Radiotherapy for Bile Duct Cancer

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Introduction

The biliary tract includes the intra- and extra-hepatic bile duct and the gallbladder and the term cholangiocarcinoma refers to all tumors arising from bile duct epithelium. In Korea, cholangiocarcinoma is uncommon cancer, which develops in 8 per 100,000 populations every year and the incidence rate is only 2.9% of all cancers. This cancer is highly lethal cancer, however, 5-year survival has improved. According to the report of the Korea Central Cancer Registry, 5-year survival rate was 22.3% during the period of 2001-2005.

The standard treatment for patients with biliary tract cancer is not defined yet, but a multidisciplinary team approach that includes surgical oncologist, gastroenterologist, interventional radiologist, pathologist, medical oncologist, and radiation oncologist is required for the effective management of the patient.

Extrahepatic Bile Duct Cancer and Radiotherapy

1. Adjuvant Radiotherapy

The role of preoperative radiotherapy with or without chemotherapy remains investigational and the neoadjuvant radiochemotherapy could be an option for patients with marginally resectable cancers. However, from the practical standpoint, downstaging the cancer and achieving respectability is unrealistic. On the other hand, to reduce the risk of local and regional recurrences after curative surgery, postoperative adjuvant radiotherapy has been administered. In case of hilar cholangiocarcinoma, recurrences occurred most commonly at the bed of resection, followed by retroperitoneal lymph nodes. Distant metastases occur in one third of cases. The high rate of local recurrence comes from the proximity between bile duct and surrounding major vessels (portal triad) and the possibility of microscopic residual tumor in proximal, distal and radial resection margin.

2. Postoperative Radiotherapy

The radiotherapy can be administered either by external-beam radiotherapy (EBRT), intraluminal brachytherapy (ILBT), intra-operative radiotherapy (IORT), or combined radiotherapy modalities. The
most commonly applied radiotherapy modality is EBRT. Total dose of 40 to 50 Gy over 5 to 6 weeks is administered in a continuous course to the tumor bed and draining lymph node stations. The radiotherapy volume for draining lymph nodes can be modified as the location of tumor in extrahepatic bile duct. According to the status of residual disease, a boost of radiotherapy with a smaller volume can be applied with additional EBRT, ILBT, or IORT and the total radiation dose is 54 to 60 Gy or more. The organs within the upper abdomen such as the spinal cord, kidneys, liver, stomach, duodenum, and small bowel have relatively low tolerance to radiation. Therefore, the low tolerance of these organs induces significant limitations to the total therapeutic dose of radiation and this can decrease the possibility of loco-regional tumor control. To reduce dose to normal structures and to increase dose to the target volume, ILBT or IORT has been applied.

The ILBT is a radiotherapy modality using radioactive isotope. After the placement of a catheter within bile duct, the radioactive isotope could be located into the involved portion of the biliary tract. ILBT has been used to boost the radiation dose after EBRT or used alone for biliary tract tumors. The usual boost dose is 10 to 20 Gy at 0.5 to 1.0 cm from the isotope. The advantages of ILBT are delivery of a high dose to a localized, relatively small target and rapid radiation dose fall-off. The disadvantage is that the insertion of a catheter into the biliary tract should be done before brachytherapy and this is invasive technique and can increase the risk of cholangitis and hemorrhage.

IORT is administered using an electron beam during the surgery. The attractive point of IORT is that radiation can be directly delivered to the tumor bed with high accuracy while the sensitive organs such as the stomach, duodenum and small intestine can be displaced away from the radiation. However, the linear accelerator should be situated within, or very close to, the operating room and the lack of clinical studies are the main limiting factors for use of IORT.

Because extrahepatic cholangiocarcinoma is rare and the curative resection is done to only small proportion of patients, the efficacy of adjuvant radiotherapy has never been evaluated in prospective randomized trials. Therefore, the available data of adjuvant radiotherapy for patients with biliary tract cancer are from some retrospective studies, but the radiotherapy modalities, techniques and the patient populations are very heterogeneous.

The above Table shows the clinical studies of adjuvant radiotherapy or radiochemotherapy for extrahepatic cholangiocarcinoma. Most retrospective reviews of adjuvant radiochemotherapy have reported the favorable outcomes in patients receiving adjuvant therapy. However, it is very difficult to compare these retrospective studies because of the difference of patient population, indication of adjuvant radiotherapy and the extent of curative resection.

Until now, the adjuvant therapy cannot be considered standard treatment for the patients of extrahepatic cholangiocarcinoma. However, adjuvant radiochemotherapy can be recommended for patients with curative resection, when the tumor has invaded into or through the muscularis layer (pathologic T2 or T3), the resection margins are microscopically involved (R1), or regional lymph nodes are involved (N+). The recommended radiation dose is that initially 45 Gy is delivered to
Table. Adjuvant Radiotherapy or Radiochemotherapy for Extrahepatic Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of patients</th>
<th>R0 (%)</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>LRF (%)</th>
<th>MS (Months)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh et al.</td>
<td>60</td>
<td>40</td>
<td>EBRT 45 Gy</td>
<td>20% of patients</td>
<td>67</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>72</td>
<td>65</td>
<td>EBRT 40 Gy (split course)</td>
<td>Bolus 5-FU</td>
<td>47</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Todoroki et al.</td>
<td>29</td>
<td>4</td>
<td>IORT 21 Gy, EBRT 43 Gy or combination</td>
<td>No</td>
<td>20</td>
<td>32</td>
<td>0.01</td>
</tr>
<tr>
<td>Sagawa et al.</td>
<td>39</td>
<td>49</td>
<td>EBRT 37 Gy + ILBT 37 Gy or EBRT 38Gy</td>
<td>No</td>
<td>69</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Gerhards et al.</td>
<td>71</td>
<td>14</td>
<td>EBRT 46Gy or EBRT 42Gy + ILBT 10Gy</td>
<td>No</td>
<td>20</td>
<td>-</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pitt et al.</td>
<td>14</td>
<td>68</td>
<td>EBRT w/o ILBT 13Gy</td>
<td>No</td>
<td>20</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Ben-David et al.</td>
<td>28</td>
<td>43</td>
<td>EBRT 54Gy</td>
<td>54% of pts</td>
<td>39</td>
<td>24.1 (R0)</td>
<td>15 (R1)</td>
</tr>
</tbody>
</table>

R0, resection with negative margins; LRF, loco-regional failure; MS, median survival; EBRT, external-beam radiation therapy; 5-FU, 5-fluorouracil; IORT, intraoperative radiotherapy; ILBT, intraluminal brachytherapy; NS, not significant; R1, resection with microscopically positive margins CI, continuous infusion.

the tumor bed and regional lymph node stations followed by a boost dose of 9 to 15 Gy to the tumor bed according to the presence of high-risk area. Three-dimensional conformal radiotherapy is used with CT-based treatment planning.

3. Radiotherapy in Locally Advanced Cholangiocarcinoma

In locally advanced cholangiocarcinoma, a few data with radiotherapy or radiochemotherapy have been published, EBRT with or without ILBT is applied and the usual radiation doses are 45 to 54 Gy with EBRT and 15 to 25 Gy with ILBT. The median survival of radiotherapy alone or radiochemotherapy is approximately 12 months. However, there is no randomized or comparative study to compare radiotherapy with other treatment modality including supportive care only. There is a controversy over the radiation dose and tumor response relationship and long-term survivors have been rarely reported. Although the evidence level of radiotherapy alone or radiochemotherapy for patients with extrahepatic cholangiocarcinoma is low, patients with good performance should be considered for such therapy.
Conclusion

The standard treatment for patients with biliary tract cancer is not defined yet, but a multidisciplinary team approach is essential both in curative and palliative setting. Although there is no randomized study evaluating the efficacy of radiotherapy, radiotherapy alone or radiochemotherapy has been administered and some retrospective studies showed favorable outcomes. However, the final results for the patients with biliary tract cancer are unsatisfactory. In these days, there has been a rapid development in the radiotherapy field and many chemotherapeutic agents are investigated for the treatment of biliary tract cancer. Therefore, multi-institutional clinical studies for combined treatment modalities should be designed and tried to increase the clinical results of the patients with biliary tract cancer.

References

1. 2008 Report of the Korea Central Cancer Registry