Original Article

Clinical features of biliary tract cancer in Japanese individuals with Lynch syndrome

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Background: Biliary tract cancer (BTC) is a Lynch syndrome (LS)-associated cancer with a high mortality rate. This study aimed to clarify the clinical features of BTC in individuals with LS and to discuss its management.

Methods: We obtained data from genetically verified Japanese individuals with LS who were diagnosed at a single institution, between January 2003 and April 2021. Moreover, 21 individuals with sporadic BTC (n=15) and LS associated BTC (n=6) underwent microsatellite instability (MSI) testing.

Results: Among 92 individuals with LS, 6 individuals with *MLH1* variants developed BTCs (10 lesions, male/female, 2:1). The median age at diagnosis of initial BTC was 69 years (range, 34–78 years). Histological examination revealed a predominance of differentiated adenocarcinoma (89%). Then, 2 individuals had multiple BTCs. All available 7 BTC lesions showed high-frequency of microsatellite instability (MSI-H). *MLH1* carriers showed a 7.2% cumulative risk of BTC development at an age of 70 years. Five of the six individuals died of BTC.

Conclusions: MSI analysis could facilitate LS identification in individuals with BTC. Surveillance for BTC should be considered for *MLH1* carriers in Japan.

Keywords: Lynch syndrome (LS); mismatch repair gene (MMR gene); microsatellite instability (MSI); biliary tract cancer (BTC); cumulative risk

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Introduction

Biliary tract cancer (BTC) accounts for approximately 3% and 10–15% of gastrointestinal and hepatobiliary malignancies, respectively (1). The biliary tract mainly comprises the biliary epithelium of small ducts in the liver periphery (intrahepatic), the common hepatic and common bile duct (extrahepatic), gallbladder, and ampulla of Vater. The epidemiological characteristics of sporadic BTCs include a higher and lower frequency of gallbladder cancer and BTC development, respectively, in females than in

males (2). Compared with Caucasian or African Americans, Asian-Pacific Islander men and women have a higher rate of extrahepatic BTC development (2). Moreover, geographic regions, including North India, South Chili, and Poland, are risk factors for gallbladder cancer (3). Surgical resection with lymph node dissection is the main treatment (4-7). Although novel chemotherapies have been developed, BTCs remain highly malignant, with even complete surgical resection yielding a low 5-year survival rate (11–30%) (8,9).

Several risk factors for BTCs have been identified, including primary sclerosing cholangitis, biliary tract stones, pancreaticobiliary malfunction, infection, and toxic exposure (1,4). Additionally, several genetic factors, including Lynch syndrome (LS), *BAP1* tumor predisposition syndrome, cystic fibrosis, and multiple biliary papillomatosis, are associated with an increased risk of BTC (10,11).

LS is among the most common inherited cancer syndromes related to pathogenic germline variants in mismatch repair (MMR) genes or epithelial cell adhesion molecule (*EPCAM*) (12). LS is associated with various tumor types, including colorectal, endometrial, ovarian, and biliary cancers (13,14). Compared with sporadic cancers, colorectal cancer (CRC) and endometrial cancer (EC) have longer survival (15,16). On the other hand, relatively rare LS-associated cancers, including brain tumors, pancreatic cancer, and BTC, have high mortality rates.

This study aimed to investigate the clinical features of BTC in individuals with LS, assess the utility of microsatellite instability (MSI) testing for LS identification in individuals with BTC, and discuss the surveillance indications for BTC in individuals with LS. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-165/rc).

Methods

Clinical features of BTC in LS

We conducted a retrospective review of LS individuals at the Iwakuni Clinical Center between January 2003 and April 2021. MSI testing on individuals who met Bethesda guidelines was performed (17). Probands underwent genetic testing if they presented with high-frequency of microsatellite instability (MSI-H) tumors or met a modified Amsterdam II criteria (18), which includes gastric cancer as among the LS-associated tumors since it is common in Asian individuals with LS. Data regarding age at diagnosis, variant type, tumor location, histological type, stage, treatment, follow-up, and surveillance were collected from pathological germline variant carriers and obligate carriers. The BTC location was classified according to WHO classification (5th edition). The spectrum and clinicopathological characteristics of BTCs in individuals with LS were explored.

Germline mutation analyses

Genomic DNA was extracted from peripheral blood samples using a standard phenol extraction and purification procedure. Germline variant analyses were performed by direct sequencing of the entire coding region of *MLH1*, *MSH2*, and *MSH6* (19,20). In case there were no deleterious gene variants, multiplex ligation-dependent probe amplification was performed using a SALSA MLPA *MLH1/MSH2* probemix assay. From 2014, genetic analysis was performed using a multi-gene panel that included *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* (20), as previously described. Variants were assessed using the InSiGHT classification criteria (http://insight-group.org/variants/classifications/); moreover, individuals with Class 4 (likely pathogenic) or Class 5 (pathogenic) variants were considered to have LS. Before genetic testing, individuals underwent genetic counseling from clinical geneticists; further, they provided written informed consent. This study was approved by the institutional review board of the Iwakuni Clinical Center (No. 2774). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

MSI analysis for sporadic and LS cases

To compare the MSI status of BTC between sporadic and LS cases, we collected tissue samples from 21 consecutive individuals with primary BTC who underwent surgical resection between July 2008 and May 2014 at Iwakuni Clinical Center. Among 21 lesions of BTCs, 6 lesions have been obtained from 5 individuals with LS (Figure S1). MSI analysis was performed on surgically resected paraffin-embedded tumor specimens. Polymerase chain reaction analysis was performed targeting five markers: BAT25, BAT26, D2S123, D5S346, and D17S250. Tumors were classified as MSI-H (≥2 out of 5 markers), low-frequency of microsatellite instability (MSI-L, 1 out of 5), or microsatellite stable (MSS; 0 out of 5) (17).

Table 1 Background of individuals with LS

Background	Values
Individuals	92
Male/female	42/50
Germline variant	
MLH1 [obligation carrier]	75 [20]
MSH2	16
MSH6	1
Age at the last follow-up, years	56 (23–90)
Individuals who developed any cancer	70 (76%)
Age at initial cancer, years	44 (17–78)
Origin of initial cancer	
Colorectum	43
Endometrium	14
Gastric	5
Ovary	4
Biliary tract	2
Small intestine	1
Brain	1
Individuals who developed BTC	6
Age at initial BTC, years	69 (34–78)

Data are presented as number, median (range) or n (percentage). LS, Lynch syndrome; BTC, biliary tract cancer.

Statistical analysis

Data are presented as medians (range) or percentages. The cumulative risk of developing BTC in individuals with LS was analyzed using a Kaplan-Meier plot. Statistical analyses were performed using JMP software (version 14, SAS Institute Inc.).

Results

The spectrum of the initial cancer

A total of 92 individuals from 30 families were identified to have pathogenic MMR gene variants (*Table 1*). The male-to-female ratio of the 92 individuals was 42:50. Moreover, 75, 16, and 1 patient had *MLH1*, *MSH2*, and *MSH6*, respectively. Among the 92 individuals, 70 developed cancers. The initial cancers included colorectum (43/70, 61%), endometrium (14/38, 37% among females), gastric (5/70, 7%), ovary (4/38, 11% among females), and biliary tract (2/70, 3%) cancers. The median age at initial cancer diagnosis was 44 years (range, 17–78 years).

Clinical features of the BTC in individuals with LS

Among the 92 individuals, 6 individuals developed BTCs (*Figure 1*, *Table 2*). Six patients with BTC had *MLH1* variants, with a male-to-female ratio of 2:1 (*Tables 2,3*). The median age at diagnosis of initial BTC was 69 years (range,

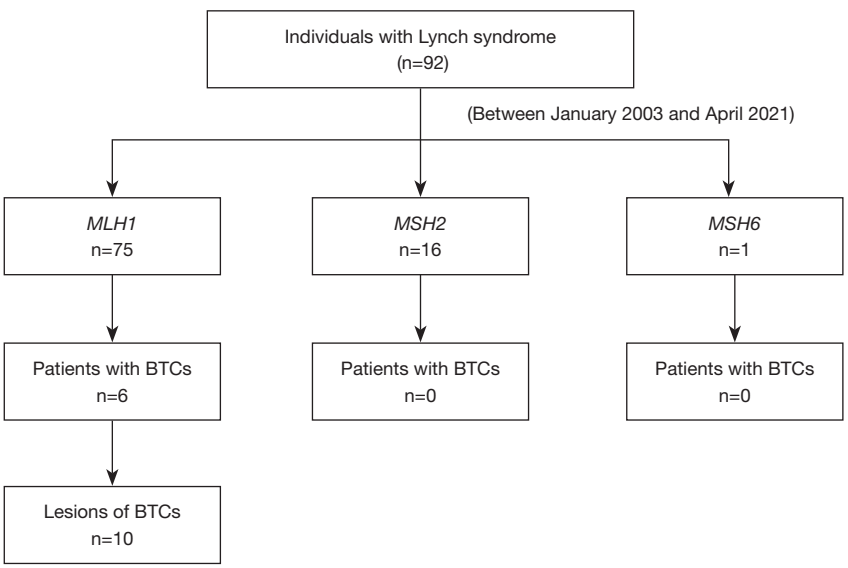

Figure 1 Flow diagram for BTC in individuals with LS. BTC, biliary tract cancer; LS, Lynch syndrome.

Table 2 Clinicopathological characteristics of individuals with BTC in LS

Case	Gender	Initial cancer	Age at initial cancer (years)	BTC								
				Age (years)	Location	Symptom	Family history of BTC	Histologic type	MSI status	Stage	Treatment	Outcome
1	Male	CRC	25	65	P. Vater	No	Yes	tub1	MSI-H	I	Partial resection	N.D
				67	Distal	No	Yes	tub2	MSI-H	II	Pancreaticoduodenectomy	Cancer death
2	Male	CRC	54	76	Intrahepatic	No	Yes	tub2	MSI-H	II	Right posterior segmentectomy	Cancer death
3	Male	CRC	54	73	Perihilar	No	No	tub1	MSI-H	I	Left hepatectomy	Alive without recurrence
				75	Distal	No	No	tub2	MSI-H	II	Pancreaticoduodenectomy	Alive without recurrence
				75	Distal	No	No	tub1	N.A	I		Alive without recurrence
				75	Distal	No	No	tub1	N.A	I		Alive without recurrence
4	Female	BTC	78	78	Perihilar	Yes	No	tub2	MSI-H	IVa	Extended left hepatectomy	Cancer death
5	Female	CRC	29	42	Perihilar	Yes	No	por	MSI-H	IVb	Best supportive care	Cancer death
6	Male	BTC	34	34	N.D	Yes	No	N.D	N.D	N.D	N.D	Cancer death

BTC, biliary tract cancer; LS, Lynch syndrome; MSI, microsatellite instability; CRC, colorectal cancer; P. Vater, duodenal papilla of Vater; tub1, well-differentiated tubular adenocarcinoma; MSI-H, high-frequency of microsatellite instability; N.D, no data; Distal, distal biliary tract; tub2, moderately differentiated tubular adenocarcinoma; Intrahepatic, intrahepatic biliary tract; Perihilar, perihilar biliary tract; N.A, not available; por, poorly differentiated adenocarcinoma.

34–78 years). The BTC locations included 1 (1/9, 11%), 3 (3/9, 33%), 4 (4/9, 44%), 1 (1/9, 11%) in the intrahepatic biliary tract, peri-hilar biliary tract, distal biliary tract, and duodenal papilla of Vater (P. Vater), respectively. Histological subtypes of the nine specimens included four (4/9, 44%), four (4/9, 44%), and one (1/9, 11%) well, moderately, and poorly differentiated adenocarcinomas, respectively. Then, biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct were not detected in the nine lesions. Further, medullary growth pattern, which is the one of the unique features of LS associated CRC, was also not found in the lesions. Then, MSI analysis was tested in 7 lesions because other 2 lesions in case 3 was too small. All seven specimens showed MSI-H. The UICC (7th revision) stages included four (4/9, 44%), three (3/9, 33%), and two (2/9, 22%) at stages I, II, and IV, respectively. The incidence of synchronous and metachronous BTC was 17% (1/6) and 33% (2/6), respectively. Interestingly, case 3 had synchronous four lesions, in which two tumors showed MSI-H. The cumulative risks of individuals with an *MLH1* pathogenic variant at 60, 70, and 75 years of age were 3.2%, 7.2%, and 13.4%, respectively (*Figure 2*).

MSI analysis for sporadic and LS cases

MSI analysis for BTC samples was performed to assess the MSI-H among individuals with BTC, including sporadic and LS cases. Among the 21 lesions, 6 and 15 lesions had MSI-H and MSI-L/MSS, respectively (Figure S1). All six MSI-H lesions were obtained from individuals with LS.

Discussion

Our findings suggest that MSI analysis is an effective screening tool for identifying LS in individuals with BTC. Additionally, our findings indicate the need to conduct surveillance for BTC in *MLH1* carriers living in countries with high risks for BTC.

Accurate LS diagnosis is crucial since various risk-reduction strategies, including surveillance, prophylactic surgery, and chemoprevention, might improve clinical outcomes. The efficacy of surveillance for LS has been demonstrated in CRC. Specifically, a 3-year colonoscopy surveillance was found to reduce CRC-caused mortality by 65% (21). Even an extended surgery can be an alternative treatment for CRC since there is a higher risk of metachronous CRC in *MLH1* and *MSH2* carriers (22).

Table 3 Identified pathogenic germline MMR gene variants in individuals with BTC

Case	Proband	Reason for genetic testing*	Gene variant	InSiGHT classification	Gene variant status
1	Yes	Colon cancer	*MLH1* (c.381-415_453 + 733del)	Class 5	Carrier
2	No	Colon cancer	*MLH1* (c.381-415_453 + 733del)	Class 5	Carrier
3	Yes	Colon cancer	*MLH1* (c.70_72delAAG)	Class 5	Carrier
4	No	N.D	*MLH1* (c.381-415_453 + 733del)	Class 5	Obligation
5	Yes	BTC	*MLH1* (c.545+1G>C)	Class 5	Carrier
6	No	BTC	*MLH1* (c.381-415_453 + 733del)	Class 5	Carrier

*, cancer types that led to the implementation of genetic testing. MMR, mismatch repair; BTC, biliary tract cancer; N.D, no data.

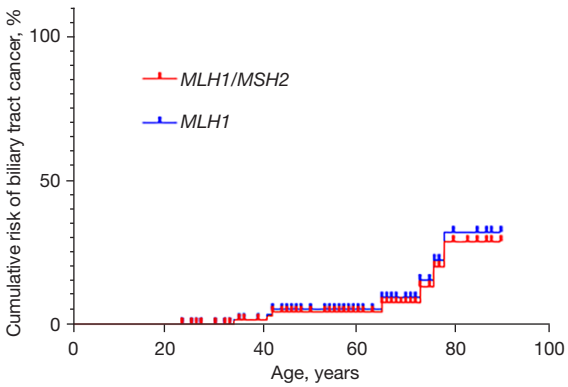

Figure 2 The cumulative risks of developing BTC in individuals with LS. BTC, biliary tract cancer; LS, Lynch syndrome.

Since MSI is a hallmark of LS tumors, many guidelines recommend universal screening for individuals with CRC and/or EC through MSI analysis. In LS, 90% of CRCs showed MSI-H. However, the frequencies of LS-associated tumors with MSI-H vary depending on the cancer origin. Specifically, colon, stomach, ovary, and ureter cancers show MSI-H >80%; bladder, endometrium, and kidney cancers show MSI-H ≤50%; and breast and brain tumors show MSI-H <35% (23). Unfortunately, there have been limited studies on the MSI status of BTC for both sporadic and LS cases. Additionally, MSI-H is not specific to LS. In most cases, MSI-H presence is indicative of epigenetic hypermethylation of the *MLH1* promoter region. Recent studies have reported a 1–3% frequency of sporadic MSI-H tumors in BTCs (24,25). In this study, all BTC lesions (n=7) in 5 individuals with LS showed MSI-H. On the other hand, all BTC lesions (n=15) in 15 individuals with sporadic BTCs showed MSS or MSI-L. Therefore, MSI analysis might be an efficient screening tool for BTCs to identify LS. Given the fact that life time risk of BTC is lower than CRC, MSI analysis might be recommended when patients with BTC have family or personal history of LS.

Although the cumulative risk of BTC in LS is relatively low, BTC is highly malignant, with an average 5-year survival rate of 29% (26); further, it is among the main mortality causes in LS (27). Additionally, the *MLH1* variant was predominant in BTC (28). A recent prospective study reported that the cumulative risk of BTC at 75 years of age was 3.7%, 1.7%, and 0% for *MLH1*, *MSH2*, and *MSH6*, respectively (26). In our study, the cumulative risk of BTC in Japanese *MLH1* carriers was notably high, which was at 7.2% and 13.4% at 70 and 75 years of age, respectively. The BTC risk in Japanese individuals with the *MLH1* variant is similar to that in individuals with primary sclerosing cholangitis, which is associated with an increased lifetime risk of BTC (5–20%) (29). Of the two patients who developed BTC as their initial cancer, one developed BTC at 78 years old. In individuals with LS, *MLH1* variant is reported to be a risk factor to develop BTC (26). Besides, family history of BTC was observed in three of the six presented cases, suggesting that a family history of BTC may also be a risk factor. Aside from development of BTC as an initial cancer, it is important to detect asymptomatic BTCs by surveillance in order to improve the prognosis of individuals with LS. In our institution, we recommend that individuals with LS undergo surveillance with hematological examination and ultrasound (US), or computed tomography (CT) every 12 months beginning at age 40–50 years, 5 years prior to the earliest age of BTC diagnosis in the family according to some guidelines.

Despite the lack of evidence, several guidelines recommend surveillance for BTC in individuals with primary sclerosing cholangitis through imaging, including US, CT, magnetic resonance imaging, and/or serum carbohydrate antigen 19-9, at 6–12-month intervals (30).

Since some BTC present with increased levels of the liver and bile duct enzymes, the blood biochemical tests are also applicable in surveillance for BTC (5). In this study, we have been able to diagnose 7 asymptomatic BTCs among 3 individuals by CT scan and blood biochemical tests performed during postoperative follow-up for CRCs or BTCs. Then, the three asymptomatic individuals with BTCs showed earlier clinical stages and better clinical outcomes than other three symptomatic individuals. Therefore, surveillance for BTC should be considered for *MLH1* carriers in Japan with high risk for BTC.

This study has several limitations, including the small initial sample size (BTCs, n=10), the majority of *MLH1* variant, and its retrospective single-center design. However, to our knowledge, this is the first report in Asia to demonstrate the importance of MSI analysis of BTCs in identifying LS, as well as to describe the clinical features of LS-associated BTC. Then, the unique features of LS-associated BTC should be investigate by prospective and/or multiple center design and further, it is very critical to build useful surveillance tool for BTC to improve overall survival.

Conclusions

Our findings suggested that LS-associated BTC has features similar to those of LS-associated CRC, including a high cumulative cancer risk, multiple occurrences, and high MSI-H incidence. MSI analysis could facilitate LS identification in patients with BTC when these patients are suspect to be LS by their family history and medical history. Therefore, BTC surveillance could be considered for individuals with *MLH1* variants in countries with a high BTC incidence.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-165/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-165/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-165/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-165/coif). KA had lecture fee from Merck Sharp & Dohme (MSD). The other 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. The study was approved by the institutional review board of the Iwakuni Clinical Center (No. 2774). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Before genetic testing, individuals received genetic counseling from clinical geneticists. Informed consent was obtained from all subjects involved in the study.

References

1. Khan AS, Dageforde LA. Cholangiocarcinoma. Surg Clin North Am 2019;99:315-35.
2. Goodman MT, Yamamoto J. Descriptive study of gallbladder, extrahepatic bile duct, and ampullary cancers in the United States, 1997-2002. Cancer Causes Control 2007;18:415-22.
3. Serra I, Yamamoto M, Calvo A, et al. Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer 2002;102:407-11.
4. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168-79.
5. Miyazaki M, Yoshitomi H, Miyakawa S, et al. Clinical practice guidelines for the management of biliary tract

cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci 2015;22:249-73.
6. Benavides M, Antón A, Gallego J, et al. Biliary tract cancers: SEOM clinical guidelines. Clin Transl Oncol 2015;17:982-7.
7. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013;31:1188-95.
8. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755-62.
9. Anderson C, Kim R. Adjuvant therapy for resected extrahepatic cholangiocarcinoma: a review of the literature and future directions. Cancer Treat Rev 2009;35:322-7.
10. Cloyd JM, Chun YS, Ikoma N, et al. Clinical and Genetic Implications of DNA Mismatch Repair Deficiency in Biliary Tract Cancers Associated with Lynch Syndrome. J Gastrointest Cancer 2018;49:93-6.
11. Chan-On W, Nairismägi ML, Ong CK, et al. Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. Nat Genet 2013;45:1474-8.
12. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919-32.
13. Barrow E, Alduaij W, Robinson L, et al. Colorectal cancer in HNPCC: cumulative lifetime incidence, survival and tumour distribution. A report of 121 families with proven mutations. Clin Genet 2008;74:233-42.
14. Aarnio M, Mecklin JP, Aaltonen LA, et al. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995;64:430-3.
15. Biller LH, Syngal S, Yurgelun MB. Recent advances in Lynch syndrome. Fam Cancer 2019;18:211-9.
16. Møller P, Seppälä T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2017;66:464-72.
17. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-8.
18. Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18:81S-92S.
19. Yamaguchi T, Furukawa Y, Nakamura Y, et al. Comparison of clinical features between suspected familial colorectal cancer type X and Lynch syndrome in Japanese patients with colorectal cancer: a cross-sectional study conducted by the Japanese Society for Cancer of the Colon and Rectum. Jpn J Clin Oncol 2015;45:153-9.
20. Kohda M, Kumamoto K, Eguchi H, et al. Rapid detection of germline mutations for hereditary gastrointestinal polyposis/cancers using HaloPlex target enrichment and high-throughput sequencing technologies. Fam Cancer 2016;15:553-62.
21. Wullen B, Mühlhöfer A, Zoller WG. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Z Gastroenterol 2001;39:981-4.
22. Quezada-Diaz FF, Hameed I, von Mueffling A, et al. Risk of Metachronous Colorectal Neoplasm after a Segmental Colectomy in Lynch Syndrome Patients According to Mismatch Repair Gene Status. J Am Coll Surg 2020;230:669-75.
23. Peltomäki P. Update on Lynch syndrome genomics. Fam Cancer 2016;15:385-93.
24. Akagi K, Oki E, Taniguchi H, et al. Real-world data on microsatellite instability status in various unresectable or metastatic solid tumors. Cancer Sci 2021;112:1105-13.
25. Ando Y, Kumamoto K, Matsukawa H, et al. Low prevalence of biliary tract cancer with defective mismatch repair genes in a Japanese hospital-based population. Oncol Lett 2022;23:4.
26. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 2018;67:1306-16.
27. Tanakaya K, Yamaguchi T, Ishikawa H, et al. Causes of Cancer Death Among First-Degree Relatives in Japanese Families with Lynch Syndrome. Anticancer Res 2016;36:1985-9.
28. Takamizawa S, Morizane C, Tanabe N, et al. Clinical characteristics of pancreatic and biliary tract cancers associated with Lynch syndrome. J Hepatobiliary Pancreat Sci 2022;29:377-84.
29. Nicoletti A, Maurice JB, Thorburn D. Guideline review: British Society of Gastroenterology/UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Frontline Gastroenterol 2021;12:62-6.
30. Bowlus CL, Lim JK, Lindor KD. AGA Clinical Practice Update on Surveillance for Hepatobiliary Cancers in Patients With Primary Sclerosing Cholangitis: Expert Review. Clin Gastroenterol Hepatol 2019;17:2416-22.

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Supplementary

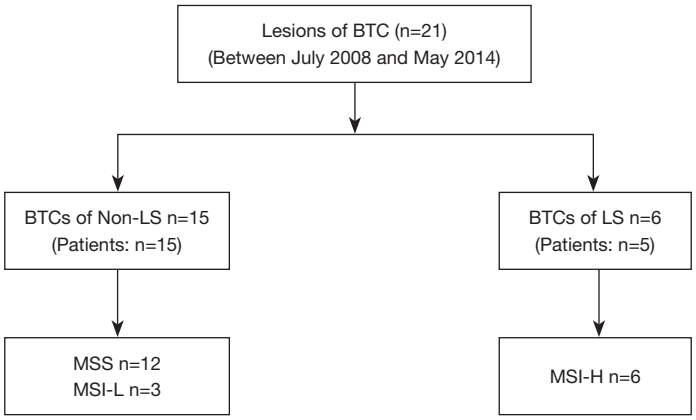

Figure S1 Flow diagram for MSI testing of BTC. BTC, biliary tract cancer; LS, Lynch syndrome; MSS, microsatellite stable; MSI-L, low-frequency of microsatellite instability; MSI-H, high-frequency of microsatellite instability; MSI, microsatellite instability.

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