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Clinical analysis of cholangiocarcinoma patients receiving adjuvant radiotherapy

DANUPON NANTAJIT[1], PORNWAREE TRIRUSSAPANICH[1], SUNANTA ROJWATKARNJANA[1], KAMONWAN SOONKLANG[2], POOMPIS PATTARANUTRAPORN[1], KANYANEE LAEBUA[1] and SASIKARN CHAMCHOD[1]

[1]Department of Radiation Oncology; [2]Data Management Unit, Chulabhorn Hospital, Bangkok 10210, Thailand

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Abstract. Cholangiocarcinoma (CCA) or bile duct cancer is a rare cancer type in developed countries, while its prevalence is increased in southeast Asia, affecting ~33.4 men and ~12.3 women per 100,000 individuals. CCA is one of the most lethal types of cancer. Neo-adjuvant and adjuvant therapies have been shown to have limited efficacy in improving the overall prognosis of patients. Radiotherapy has been reported to prolong the survival times of patients with certain characteristics. The present study retrospectively evaluated the medical records and follow-up data from 27 CCA patients who received radiotherapy at Chulabhorn Hospital (Bangkok, Thailand) between 2008 and 2014. A total of 14 patients underwent surgery followed by adjuvant chemoradiotherapy. Of the 27 CCA patients, 14 had intrahepatic CCA, 2 had extrahepatic CCA and 11 had hilar CCA. The 2-year survival rate was 40.7%. Tumor resectability, clinical symptoms and the Eastern Cooperative Oncology Group performance status score were found to be indicative of patient prognosis. In addition, the planning target volume and biologically effective radiotherapy dose were of prognostic value; however, initial treatment response was ambiguous in predicting survival time. The findings of the present study suggested that the currently used radiotherapy protocols for CCA may require modification to improve their efficacy.

Introduction

Cholangiocarcinoma (CCA) is one of the most lethal cancer types, with a 5-year survival rate of <5% (1,2). Mostly consisting of adenocarcinomas, CCAs are topographically categorized into two major subtypes, namely intrahepatic and extrahepatic CCAs, with the hilar subtype also being considered as extrahepatic. CCA is rare in developed countries, with an incidence of ~0.5-2 per 100,000 individuals; however, intra- as well as extrahepatic CCA is common in southeast Asia, particularly Thailand. Compared with liver cancer, the prevalence of CCA is considered to account for 10-25% of liver cancer cases in the country, particularly in the northeastern region, where incidence rates of 36.3 and 87.7 per 100,000 individuals have been reported in women and men, respectively (3-6). The exact cause of bile duct cancer remains unknown; however, infection with the southeast Asian liver fluke (*Opisthorchis viverrini*) is considered a major risk factor for the development of intrahepatic CCA. Furthermore, liver cirrhosis, chronic hepatitis C virus infection, hepatolithiasis, smoking and obesity, as well as mutations of the K-ras and p53 genes, may also contribute to the development of intrahepatic CCA (7-11). While the risk factors for hilar and extrahepatic CCA largely remain elusive, excessive alcohol consumption has been reported to be a major risk factor for the development of extrahepatic CCA (12).

At present, complete surgical resection is considered as the only effective treatment available for CCA. Negative histological margins and well-differentiated tumor histology are associated with long-term survival of patients following tumor resection (13,14). Liver transplantation combined with neoadjuvant chemoradiotherapy is another available option for effective CCA treatment (15,16). In unresectable CCA, conventional treatment modalities, including chemotherapy and radiotherapy, may prolong patient survival; however, the results thus far are discouraging (17-19). An alternative radiation modality, stereotactic body radiation therapy, has also failed to improve the survival of unresectable CCA patients (20). Tumor -related hepatic failure due to disease recurrence is the leading cause of patient mortality, exceeding that of other causes combined, such as distant metastasis, infection or angiocholitis (21). For patients with resectable CCA, the effectiveness of postoperative adjuvant radiotherapy remains controversial, as diverse studies report either positive or null results. Although the debate regarding the benefit of radiotherapy for patients with CCA is ongoing, certain factors have been shown to affect treatment outcomes and patient survival (18,22-26). Age, ethnicity, tumor stage and year of diagnosis, as the numbers of patients receiving radiotherapy were growing, have been associated with the prognosis of CCA patients following radiotherapy (22). Negative margins, lymph

Correspondence to: Dr Sasikarn Chamchod, Department of Radiation Oncology, Chulabhorn Hospital, 54 Kamphaeng Phet 6, Talat Bang Khen, Lak Si, Bangkok 10210, Thailand
E-mail: sasikarnbm@yahoo.com

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node metastasis and tumor histopathology are also significant prognostic factors following treatment (27). The aim of the present study was to evaluate clinical factors which may affect the survival of CCA patients receiving radiotherapy treatment.

Patients and methods

Patient selection. The medical and follow-up records of CCA patients treated with radiotherapy between February, 2008 and June, 2014 at Chulabhorn Hospital (Bangkok, Thailand), were retrospectively reviewed. The patients were followed up until July, 2015, which was the end of the study period. Patients who had received and completed a radiotherapy course for primary CCA as part of their treatment scheme, as well as those who had received chemotherapy, either as a concurrent or an adjuvant treatment, in addition to radiotherapy, were included in the study. Patients who had received neo-adjuvant chemo-radiotherapy or radiotherapy prior to surgery were excluded from the study. Gender, age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance score, tumor subtype, tumor stage, regional lymph node involvement, presence of distant metastasis, resection margin, histological grading, planning target volume (PTV) for radiotherapy and prescribed radiation dose were considered as independent variables, while patient survival time was considered as a dependent variable.

Statistical analysis. Patient data were presented using descriptive statics, and logistic regression analysis, the Yates' χ^2 test and Fisher's exact test. The patient survival rate was analyzed using the Kaplan-Meier method and the log-rank test. The significance level was set at $P<0.05$. Values are expressed as the mean ± standard deviation (SD). All statistical analyses were performed using Stata/SE 12 software (StataCorp LP, College Station, TX, USA).

The present study was approved by the Committee on Human Rights Related to Research Involving Human Subjects of Chulabhorn Research Institute (Bangkok, Thailand). A waiver of informed consent was approved by the committee (reference no. 07/2557).

Results

Patient characteristics. A total of 39 patients diagnosed with CCA were treated at Chulabhorn Hospital during the study period; 2 patients were treated in 2008, when the hospital was initially established, 3 in 2009, 7 in 2010, 8 in 2011, 9 in 2012, 6 in 2013 and 4 in 2014 (until June). However, only 27 patients were included in the study after applying the inclusion and exclusion criteria. At diagnosis, the median age was 54 years (range, 42-77 years) and the mean age ± SD was 55.2 ± 9.04 years. The clinical characteristics of the patients are listed in Table I. The majority of patients (n=16) were men. A total of 14 patients had intrahepatic CCA, 11 had hilar CCA and the 2 remaining patients had extrahepatic CCA. According to the TNM staging system (based on the quidelines of the American Joint Committee on Cancer) the tumors of 4 patients were classified as stage I, those of 7 patients as stage II, those of 8 patients as stage III and those of 4 patients as stage IV, while stage was unknown for the remaining 4 patients. The tumor size ranged from 0.9 to 11.5 cm. Furthermore, involvement of 1 lymph node was found in 17 patients, while there was no lymph node involvement detected in the remaining 10 patients. None of the 27 patients had distant metastasis at initial diagnosis.

Treatment and outcome. Of the 27 patients, 15 were eligible for resection, of whom 14 underwent surgical treatment and 1 patient refused to undergo surgery. Among the patients who underwent surgical resection, 9 had positive resection margins and 5 had negative margins. In total, 23 patients received chemotherapy, either as an adjuvant therapy or concurrent chemoradiotherapy. Of these patients, 19 received 5-fluorouracil, 3 received gemcitabine and 1 received cisplatin with gemcitabine. Regarding radiotherapy, the patients received radiation doses of 46-66 Gy, depending on their condition (mean radiation dose, 48.3±6.3 Gy). The dose per fraction was typically 1.8 or 2 Gy; however, two patients received higher doses per fraction, 2.2 or 2.3 Gy each. One patient received stereotactic body radiation therapy (SBRT; 6 fractions of 9 Gy each). With the assumption of an α/β ratio of 10 Gy, the calculated biologically effective dose (BED) ranged from 55.2 to 102.6 Gy.

Due to the low 5-year survival rate of CCA patients and a median survival of 14 months (28), the 2-year survival rate of the patients of the present study was determined. The survival rate of the patients is shown in Fig. 1. Furthermore, statistical analysis of factors affecting survival was performed within the patients' survival period. Among the 27 cases, the mean and median survival times were 699 and 637 days (23.0 and 20.9 months), respectively. A number of factors appeared to be prognostic for survival: Resectability of the tumor, patient ECOG performance status and clinical symptoms were the main indicators of prognosis (Table I). In terms of radiotherapy, PTV and BED applied during treatment were also significantly associated with patient survival (Table II).

Discussion

CCA is a lethal cancer that predominantly affects individuals in developing countries; to date, means to reduce its incidence have not been implemented. Numerous potential prognostic factors have been suggested for patients with CCA. Orthotopic liver transplantation along with chemo-radiotherapy have significantly improved overall survival in CCA patients, with fewer complications of locoregional dissemination and tumor recurrence; thus, this approach is considered as standard treatment procedure for CCA (29,30). However, this option may not be feasible for all patients; conventional therapies, including surgical resection, chemotherapy and radiotherapy, may remain useful for CCA patients with certain characteristics.

The clinical condition of affected patients provides an initial indicator regarding the prediction of survival; as previously reported, the ECOG status and clinical symptoms provide information regarding the severity of the disease and treatment outcome (31). It has been reported that patients considered suitable for surgery also have a higher survival rate (32). However, in the present study, neither lymph node involvement nor histological grading were predictive factors for patient survival according to the statistical analysis.

Table I. Characteristics and factors affecting the survival of patients with cholangiocarcinoma.

Factors	n	2-year survival n (%)	P-value (logistic regression)	P-value (χ^2/Fisher's exact test)
Gender			0.052	0.061
Male	16	4 (25.0)		
Female	11	7 (63.6)		
Age (years)			0.080	0.159
≤55	14	8 (57.1)		
>55	13	3 (23.1)		
Performance status[a]			0.028	0.018
0	17	10 (58.8)		
1 -2	10	1 (10.0)		
TNM stage			0.485	0.696
T1/T2/Tx	15	7 (46.7)		
T3/T4	12	4 (33.3)		
Subtype			0.816	1.000
Intrahepatic	14	6 (42.9)		
Extrahepatic/hilar	2/11	5 (38.5)		
Resectability			0.032	0.047
Resectable	15	9 (60.0)		
Unresectable	12	2 (16.7)		
Clinical symptoms			0.016	0.028
No	14	9 (64.3)		
Yes	13	2 (15.4)		
Lymph node involvement			0.952	1.000
N0	10	4 (40.0)		
N1	17	7 (41.2)		
Histological grading			0.060	0.066
Well-differentiated	11	7 (63.6)		
Moderately -poorly differentiated	7	1 (14.3)		
Largest tumor diameter (cm)			0.952	1.000
≤4	17	7 (41.2)		
>4	10	4 (40.0)		
Lesion			0.970	1.000
Single	22	9 (40.9)		
Multiple	5	2 (40.0)		

[a]According to the Eastern Cooperative Oncology Group classification.

The efficacy of radiotherapy in the treatment of CCA has been questioned; it has previously been reported that postoperative radiotherapy exerts a limited effect on the survival of patients with hilar CCA (33). However, radiation as an adjuvant or palliative treatment appears to confer a survival advantage in patients with intra- or extrahepatic CCA (22,24,33,34). Radiotherapy has been shown to prolong patient survival by ~4 months in unresectable intrahepatic CCA (35). It has also been suggested that liver transplantation with neoadjuvant chemoradiotherapy may achieve improved survival rates in patients with hilar CCA in comparison with surgical resection (36).

In the present study, retrospective analysis of the data of CCA patients who had received radiotherapy was performed. Although TNM-staging did not provide any prognostic information, PTV, which was adjusted according to the tumor size, was a significant predictive factor ($P<0.05$). From this, it can be deduced that a smaller tumor size is associated with a higher survival rate. In addition, although patient survival was not significantly associated with the total therapeutic dose, once the total radiation doses and fractionation frequencies were converted into BED, the difference in survival became significant between patients who received a BED >60 vs. those who received a lower BED. The BED is prescribed based on the

Table II. Radiotherapy factors affecting the survival of cholangiocarcinoma patients.

Factors	n	2-year survival, n (%)	P-value (logistic regression)	P-value (χ^2/Fisher's exact test)
Radiotherapy dose (Gy)			0.080	0.159
≤54	14	8 (57.1)		
>54	13	3 (23.1)		
Planning target volume (cm^3)			0.016	0.028
≤600	14	9 (64.3)		
>600	13	2 (15.4)		
Biologically effective dose (Gy)			0.019	0.022
≤60	12	8 (66.7)		
>60	15	3 (20.0)		
Treatment response after 3 months			0.047	0.056
Complete response	6	5 (83.3)		
Partial response, stable and progressive disease	19	6 (31.6)		

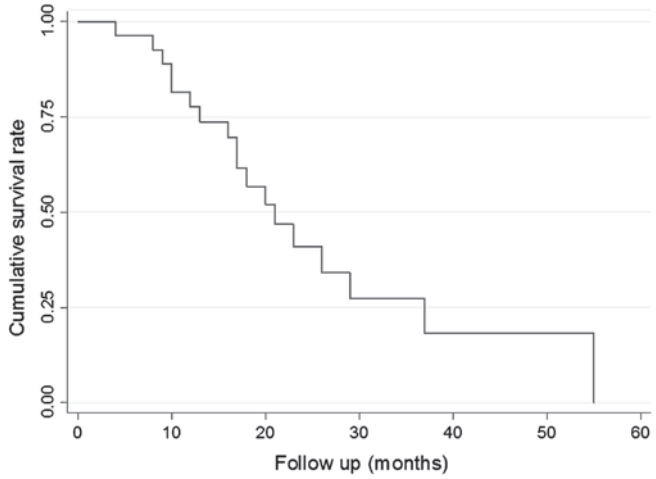

Figure 1. Cumulative survival rate of the 27 patients with cholangiocarcinoma.

clinicopathological condition of each patient and corresponds with the tumor status, including its resectability or whether there is residual tumor following surgery; thus, a larger BED was associated with poor patient prognosis. The fact that a larger BED translated to a poorer prognosis also indicated that current radiotherapy protocols may not address the severity of the disease, and that radiotherapy is ineffective against CCA as previously hypothesized (37). It has been reported that SBRT may achieve higher survival rates for selected patients (38); SBRT concurrent with gemcitabine has also been suggested to be a promising approach (39).

Based on logistic regression analysis, treatment response at 3 months was considered to be of prognostic value (P=0.047); however, when analyzed using the Fisher's exact test, this factor could no longer be used to predict between-group differences (P=0.056). Re-grouping between complete and partial response vs. stable and progressive disease also revealed no significant difference (P=0.325). Thus, based on the findings of the present study, initial treatment response may be of limited value in determining patient prognosis. Future studies using a larger patient cohort may help determine whether patient response at 3 months after treatment may be used to predict the prognosis.

CCA is a heterogeneous cancer type and complete surgical resection is the most effective treatment for either perihilar or peripheral CCA. In addition to surgery, the majority of the patients undergo postoperative adjuvant treatment. Although these adjuvant treatments have conferred certain survival benefit, the actual standard protocols vary, particularly regarding radiotherapy; at present, there is no consensus regarding the optimal definition of target contouring, radiation dose and fractionation schedule. Novel radiological modalities, including dynamic computed tomography (CT), magnetic resonance cholangiopancreatography and positron emission tomography/CT, have been developed and have become useful for target contouring. Moreover, liver motion is a critical factor that requires consideration during contouring (40-42). Fluoroscopy or 4D-CT have been proven to be useful in the precise definition of the internal target volume. All these technologies enhance the accuracy of radiation delivery and improve local tumor control. Further development of these procedures may improve the efficacy of radiotherapy for CCA.

Besides standard external beam radiotherapy, yttrium-90 radioembolization is currently used as an alternative procedure for radiation delivery. It may be employed for the treatment of intrahepatic CCA and has appeared to confer survival benefits to patients. Radioembolization has also been reported to transform unresectable into resectable tumors (43,44). Therefore, the effectiveness of this approach for treating intrahepatic CCA should also be further investigated.

In conclusion, the present study investigated clinical characteristics of CCA patients, such as performance status, clinical symptoms and resectability of the tumor, as predictive factors of prognosis. Tumor volume, represented by PTV, and

radiation dose delivered to the tumor, expressed as the BED, may be used as predictors of survival. CCA patients subjected to radiotherapy with a lower PTV and BED had higher 2-year survival rates. However, as these factors were adjusted based on tumor size and the clinicopathological status, increased survival rates may have been due to the lower degree of disease progression. Further studies involving larger patient numbers are required to further validate the findings of the present study.

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