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Radiation therapy for biliary tract tumors: the joint experience of three centers*

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Background/aim: This study presents the joint experience of three centers in the treatment of patients with biliary tract tumors with radiation therapy (RT).

Materials and methods: The records of 27 patients were retrospectively reviewed. All of the patients who had undergone surgical resection received postoperative adjuvant RT, whereas all of the patients who had not undergone a surgical resection received RT with palliative intent. Twenty patients with adequate performance status were treated with RT and chemotherapy, while the remaining seven patients were treated with RT alone.

Results: Follow-up ranged from 1 to 44 months. Local control was not achieved in 10 out of 11 patients who had received RT with palliative intent. Systemic failure was observed in eight patients at 5 to 16 months. Fifteen patients died due to disease-related causes at 1 to 22 months. At 2 years, overall survival was 33% and disease-free survival was 19%. A surgical resection with curative intent predicted improved local failure-free survival and improved disease-free survival.

Conclusion: Since local recurrence is still the leading cause of failure following postoperative RT and the outcome following palliative RT is far from satisfactory, the indications, the target volume, and the doses for RT should be reconsidered.

Key words: Biliary tract tumors, surgery, radiation therapy, chemotherapy

1. Introduction

Biliary tract tumors constitute 10% to 15% of all tumors involving the hepatobiliary system. They might arise from the intrahepatic biliary tract, or more commonly the extrahepatic biliary tract (1). Surgical resection is the mainstay of treatment for biliary tract tumors, which should aim for uninvolved margins in an attempt to exploit any potential for cure. In the majority of patients, however, the attempts at a potentially curative surgical resection are hindered by the extent of the tumor at the time of diagnosis or the presence of comorbidities (2). In patients with biliary tract tumors, radiation therapy and chemotherapy might be indicated as adjuvant measures for those that have undergone surgical resection with a curative intent or as palliative measures for those that have been deemed inoperable (3). Regarding the medical literature that attempts to evaluate the effectiveness of adjuvant measures in patients with biliary tract tumors, retrospective studies from individual centers are abundant, whereas prospective studies from multiple centers are absent. Therefore, the adjuvant treatment approach for biliary tract tumors is governed by personal tendencies or institutional policies rather than evidence. This study presents the joint experience of three centers in the treatment of patients with biliary tract tumors with radiation therapy.

2. Materials and methods

The study design was approved by the Institutional Review Board of Kocaeli University.

2.1. Patient characteristics

The medical records of 27 patients who had been treated with radiation therapy with the diagnosis of biliary tract tumors (with no evidence of metastatic disease at the time of diagnosis) from July 2007 through June 2013 were

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retrospectively reviewed. The clinical data (including physical examination, imaging studies, surgical reports, radiation therapy charts, and chemotherapy charts) and the histopathological data for all of the patients were reclassified. There were 14 males (52%) and 13 females (48%), their ages ranging from 46 to 86 years (median: 61 years).

For 19 patients, a tissue diagnosis of adenocarcinoma had been obtained through an invasive intervention or surgical procedure prior to the management approach. For five patients, the invasive interventions or the surgical procedures that had been attempted had failed to produce a tissue diagnosis, whereas for three patients, no invasive interventions or surgical procedures had been attempted due to the presence of comorbidities. For these eight patients for whom a tissue diagnosis had not been obtained, a decision was made by the Tumor Board of the respective institution to proceed with a management approach governed by the assumptive diagnosis of a "malignant tumor originating from the biliary tract" based on the available clinical data and the imaging studies.

The tumor location was the extrahepatic biliary tract in 14 patients, the intrahepatic biliary tract in four patients, and the perihilar region in nine patients. The tumor size ranged from 1 to 6 cm (median: 2.5 cm). Staging was made in accordance with the TNM classification system of the American Joint Committee on Cancer (4). Of patients with extrahepatic biliary tract tumors, four were at Stage IA, one was at Stage IB, three were at Stage IIA, four were at Stage IIB, and two were at Stage III. Of patients with intrahepatic biliary tract tumors, one was at Stage I, one was at Stage III, and two were at Stage IVA. Of patients with tumors of the perihilar region, two were at Stage II, three were at Stage IIIA, three were at Stage IVA, and one was at Stage IVB.

2.2. Treatment characteristics

Surgical resection with a curative intent was performed on 16 patients. Of 10 patients with extrahepatic biliary tract tumors, seven had undergone a biliary tract excision, whereas three had undergone a pancreaticoduodenectomy. Of three patients with intrahepatic biliary tract tumors, all had undergone a biliary tract excision (combined with a hepatic resection in one patient). Of three patients with tumors of the perihilar region, all had undergone a biliary tract excision (combined with a hepatic resection in one patient). Of patients who had undergone surgical resection with a curative intent, 11 had microscopically involved surgical margins.

All of the patients who had undergone surgical resection with a curative intent received postoperative adjuvant radiation therapy, whereas all of the patients who had not undergone a surgical resection received radiation therapy with palliative intent. Time to postoperative adjuvant radiation therapy ranged from 1 to 3 months (median: 1 month) and only one patient started radiation therapy at 3 months following surgery. Gross tumor volume (GTV) was defined as any visible tumor on CT and/or MRI, clinical target volume (CTV) was defined with a 1.5 cm margin to GTV (especially along the bile duct and potential lymphatic drainage areas, including nodes along the port hepatis, pancreaticoduodenal system, celiac axis, and paraaortic lymph nodes), and planning target volume (PTV) was defined by adding a margin of 5 to 10 mm to the CTV. The target volume for radiation therapy included the tumor bed and the regional lymph nodes in 20 patients, and additionally the paraaortic lymph nodes in seven patients. Radiation therapy doses ranged from 45 to 60 Gy (median: 50.4 Gy), using a daily fraction size of 1.8 to 2 Gy (median: 1.8 Gy).Twenty patients with adequate performance status were treated with radiation therapy and chemotherapy, while the remaining seven patients had been treated with radiation therapy alone. Of patients who were treated with radiation therapy and chemotherapy, 14 received concurrent treatments (using gemcitabine in eight patients and fluorouracil in six patients), whereas six received sequential treatments (using gemcitabine in two patients, fluorouracil in two patients, and carboplatin with fluorouracil in two patients).

2.3. Statistical analysis

Overall survival was defined as the time from diagnosis to death from any cause. Patients who were alive were classified as censored observations at the time of the last follow-up for overall survival. Local failure-free survival was defined as the time from diagnosis to local failure or death from any cause, whichever came first. Patients who were alive without local failure were classified as censored observations at the time of the last follow-up for local failure-free survival. Systemic failure-free survival was defined as the time from diagnosis to systemic failure or death from any cause, whichever came first. Patients who were alive without systemic failure were classified as censored observations at the time of the last follow-up for systemic failure-free survival. Disease-free survival was defined as the time from diagnosis to local failure, systemic failure, or death from any cause, whichever came first. Patients who were alive without local failure or systemic failure were classified as censored observations at the time of the last follow-up for disease-free survival. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Survival estimations were performed using the method of Kaplan and Meier, and univariate analysis was performed using the log-rank test and log-rank test for linear trends. Statistical significance was considered when the P-value was 0.05 and below.

3. Results

Follow-up ranged from 1 to 44 months (median: 17 months). Local control was not achieved in 10 out of 11 patients who had received radiation therapy with palliative intent. Local failure was observed in five out of 16 patients who had received postoperative adjuvant radiation therapy. Time to local failure ranged from 4 to 23 months (median: 7 months). Systemic failure was observed in eight patients at 5 to 16 months (median: 8 months). Fifteen patients died due to disease-related causes at 1 to 22 months (median: 9 months). At 2 years, overall survival was 33%, local failure-free survival was 33%, systemic failure-free survival was 57%, and disease-free survival was 19%. A surgical resection with curative intent predicted improved local failure-free survival ($P < 0.001$) and improved disease-free survival ($P < 0.001$).

4. Discussion

The majority of patients with biliary tract tumors present with locally advanced or metastatic disease, with an overall survival rate at 2 years well below 10%. The median survival time is 2 to 3 months for patients treated in the absence of a surgical resection, 6 to 12 months for patients undergoing biliary bypass surgery with palliative intent, and 12 to 24 months for patients undergoing surgical resection with curative intent. Although a complete surgical resection is the only management approach with a potential for cure, the resectability rates range from 10% to 35% in the relatively older series and from 50% to 55% in the more recent series (3,5). Patients presenting with more distally located tumors are more likely to undergo surgical resections with curative intent, whereas the chances are slim for those presenting with more proximally located tumors. Almost half of the patients that have preoperatively been deemed to have a resectable disease have intraoperatively been regarded to have an unresectable disease. Furthermore, uninvolved surgical margins are achievable in only 30% of patients who undergo surgical resections with a curative intent (2,6). The prognosis remains poor even for those patients who have undergone a complete surgical resection with uninvolved surgical margins, with local failure rates exceeding 50% and resulting in death from biliary tract obstruction, sepsis, or hepatic failure (7–9).

Radiation therapy might have a role in the management of patients with biliary tract tumors that have undergone a surgical resection with curative intent in attempt to "sterilize the surgical margins" and reduce local failure rates. Although radiation therapy in the postoperative adjuvant setting has been addressed in various retrospective studies from individual centers, the effectiveness of such a management approach has not been tested in prospective studies from multiple centers (10,11). Vern-Gross et al. examined the role of postoperative adjuvant radiation therapy in patients with extrahepatic biliary tract tumors. They reported that out of 1491 eligible patients with resected extrahepatic biliary tract tumors that had been registered in the Surveillance, Epidemiology, and End Results (SEER) database from 1973 through 2003, 473 (32%) had received postoperative adjuvant radiation therapy. For patients with "localized disease", the median survival time was 36 months with radiation therapy as opposed to 28 months without radiation therapy, whereas for patients with "regional disease", the median survival time was 18 months with radiation therapy as opposed to 18 months without radiation therapy. The authors concluded that postoperative adjuvant radiation therapy was not associated with an improvement in survival in patients with resected extrahepatic biliary tract tumors (12). In a similar study, on the other hand, Shinohara et al. examined the role of postoperative adjuvant radiation therapy in patients with intrahepatic biliary tract tumors. They reported that out of 1234 eligible patients with resected intrahepatic biliary tract tumors that had been registered in the SEER database from 1988 through 2003, 286 (29%) had received postoperative adjuvant radiation therapy. The median survival time was 11 months with radiation therapy as opposed to 6 months without radiation therapy. The authors concluded that postoperative adjuvant radiation therapy was associated with an improvement in survival in patients with resected intrahepatic biliary tract tumors (13).

The role of chemotherapy, either alone or in combination with radiation therapy, in the management of patients with biliary tract tumors has been loosely defined. The justification for fluorouracil-based regimens to be used in combination with radiation therapy has largely been extrapolated from the improvement in survival that has been achieved with such combinations in other tumors involving the gastrointestinal system and the hepatobiliary system (14,15). Takada et al. evaluated the effect of postoperative adjuvant chemotherapy in patients with resected pancreaticobiliary tumors. Of 118 eligible patients with resected biliary tract tumors, 58 had been treated with chemotherapy consisting of a combination of mitomycin and fluorouracil while 60 had been treated without chemotherapy. At 5 years, overall survival was 27% with chemotherapy and 24% without chemotherapy, with the difference not being statistically significant (16). Elsewhere, Kim et al. analyzed the outcome following postoperative adjuvant chemoradiotherapy in patients with resected extrahepatic biliary tract tumors. Radiation therapy was delivered to the tumor bed and the regional lymph nodes at a dose of 40 Gy while chemotherapy consisted of fluorouracil. At 5 years, overall survival was 45%, locoregional failure-free survival was 70%, and systemic failure-free survival was 54%. They reported that

poor histopathological differentiation predicted worsened overall survival, involved surgical margins predicted worsened locoregional failure-free survival, and increased number of involved lymph nodes predicted worsened systemic failure-free survival (17).

Radiation therapy with palliative intent has frequently been employed in the management of patients with biliary tract tumors that have failed to undergo a surgical resection, mainly having locally advanced tumors but no evidence of metastatic disease at the time of diagnosis. In the palliative setting, radiation therapy has been associated with relief of pain, maintenance of a patent biliary tract, and, least commonly, improved survival (18,19). Crane et al. evaluated the limitations of chemoradiotherapy in the palliative setting in patients with extrahepatic biliary tract tumors that had failed to undergo a surgical resection. For the majority of the patients, radiation therapy was delivered at a dose of 30 to 50.4 Gy, while chemotherapy consisted of fluorouracil. The local recurrence rate at 1 year was 59% and the median survival time was 10 months. They reported that higher radiation therapy doses were associated with improved local control rates (20). Although the optimal target volume, dose, and fractionation schedule for radiation therapy remain to be decided not only in the postoperative adjuvant setting but also in the palliative setting, a selection bias that favors higher radiation therapy doses for those patients having a good performance status is apparent. Since radiation therapy doses in excess of 40 Gy have frequently been associated with life-threatening side effects such as radiation-induced liver disease in most series, higher doses are typically administered to patients having well-localized and smaller tumors in an attempt to limit the liver volume that would receive a higher dose (21,22).

In conclusion, in the present study local failure was observed in 31% of patients who had received postoperative adjuvant radiation therapy, whereas local control was not achieved in 91% of patients who had received radiation therapy with palliative intent, with 56% of patients dying due to disease-related causes. The limitations of the present study are the retrospective nature as well as the limited number of patients who happen to build a heterogeneous group, resulting in difficulties in terms of statistical analysis. Local recurrence is still the leading cause of treatment failure for patients who undergo a surgical resection with curative intent followed by postoperative adjuvant radiation therapy, whereas the outcome following radiation therapy with palliative intent is far from satisfactory for patients who fail to undergo a surgical resection. Therefore, the indications, the target volume, and the doses for postoperative radiation therapy might be reconsidered.

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