of initially unresectable cases so as to receive curative resection, reduction of the R+ rate, evaluation of tumor biology, and avoidance of administering radiation therapy in the hypoxic postoperative setting (41,42). Furthermore, preliminary data from the randomized Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) trial shows that preoperative therapy may offer locoregional, disease-free, and OS advantages as compared to up-front resection (43).

Both chemotherapy alone and chemotherapy plus radiation therapy have been utilized in the literature. Although in the adjuvant setting, chemotherapy alone was administered in the SWOG S0809 trial (23) and was effective to better address micrometastatic disease and select for favorable biology prior to chemotherapy plus radiation therapy. Conversely, up-front chemotherapy plus radiation therapy could avoid the excess toxicities from induction chemotherapy and may better address the risk of local progression than systemic therapy alone.

Most available data for neoadjuvant chemotherapy or chemotherapy plus radiation therapy are retrospective in nature, and are summarized in a recent systematic review (44). From this investigation, 40% of all subjects were able to eventually undergo surgery; for the limited studies of neoadjuvant chemotherapy plus radiation therapy, the rate of post-therapy partial/complete response ranged from 40–70%. These values are encouraging, in part because most radiation therapy approaches have been conventionally fractionated; together with the equally promising data regarding ablative radiation therapy, it is certainly possible that neoadjuvant ablative radiation therapy may offer an even higher ability to proceed with resection. Hence, neoadjuvant approaches represent an exciting frontier that warrants further prospective investigation.

**Conclusions**

This review describes the contemporary landscape of radiation therapy for gallbladder cancer, chiefly highlighting the rationale to reduce local failure in the adjuvant setting and locoregional disease burden in the definitive setting. Clinical data are limited and of low quality, but nevertheless...
remain encouraging, especially for high-risk (R+ and/or node-positive) cases in the adjuvant setting and ablative radiation therapy in the definitive setting. Application of advanced radiation therapy technologies such as soft tissue image guidance, adaptive planning, internal organ motion management, and PBT may better facilitate safe delivery of ablative RT. Lastly, neoadjuvant chemotherapy plus radiation therapy is an emerging paradigm that may allow more patients to receive curative resection, which should also be further elucidated going forward.

**Acknowledgments**

None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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