



## Biliary tract cancer

## Factors influencing survival outcome for radiotherapy for biliary tract cancer: A multicenter retrospective study



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## ABSTRACT

**Purpose:** To seek for the possible factors influencing overall survival (OS) with radiotherapy (RT) for biliary tract cancer.

**Materials and methods:** Data were collected retrospectively from RT database of 31 institutions in Japan. All patients underwent at least external beam RT. The factors influencing OS were investigated.

**Results:** Data of 498 patients were analyzed. Median OS of the 212 patients who underwent surgery was significantly better than that of the 286 patients without surgery (31 vs. 15 months,  $p < 0.001$ ). The OS for the R0 or R1 resection group was significantly longer than that for the R2 or non-surgery group, as well as for n0 compared to n1 (all  $p < 0.001$ ). Chemoradiotherapy (CRT), both sequential and concurrent, resulted in a better OS than RT alone for the n1 group (31 vs. 13 months,  $p < 0.001$ ), and marginally better for the R0/R1 group ( $p = 0.065$ ;  $p = 0.054$  for concurrent CRT). However, no such benefit was observed for the R2/non-surgical patients. Multivariate analysis identified performance status, clinical stage, and surgery as significant factors.

**Conclusion:** Surgery, especially R0/R1 resection, seemed as the gold standard for treatment of biliary tract cancer including RT, even in the highly heterogeneous population obtained from the multicenter retrospective study. The possibility was shown that CRT yielded better survival benefit especially for n1 patients. We recommend that future prospective trials include an arm of adjuvant CRT at least for n1 and possibly R0/R1 patients.

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Biliary tract cancer is a rare disease, with approximately 9810 new cases diagnosed annually in the United States [1]. In Japan, however, the incidence rate is higher, with an estimated 20,734 new cases in 2007 and a more than 3-fold increase over the past three decades [2].

Surgical resection offers the best chance at long-term survival, but the results are not satisfactory and local relapses are frequent

[3]. Unfortunately, the majority of patients present with locally advanced or metastatic disease, which is not amenable to surgical resection, resulting in poor survival outcomes [4]. Adjuvant or definitive radiotherapy (RT) with or without chemotherapy is therefore favored and used in many centers worldwide for better local control and with the expectation that it will have a favorable effect on survival. However, the lack of appropriate prospective randomized trials, as well as the small size of the published series and their retrospective nature, has produced insufficient evidence for the best treatment for these patients. A retrospective study based on a nationwide survey was therefore deemed justified, and to this end we constructed a database of RT for biliary tract

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cancer from multiple institutions in Japan. Using this database, to seek for the possible factors influencing overall survival (OS) is the purpose of this study.

## Materials and methods

### Study scheme

This retrospective study was based on a survey conducted by the Japanese Radiation Oncology Study Group (JROSG), which is a nationwide study group of Japanese radiation oncologists [5]. Ethical approval for the study was obtained from the institutional review board. For the survey, a questionnaire designed to elicit detailed information regarding patient characteristics, treatment characteristics and outcomes of treatments (Appendix 1) was sent to the radiation oncology centers belonging to the JROSG, and 31

centers (Appendix 2) agreed to participate in this survey. Data of 555 patients had been accumulated by the end of 2011.

### Eligibility criteria

Eligible patients were those with non-metastatic biliary tract cancers, defined as tumors of the gallbladder, intrahepatic and extrahepatic bile ducts, and ampulla. The extrahepatic bile ducts were divided into four subsites including perihilar, upper, middle, and lower bile ducts. All the patients underwent RT as adjuvant or definitive treatment, while part of them underwent surgery and/or chemotherapy. Note that surgery included non-curative resections (R2: macroscopic residual tumor) as well as curative-intent resections (R0: negative margins, or R1: microscopic positive margins),

**Table 1**  
Patient characteristics.

	All patients (%)	Surgery group (%)	Non-surgery group (%)	<i>p</i>
Number of patients	498 (100)	212 (100)	286 (100)	
Gender				0.044
Male	332 (67)	152 (72)	180 (63)	
Female	166 (33)	60 (28)	106 (37)	
Age				0.008
Median	69	68	71	
Range	33–90	41–86	33–90	
Drinking				0.111
Drinker	174 (35)	73 (34)	101 (35)	
Non-drinker	208 (42)	70 (33)	138 (48)	
Unknown	116 (23)	69 (33)	47 (16)	
Smoking				0.391
Smoker	158 (32)	63 (30)	95 (33)	
Non-smoker	223 (45)	79 (37)	144 (50)	
Unknown	117 (23)	70 (33)	47 (16)	
Diabetes mellitus				0.071
Yes	65 (13)	18 (8)	47 (16)	
No	353 (71)	142 (67)	211 (74)	
Unknown	80 (16)	52 (25)	28 (10)	
Jaundice				0.003
Yes	324 (65)	121 (57)	203 (71)	
No	152 (31)	79 (37)	73 (26)	
Unknown	22 (4)	12 (6)	10 (3)	
Performance status				<0.001
0	206 (41)	108 (51)	98 (34)	
1	200 (40)	83 (39)	117 (41)	
2	69 (14)	15 (7)	54 (19)	
3	16 (3)	3 (1)	13 (5)	
4	1 (0)	0 (0)	1 (0)	
Unknown	6 (1)	3 (1)	3 (1)	
Histology				0.374
Adenocarcinoma	378 (76)	196 (92)	182 (64)	
Adenosquamous carcinoma	5 (1)	4 (2)	1 (0)	
Unknown	115 (23)	12 (6)	103 (36)	
Primary tumor site				0.002
Gallbladder	38 (8)	22 (10)	16 (6)	
Intrahepatic bile duct	68 (14)	17 (8)	51 (18)	
Ampulla	2 (0)	1 (0)	1 (0)	
Extrahepatic bile duct	390 (78)	172 (81)	218 (76)	
Perihilar	217 (44)	66 (31)	151 (53)	
Upper	38 (8)	11 (5)	27 (9)	
Middle	77 (15)	53 (25)	24 (8)	
Lower	45 (9)	31 (15)	14 (5)	
Unknown	13 (3)	11 (5)	2 (1)	
Clinical stage				0.025
I	83 (17)	41 (19)	42 (15)	
II	179 (36)	74 (35)	105 (37)	
III	132 (27)	40 (19)	92 (32)	
IV	24 (5)	7 (3)	17 (6)	
Unknown	80 (16)	50 (24)	30 (10)	

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