1 | INTRODUCTION

Lynch syndrome is the most common hereditary cancer syndrome caused by the following pathogenic germ-line variants of the DNA mismatch repair genes: MLH1, MSH2, MSH6, or PMS2.1,2 Patients with Lynch syndrome are susceptible to multiple malignancies, including colorectal, endometrial, gastric, ovarian, ureteral/kidney, bladder, prostate, breast, brain, small bowel, skin, pancreatic, and biliary tract cancers. Colorectal and endometrial cancers are the most common cancers in patients with Lynch syndrome. Lynch syndrome-associated colorectal...
or endometrial cancers account for approximately 3% and 2%-3% of newly diagnosed colorectal and endometrial cancer cases, respectively. Lynch syndrome-associated colorectal or endometrial cancers generally occur at a younger age (before the age of 50 years) than sporadic colorectal or endometrial cancer, and patients also often have family histories of cancer. The typical pathological findings of patients with Lynch syndrome are the presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, and a medullary growth pattern.

Pancreatic and biliary tract cancers are one of the Lynch syndrome-associated malignancies. Although the cumulative risk of pancreatic cancer (PC) over a lifetime is 1.6% in the general population, that for Lynch syndrome-associated PCs through 80 years are 6.2%, 0.5%-1.6%, 1.4%-1.6%, and ≤1%-1.6% for MLH1, MSH2, MSH6, and PMS2, respectively. Another study has shown that the cumulative risk of developing PC in patients with Lynch syndrome is 8.6-fold higher than that in the general population. Data of the estimated average age of presentation are not yet available. Although the cumulative risk of biliary tract cancer (BTC) over a lifetime is 0.2% in the general population, that for patients with Lynch syndrome through 80 years is 1.9%-3.7%, 0.02%-1.7%, and 0.2%-≤1% for MLH1, MSH2, and MSH6 and PMS2, respectively. The estimated average age at presentation of BTC in patients with Lynch syndrome for MLH1 and MSH2 is 50 and 57 years, respectively. However, there are no data on the estimated average age at presentation of BTC in patients with Lynch syndrome for MSH6 and PMS2.

As mentioned above, patients with Lynch syndrome have a significantly high lifetime risk of developing pancreatic or biliary tract cancers, which are highly fatal and have a significant impact on prognosis. However, there are few reports on the background and clinical characteristics of patients with Lynch syndrome-associated pancreatic or biliary tract cancers. Hence, that was the objective of this study.

Patients were able to opt out of the study on the hospital’s website. The study was conducted according to the principles of the Declaration of Helsinki.

### 2.2 Statistical analyses

Overall survival (OS) was defined as the time from treatment initiation until death from any cause or the last date of confirmed survival and was analyzed using the Kaplan-Meier method.

### 2.3 Pathological analyses

Surgically resected specimens were fixed in 10% neutral buffered formalin and cut into serial 5-mm-thick slices and all sections were stained with hematoxylin and eosin for pathological examination. They were histologically classified according to the WHO classification of tumours, 5th edition.

### 2.4 The diagnosis of Lynch syndrome

Initially, germline genetic analyses were performed when Lynch syndrome was suspected based on family history and/or history of cancer without screening tests for Lynch syndrome. In subsequent years, screening tests for Lynch syndrome including DNA mismatch repair gene immunohistochemistry (IHC) or microsatellite instability test (including companion diagnosis of pembrolizumab) were conducted when Lynch syndrome was suspected (refer to Amsterdam Criteria II). If screening tests suggest a deficiency of DNA mismatch repair gene, germline genetic analyses will be performed. Hence, the diagnosis of Lynch syndrome was confirmed at the medical genetics outpatient clinic of NCCH after genetic counseling regarding hereditary cancer syndromes.

### 3 RESULTS

#### 3.1 Patient characteristics

Between 1992 and 2019, 14 patients were diagnosed with pancreatic or biliary tract malignant tumor and Lynch syndrome (Figure 1). Among them, six patients (all were probands) had been diagnosed with Lynch syndrome before they developed pancreatic or biliary tract malignant tumors. The types of cancer predisposition genes were MLH1 in seven patients, MSH2 in six patients, and PMS2 in one patient.
Between 1992 and 2019, 5688 patients with pancreatic malignant tumor and 1899 patients with biliary tract malignant tumor were treated in our hospital. The proportion of patients with Lynch syndrome-associated pancreatic and biliary tract malignant tumors was 0.1% (6/5688) and 0.4% (8/1899), respectively. In our hospital, 190 patients were diagnosed with Lynch syndrome between 1992 and 2019. The cancer predisposition genes were MLH1 in 74 patients, MSH2 in 94 patients, MSH6 in 13 patients, and PMS2 in nine patients. The proportion of Lynch syndrome-associated pancreatic and biliary tract cancers among patients with Lynch syndrome was 3% (6/190) and 4% (8/190), respectively.

For the six patients with pancreatic malignant tumor, their median age was 63 years, and four patients were female. Based on medical or family history, five patients had findings suggestive of Lynch syndrome. For one patient, hereditary breast and ovarian cancer syndrome was suspected due to her medical history and germline BRCA1/2 testing was performed, but the test result was negative. Therefore, a germline multi-gene panel testing was performed, and she was diagnosed with Lynch syndrome. The primary site of pancreatic malignant tumor in five of them was the body or tail. Only one patient had pancreatic head cancer. There was a patient with non-functioning neuroendocrine tumor (NET), G1 with no metastases, whose maximum diameter was 8 mm. Cancer with metastases was not observed. Three patients had a family history of colorectal cancer, and one patient had a family history of endometrial cancer. The median OS was 68 (range, 17-198) months. Two of the six patients died: one from PC and the other from a pituitary tumor.

For the eight patients with biliary tract malignant tumor, the median age was 65.5 years, and six patients were female. Based on medical or family history, six patients had findings suggestive of Lynch syndrome. One patient who had a history of colorectal cancer with a high microsatellite instability was suspected of having Lynch syndrome. Another patient had findings suggestive of Lynch syndrome based on results of the mismatch repair gene IHC for the screening of a clinical trial. The primary site of biliary tract malignant tumor in five of them was the intrahepatic bile duct, whereas the primary site in two of them was the hilar bile duct. Although the cancer diagnosis had been confirmed pathologically, only one patient was diagnosed with gallbladder cancer radiologically. Ultrasonography (US) revealed an elevated lesion with a rough surface, wide base, diameter of 9 mm, and an increasing blood flow signal over time (follow-up computed tomography [CT] revealed a maximum diameter of 14 mm). This patient had glioblastoma, which was treated as a high priority. Hence, gallbladder cancer was diagnosed based on typical US and CT findings. The patient was left untreated and is

![Figure 1](image-url)
Cancer of the distal bile duct or ampulla of Vater was not observed. Only one patient had cancer with metastases. Six patients had a family history of colorectal cancer, and three patients had a family history of endometrial cancer. The median OS was 62 (range, 3-183) months. Three of the eight patients died due to BTC. None of the patients had pancreaticobiliary maljunction. Patient characteristics are shown in Tables 1 and 2.

**TABLE 1**  Patient characteristics

|                          | Pancreatic malignant tumor (N = 6) | Biliary tract malignant tumor (N = 8) |
|--------------------------|------------------------------------|--------------------------------------|
| Genes                    |                                    |                                      |
| *MLH1*                   | 2                                  | 5                                    |
| *MSH2*                   | 4                                  | 2                                    |
| *PMS2*                   | 0                                  | 1                                    |
| Age median (range), in years | 63 (48-84)                        | 65.5 (38-71)                         |
| Sex                      |                                    |                                      |
| Male                     | 2                                  | 2                                    |
| Female                   | 4                                  | 6                                    |
| Primary site             |                                    |                                      |
| Head                     | 1                                  | Intrahepatic bile duct               |
| Body or tail             | 5                                  | Hilar bile duct                      |
| Gallbladder              | 1                                  |                                      |
| Histology                |                                    |                                      |
| Ductal adenocarcinoma    | 4                                  | Adenocarcinoma                       |
| NET, G1                  | 1                                  | 7<sup>a</sup>                        |
| Ductal adenocarcinoma    | 1                                  |                                      |
| arising from IPMN        |                                    |                                      |
| Histological features    |                                    |                                      |
| Medullary growth pattern | 0                                  | 0                                    |
| Lymphoplasmacytic infiltration | 3                                | 5                                    |
| Trigger of diagnosis of Lynch syndrome | 6                              | 7                                    |
| History or family history of cancer | 0                              | 1                                    |
| Screening of a clinical trial | 0                              |                                      |
| Stage                    |                                    |                                      |
| Resectable               | 3<sup>b</sup>                      | 1                                    |
| Locally advanced         | 3                                  | 6                                    |
| Metastatic               | 0                                  | 1                                    |
| History of cancer        |                                    |                                      |
| Median number (range)    | 2.5 (1-4)                          | 1.5 (0-3)                            |
| Colorectal cancer        | 5                                  | 6                                    |
| Endometrial cancer       | 2                                  | 3                                    |
| Family history of cancers<sup>c</sup> |                       |                                      |
| Median number (range)    | 1 (0-2)                            | 1.5 (0-2)                            |
| Colorectal cancer        | 3                                  | 4                                    |
| Endometrial cancer       | 1                                  | 0                                    |
| Median OS (range), mo    | 68 (17-198)                        | 62 (3-183)                           |

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; NA, not applicable; NET, neuroendocrine tumor; OS, overall survival.

<sup>a</sup>One patient was diagnosed with gallbladder cancer radiologically.

<sup>b</sup>One patient had a resectable tumor (no detailed information because her tumor was resected in another hospital).

<sup>c</sup>Number of first-degree relatives who had Lynch syndrome-associated malignancies.
| No. | Age (y) | Sex | Cancer type | Primary site                        | Histology             | Extent of disease | Gene  | IHC | Number of past cancers | Number of family history of cancers | Treatment | OS (mo) |
|-----|---------|-----|-------------|-------------------------------------|-----------------------|------------------|-------|-----|------------------------|-------------------------------------|-----------|--------|
| 1   | 67      | Female | BTC         | Intrahepatic bile duct (small duct type) | Adenocarcinoma        | Locally advanced | MLH1  | NA  | 2                       | 2                                    | Chemo     | 67     |
| 2   | 64      | Female | BTC         | Intrahepatic bile duct (large duct type) | Adenocarcinoma        | Locally advanced | MLH1  | NA  | 2                       | 2                                    | Resection | 183    |
| 3   | 67      | Female | BTC         | Intrahepatic bile duct (large duct type) | Adenocarcinoma        | Locally advanced | MSH2  | NA  | 1                       | 1                                    | Resection | 86     |
| 4   | 56      | Male   | BTC         | Intrahepatic bile duct (large duct type) | Adenocarcinoma        | Locally advanced | MLH1  | NA  | 1                       | 2                                    | Resection | 8      |
| 5   | 71      | Female | BTC         | Intrahepatic bile duct (small duct type) | Adenocarcinoma        | Metastatic        | PMS2  | PMS2 (−) | 0                  | 0                                   | Chemo     | 3      |
| 6   | 48      | Female | BTC         | Hilar bile duct                      | Adenocarcinoma        | Locally advanced | MLH1  | MLH1 (−), PMS2 (−) | 1 | 1                        | Resection              | 40       |
| 7   | 38      | Male   | BTC         | Hilar bile duct                      | Adenocarcinoma        | Locally advanced | MLH1  | MLH1 (−), PMS2 (−) | 2 | 1                        | Resection              | 62       |
| 8   | 70b     | Female | BTC         | Gallbladder                           | Ductal adenocarcinoma | Locally advanced | MSH2  | MSH2 (−), MSH6 (−) | 3 | 2                        | Observation | NA      |
| 9   | 71      | Male   | PC          | Body or tail                          | Ductal adenocarcinoma | Locally advanced | MSH2  | MSH2 (−), MSH6 (−) | 2 | 0                        | Resection              | 53       |
| 10  | 63      | Female | PC          | Body or tail                          | Ductal adenocarcinoma | Locally advanced | MSH2  | MSH2 (−), MSH6 (−) | 2 | 1                        | Resection              | 80       |
| 11  | 63      | Female | PC          | Body or tail                          | Ductal adenocarcinoma | Locally advanced | MSH2  | MSH2 (−), MSH6 (−) | 2 | 1                        | Resection              | 80       |
| 12  | 84      | Female | PC          | Body or tail                          | Ductal adenocarcinoma | Locally advanced | MS2   | NA  | 3                       | 2                                    | Resection | 17     |
| 13  | 48b     | Female | PC          | Body or tail                          | NET G1                | Locally advanced | MSH2  | NA  | 1                       | 1                                    | Observation | NA     |
| 14  | 58      | Male   | PC          | Head                                 | Ductal adenocarcinoma | Locally advanced | MSH2  | NA  | 4                       | 2                                    | Resection | 198    |

Abbreviations: Age, age at treatment initiation; BTC, biliary tract cancer; IHC, immunohistochemistry; IPMN, intraductal papillary mucinous neoplasm; NA, not applicable; NET, neuroendocrine tumor; OS, overall survival; PC, pancreatic cancer.

*Number of first-degree relatives who had Lynch syndrome-associated malignancies.

bAge at the time of diagnosis (because of no active anticancer therapy).

cOne patient was diagnosed with gallbladder cancer radiologically.

dIHC of the glioblastoma specimens was performed.

eNo detailed information because her tumor was resected at another hospital.
3.2 | History of cancer

Among the six patients with pancreatic malignant tumor, five and two had a history of colorectal cancer and endometrial cancer, respectively. The median number of previous cancers was 2.5 (range, 1-4).

Among the eight patients with biliary tract malignant tumor, six and three had a history of colorectal cancer and endometrial cancer, respectively. The median number of previous cancers was 1.5 (range, 0-3). The patients’ cancer histories are shown in Figure 1.

3.3 | Pathological findings

As shown in Figure 2, lymphoplasmacytic infiltration was observed in three patients with pancreatic malignant tumor and five patients with biliary tract malignant tumor. However, these findings could not be referred to as common pathological findings of Lynch syndrome. Typical pathological findings of Lynch syndrome, such as Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, and medullary growth pattern, were not observed in this study.

Immunohistochemistry was not conducted for seven patients. Two patients were previously diagnosed with Lynch syndrome in a different hospital. Five patients who were highly suspicious for Lynch syndrome based on their family or multiple cancer history underwent germline analyses without IHC.

3.4 | Treatment

Ten patients underwent surgery. Two patients were treated with chemotherapy. Two patients were observed without any active anticancer therapy. Of the 10 patients who underwent surgery, two received neoadjuvant chemotherapy, and four who had recurrence were treated with palliative chemotherapy. Three patients died from tumor progression.

Two patients received gemcitabine and cisplatin as the first-line palliative chemotherapy for BTC. The best responses were a stable disease and progressive disease. One patient died.

Four patients received anti-programmed death-1 (PD-1) therapy with pembrolizumab as palliative chemotherapy. Detailed clinical outcomes of 3/4 patients could not be reported here as they are participants in an ongoing clinical trial. One female patient (No. 10 of Table 2) with PC received pembrolizumab in a clinical setting. The best response was stable disease, and the tumor progressed after 6 months following the initiation of pembrolizumab therapy.

4 | DISCUSSION

Typical Lynch syndrome-associated cancers are characterized by a diagnosis at a young age, a history of multiple cancers, a family history of cancer, and typical pathological findings. In this study, patients with Lynch syndrome-associated pancreatic or biliary tract cancers had a history of multiple cancers and a family history of cancer. In data from the Global Burden of Disease Study, the number of patients with PC peaked at age 65–69 years for males and at 75–79 years for females. The incidence ofBTCs increases with age. Patients with Lynch syndrome-associated pancreatic or biliary tract cancer were younger than those in this study. On the other hand, using the median age, patients with Lynch syndrome-associated pancreatic or biliary tract cancer were older than those with typical Lynch syndrome-associated colorectal or endometrial cancer.

Typical pathological findings were not observed. Lynch syndrome-associated pancreatic or biliary tract cancers were identified predominantly in females in our study. Analysis of data from the prospective Lynch syndrome database revealed that the cumulative risk of developing Lynch syndrome-associated colorectal cancer was generally higher in males than in females. However, the cumulative risk of Lynch syndrome-associated pancreatic
or biliary tract cancers stratified by sex has not yet been reported.

Compared to the age of onset of typical Lynch syndrome-associated colorectal or endometrial cancers, Lynch syndrome-associated pancreatic or biliary tract cancers tended to develop in patients with more advanced ages. In addition, most patients diagnosed with Lynch syndrome-associated pancreatic or biliary tract cancers had a history of multiple cancers. These features were more pronounced in patients with PC. These findings indicate the possibility that Lynch syndrome-associated pancreatic or biliary tract cancers develop late in life as after second primary cancers.

There are some hypotheses as to why Lynch syndrome-associated PCs develop late in life. The first hypothesis is the influence of KRAS mutations. KRAS mutations occur early during carcinogenesis of both colorectal and pancreatic cancers. Colonic epithelial cells undergo a histologic transition from a normal to malignant state. The activation of KRAS oncogene promotes inactivation of APC, which is a tumor suppressor.12 Also, KRAS mutations commonly occur after the onset of a deficiency of a DNA mismatch repair gene in Lynch syndrome-associated colorectal cancers.13 On the other hand, in PCs, normal duct epithelium progresses to infiltrating cancer.14 KRAS mutations are frequently detected in the precursor lesions of PC, which is a pancreatic intraepithelial neoplasia, indicating an initiation of pancreatic carcinogenesis. The activation of point mutations in the KRAS gene occurs early and initiates carcinogenesis: this phase occurs earlier, when compared to colorectal cancer carcinogenesis.12,14 There are many processes involved from the occurrence of KRAS mutations to carcinogenesis. This may lead to the fact that Lynch syndrome-associated PCs develop late in life. Second, the challenges surrounding the early detection of PC may result in the late detection of PC in patients with Lynch syndrome. Third, compared to the colorectal cancer, the pancreas is less exposed to environmental factors such as diet and intestinal bacteria. Hence, carcinogenesis occurs later in the pancreas.

Although the pancreatic head is a major site of sporadic PC, the pancreatic body or tail is the major site of Lynch syndrome-associated PC in this study. Tumors of the pancreatic body or tail are often detected later than tumors of the pancreatic head. They often progress to unresectable tumors. However, tumors of the pancreatic body or tail were detected at a resectable stage in this study. Apart from a case report that presented the case of a patient with Lynch syndrome-associated pancreatic body or tail cancer,15 there is no systematic report of the anatomical site of Lynch syndrome-associated PCs. Contrastingly, intrahepatic and hilar bile ducts were the major sites of Lynch syndrome-associated biliary tract malignant tumor in this study, and there was no cancer of the distal bile duct or ampulla of Vater. A previous study has also reported that the intrahepatic and hilar bile ducts are the most common sites of Lynch syndrome-associated BTC.16

This case series study suggests that fewer patients with Lynch syndrome-associated pancreatic or biliary tract malignant tumors had metastases, and the outcomes of patients with Lynch syndrome-associated pancreatic or biliary tract malignant tumors were apparently better than those of patients with sporadic pancreatic or biliary tract cancers. This may be because most of the patients who had been diagnosed with Lynch syndrome had other cancers before developing pancreatic or biliary tract cancers. Thus, careful follow-up and early detection of tumors in a resectable stage were possible. In 2018, the International Cancer of the Pancreas Screening Consortium recommended pancreatic surveillance for high-risk individuals with familial PC, including those with Lynch syndrome.17 However, evidence-based appropriate surveillance of patients with Lynch syndrome for pancreatic or biliary tract cancers has not been established. Practically, we perform abdominal US once a year for patients with Lynch syndrome; the aim is to detect any abdominal malignancy, including PC and hepatobiliary cancers. Hence, we carried out the prospective multi-institutional surveillance clinical study (the DIAMOND study, UMIN000039779), which is ongoing. The aim of this study was to establish a method of surveillance for early detection of PC in high-risk individuals with familial PC or hereditary neoplastic syndrome, including Lynch syndrome. More than 40 facilities across Japan are participating in this clinical trial.

A previous phase II study has demonstrated the clinical benefit of anti-PD-1 therapy (pembrolizumab) in patients with non-colorectal cancer having a high microsatellite instability and/or a deficiency in DNA mismatch repair.18 The microsatellite instability and/or mismatch repair protein IHC test is the second screening method for Lynch syndrome, and a significant number of Lynch syndrome-associated tumors have high microsatellite instability with deficient mismatch repair.19 In this study, four patients with Lynch syndrome-associated pancreatic or biliary tract cancers were treated with anti-PD-1 therapy. Anti-PD-1 therapy seems to be more effective than standard therapy for these patients.

Patient No. 5 in Table 2 had no past cancer or family history. Her cancer predisposition gene was PMS2. PMS2 mutation carriers have a lower risk of carcinogenesis than carriers of mutations of other mismatch repair genes.5,20

The penetrance for PMS2 mutation carriers appears to be lower than that for carriers of the other mismatch repair genes,21 leading to the absence of a family history.

This study has important limitations. The retrospective, single-institution design and small sample size could
limit the power of the analyses and preclude definitive conclusions. Although Lynch syndrome is a rare disease, further studies with larger sample sizes are necessary.

To conclude, this study brought out several observations on tumor location, late development, and favorable long-term outcomes. Additional studies are needed to identify the characteristics of Lynch syndrome-associated pancreatic or biliary tract cancers. In addition, an appropriate screening method for pancreatic or biliary tract cancers in patients with Lynch syndrome should be established.

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CONFLICT OF INTEREST
The authors declare no conflict of interest for this article.

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REFERENCES
1. Yurgelun MB, Hampel H. Recent advances in Lynch syndrome: diagnosis, treatment, and cancer prevention. Am Soc Clin Oncol Educ Book. 2018;38:101–9.
2. Boland CR, Lynch HT. The history of Lynch syndrome. Fam Cancer. 2013;12:145–57.
3. Moreira L, Balagué F, Lindor N, de la Chapelle A, Hampel H, Aaltonen LA, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012;308:1555–65.
4. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschhoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96:261–8.
5. Network NCC. Genetic/Familial High-Risk Assessment: Colorectal Version 1.2021. NCCN Clinical Practice Guidelines in Oncology Web site. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. (2021). Accessed July 11, 2021.
6. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparrow J, Raymond VM, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302:1790–5.
7. Bonadonna V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305:2304–10.
8. Garg K, Soslow RA. Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. J Clin Pathol. 2009;62:679–84.
9. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2019;4:934–47.
10. Van Dyke AL, Shieh MS, Jones GS, Pfeiffer RM, Petrick JL, Beebe-Dimmer JL, et al. Biliary tract cancer incidence and trends in the United States by demographic group, 1999–2013. Cancer. 2019;125:1489–98.
11. Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22:15–25.
12. Cox AD, Der CJ. Ras history. Small GTPases. 2010;1:2–27.
13. Ahadova A, Gallon R, Gebert J, et al. Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. Int J Cancer. 2018;143:139–50.
14. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res. 2000;6:2969–72.
15. Gilani M, Intenzo CM, Bar-Ad V, Lavu H, Sama AR. Pancreatic cancer in Lynch syndrome: a case report. Case Rep Pancreat Cancer. 2016;2:36–9.
16. Cloyd JM, Chun YS, Ikoma N, Vauthey JN, Aloia TA, Cuddy A, 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.
17. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69:7–17.
18. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38:1–10.
19. Latham A, Srinivasan P, Kemel Y, Shia J, Bandlamudi C, Mandelker JD, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008;135:419–28.

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