The Clinical Significance of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography in Patients with Occupational Cholangiocarcinoma

Masahiko Kinoshita1*, Shigekazu Takemura1, Shogo Tanaka1, Hiroji Shinkawa1, Genya Hamano1, Tokuji Ito1, Masaki Koda1, Takanori Aota1, Yasuni Nakanuma2, Yasunori Sato3, Shoji Nakamori4, Akira Arimoto5, Takatsugu Yamamoto6, Hideyoshi Toyokawa7, Shoji Kubo1

Abstract

Objective: The present study aimed to identify the clinical significance of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in patients with occupational cholangiocarcinoma. Methods: This study included 10 men with occupational cholangiocarcinoma who were former or current workers at a printing company in Osaka, Japan. Of the 10 patients, 2 had 2 main tumors and 1 had 3 main tumors. Twelve FDG-PET imaging findings in the 10 patients could be analyzed. We evaluated the relationships between FDG-PET imaging parameters and clinicopathological findings of occupational cholangiocarcinoma. Results: Abnormal FDG uptake was observed in 8 of the 14 main tumors, with maximum standardized uptake values ranging from 2.9 to 11.0, and the sensitivity was 57.1%. Four patients had lymph node metastases, and abnormal marrow uptake was detected in all these patients. Although precancerous lesions, such as biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct (IPNB) without any invasion, were not detected, abnormal FDG uptake was demonstrated in 2 of 4 patients with IPNB having an associated invasive carcinoma. Conclusions: Although FDG-PET may be useful for assessing tumor progression factors, such as lymph node metastasis, it cannot accurately detect precancerous lesions, such as BilIN and IPNB without invasive carcinoma.

Keywords: Occupational cholangiocarcinoma- lymph node metastasis- biliary intraepithelial neoplasia

Asian Pac J Cancer Prev, 19 (7), 1753-1759

Introduction

Studies recently reported an outbreak of cholangiocarcinoma among young workers in printing companies in Japan (Kumagai et al., 2013, Kubo et al., 2014). Such an occurrence of cholangiocarcinoma was recognized as an occupational disease by the Japanese Ministry of Health, Labour and Welfare in 2013, and 38 patients have been recognized as occupational cholangiocarcinoma in Japan until the end of 2017. It has been reported that 1,2-dichloropropane (DCP) and dichloromethane (DCM) play important roles in the development of this type of cholangiocarcinoma (Kumagai et al., 2013, Japanese Ministry of Health, Labour and Welfare, 2013, Kubo et al., 2014; Kubo et al., 2014). In June 2014, the International Agency for Research on Cancer decided to classify DCP as a group 1 (carcinogenic to humans) and DCM as a group 2A (probably carcinogenic to humans) (Benbrahim-Tallaa et al., 2014). Although the number of patients with occupational cholangiocarcinoma is still limited, our previous studies showed that in addition to the main tumor, chronic bile duct injuries, such as fibrosis of the bile duct wall and periductal tissue, and precancerous lesions, such as biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct (IPNB), were observed at various sites of the large bile ducts in patients with occupational cholangiocarcinoma (Kubo et al., 2014, 2015).
Materials and Methods

This retrospective study included 10 men with occupational cholangiocarcinoma who were former or current workers at a printing company in Osaka, Japan. In the 10 patients, FDG-PET was performed before treatment. In 1 patient (patient no. 9), FDG-PET was performed before the first operation and the second and third operations for recurrent tumors. In total, 12 FDG-PET imaging findings from 10 patients could be analyzed. Among the 10 patients, 8 underwent a total of 10 surgical procedures (patient nos. 1, 2, 3, 5, 7, 8, 9, and 10; 3 procedures in patient no. 9, as described above). Chemotherapy alone was performed in 2 patients (patient nos. 4 and 6). In another 2 patients (patient nos. 2 and 5), additional extrahepatic cholangiocarcinomas, which had not been detected before the operation, were diagnosed on macroscopic and microscopic examinations of the operative specimens. Patient no. 2 had 2 main tumors (tumor nos. 2a and 2b), and patient no. 5 had 2 main tumors (tumor nos. 5a and 5b). Patient no. 9 had 3 main tumors (primary tumor, tumor no. 9a; the first recurrent tumor, 9b; and the second recurrent tumor, 9c). The longest diameters of the tumors were measured according to macroscopic findings in patients with operative specimens and according to diagnostic imaging in patients who did not undergo surgery. In 2 tumors (tumor nos. 5a and 10), the diameter could not be measured because intraepithelial cancerous spread (without mass formation) could not be determined on macroscopic examination. The liver anatomy and operative methods were classified according to Brisbane 2000 terminology (Pang, 2000).

Pathological examinations of surgical specimens were performed in 8 patients (10 operations) (patient nos. 1–3, 5, 7, 8, 9 [3 operations], and 10) (Table 1). We evaluated clinicopathological characteristics, including the presence of BilIN or IPNB, in non-cancerous hepatic tissues. The pathological findings were evaluated by pathologists (Y.N. and Y.S.) according to the World Health Organization classification for intrahepatic cholangiocarcinoma (ICC) (Nakanuma et al., 2010). ICC was grossly classified as a mass-forming, periductal infiltrating, or intraductal growth. Extrahepatic cholangiocarcinoma (perihilar and distal cholangiocarcinoma; ECC) was grossly classified as a papillary, nodular, scirrhous constricting, or diffusely infiltrating tumor. Pre or early neoplastic lesions of the bile ducts were classified as BilIN or IPNB. BilIN lesions were histologically classified according to their cellular and structural features as BilIN-1 (mild atypia), BilIN-2 (moderate atypia), or BilIN-3 (severe atypia corresponding to in situ carcinoma). In this study, we mainly assessed BilIN-2 and BilIN-3 lesions because it was unclear whether BilIN-1 lesions included reactive hyperplastic changes. IPNB was characterized by dilated intrahepatic and extrahepatic bile ducts filled with papillary or villous biliary neoplasms that covered delicate fibrovascular stalks. The dilated bile ducts were fusiform or cystic (unilobular or multilobular), and the height of such lesions usually exceeded 10 mm, but papillary lesions <10 mm but >5 mm showing similar histologies were also occasionally encountered. IPNB was not infrequently associated with focal and minimal invasion (invasive IPNB).

We investigated abnormal marrow uptake on FDG-PET imaging, including the maximum standardized uptake value (SUVmax), through medical records and reports of radiologists. In addition, we evaluated the relationships between FDG-PET imaging parameters and clinicopathological findings of occupational cholangiocarcinomas, including main lesions and lymph node metastases in all patients, and precancerous lesions, such as BilIN-2/3 and IPNB, on pathological examination in patients who underwent surgery. The presence of lymph node metastasis was defined as follows: i) in patients who underwent surgery with lymph node dissection, the presence of metastasis was diagnosed by pathological examination; ii) in patients who underwent surgery without lymph node dissection, the presence of metastasis was assessed by intraoperative macroscopic findings first, and if any enlarged lymph nodes were not detected on diagnostic imaging for 1 year after surgery, the patients were assumed to not have lymph node metastasis; iii) in patients who did not undergo surgery, if some enlarged lymph nodes were detected on diagnostic imaging and the diameter or number of the lymph nodes increased subsequently, the patients were assumed to have lymph node metastasis.

This study was approved by the ethics committee of Osaka City University (No. 2368), and all of the participants or their legally authorized representatives (for decreased patients) provided written informed consent. This multicenter occupational cholangiocarcinoma study
involved investigators at 5 institutions.

Results

Clinicopathological findings of the 10 study patients

The age of the patients at diagnosis ranged from 31 to 48 years, and all patients were men (Table 1). Nine main tumors (tumor nos. 1, 2a, 3, 4, 5a, 7, 8, 9a, and 9c) were diagnosed as ICC, and 5 main tumors (tumor nos. 2b, 5b, 6, 9b, and 10) were diagnosed as ECC, including distal and perihilar cholangiocarcinoma. Two patients (patient nos. 2 and 5) had both ICCs (tumor nos. 2a and 5a) and ECCs (tumor nos. 2b and 5b). Six ICCs (tumor nos. 1, 2a, 3, 4, 8, and 9c) were classified as mass-forming type and 3 ICCs (tumor no. 5a, 7, and 9a) were classified as intraductal growth type. Three ECCs (tumor nos. 2b, 9b, and 10) were located at the distal side of the common bile duct, and 2 ECCs (tumor nos. 5b and 6) were located at the perihilar bile duct. Three ECCs (tumor nos. 2b, 5b, and 9b) were classified as papillary type, 1 ECC (tumor no. 6) was classified as nodular type, and 1 ECC (tumor no. 10) was classified as diffusely infiltrating type. The longest diameters of 4 tumors (tumor nos. 2b, 6, 7, and 9b) were less than 1 cm, and the longest diameters of 8 other tumors ranged from 1 cm to 17 cm. The diameters of 2 tumors (tumor nos. 5a and 10) could not be measured, as described above. Liver resection alone was performed in 4 patients (5 operations) (patient nos. 1, 3, 7, and 9 [the first and third operations]), liver resection with resection of the extrahepatic bile duct was performed in 2 patients (patient nos. 5 and 8), resection of the extrahepatic bile duct was performed in 1 patient (patient no. 9 [the second operation]), liver resection and pancreaticoduodenectomy were performed in 1 patient (patient no. 2), and pancreaticoduodenectomy alone was performed in 1 patient (patient no. 10) (Table 1).

Pathological examination showed that the main lesions in 10 surgical specimens (patient nos. 1, 2, 3, 5, 7, 8, 9 [all 3 operations], and 10) were tubular or papillary adenocarcinomas. Four main lesions (tumor nos. 5a, 7, 9a, and 9b) were diagnosed as invasive IPNB by pathological examination. BilIN-2/3 lesions were observed in 9 surgical specimens (patient nos. 1–3, 5, 7, 8, and 9 [all 3 operations]) (Table 1). In patient no. 10, the presence of BilIN-2/3 could not be evaluated sufficiently because of the presence of small numbers of non-cancerous large bile ducts. IPNB without any invasion was observed in 5 surgical specimens (patient nos. 2, 5, 7, 8, and 9 [the first and second operations]).

The diameters of 2 tumors (tumor nos. 5a and 10) could not be measured, as described above. Liver resection alone was performed in 4 patients (5 operations) (patient nos. 1, 3, 7, and 9 [the first and third operations]), liver resection with resection of the extrahepatic bile duct was performed in 2 patients (patient nos. 5 and 8), resection of the extrahepatic bile duct was performed in 1 patient (patient no. 9 [the second operation]), liver resection and pancreaticoduodenectomy were performed in 1 patient (patient no. 2), and pancreaticoduodenectomy alone was performed in 1 patient (patient no. 10) (Table 1).

Pathological examination showed that the main lesions in 10 surgical specimens (patient nos. 1, 2, 3, 5, 7, 8, 9 [all 3 operations], and 10) were tubular or papillary adenocarcinomas. Four main lesions (tumor nos. 5a, 7, 9a, and 9b) were diagnosed as invasive IPNB by pathological examination. BilIN-2/3 lesions were observed in 9 surgical specimens (patient nos. 1–3, 5, 7, 8, and 9 [all 3 operations]) (Table 1). In patient no. 10, the presence of BilIN-2/3 could not be evaluated sufficiently because of the presence of small numbers of non-cancerous large bile ducts. IPNB without any invasion was observed in 5 surgical specimens (patient nos. 2, 5, 7, 8, and 9 [the first and second operations]).

Table 1. Clinicopathological Findings of Patients with Occupational Cholangiocarcinoma

| Patient no. | Age | Sex | Location, type, and longest diameter of cholangiocarcinoma (tumor no.) | Treatment | Pathological diagnosis of the main lesion (tumor no.) | BilIN - 2/3 | IPNB without any invasion | Lymph node metastasis |
|-------------|-----|-----|---------------------------------------------------------------------|-----------|------------------------------------------------------|------------|--------------------------|----------------------|
| 1           | 34  | M   | ICC, mass-forming, 17 cm (1)                                        | Right trisectionectomy | Poorly differentiated papillary adenocarcinoma (1)    | Yes        | No                       | No                   |
| 2           | 40  | M   | ICC, mass-forming, 1.7 cm (2a)                                      | Right hepatectomy, pancreaticoduodenectomy | Well-differentiated tubular adenocarcinoma (2a)       | Yes        | Yes                      | No                   |
| 3           | 38  | M   | ICC, mass-forming, 2.5 cm (3)                                       | Segmentectomy 8        | Well-differentiated tubular adenocarcinoma (3)       | Yes        | ND                       | Yes                  |
| 4           | 39  | M   | ICC, mass-forming, 10 cm (4)                                        | Chemotherapy           | -                                                    | -          | -                        | Yes                  |
| 5           | 39  | M   | ICC, intraductal growth, 1.5 cm (5a) perihilar ECC, papillary, NM (5b) | Left hepatectomy, resection of extra hepatic bile duct | Invasive IPNB (5a), Well-differentiated tubular adenocarcinoma (5b) | Yes        | Yes                      | No                   |
| 6           | 37  | M   | Perihilar ECC, nodular,<1 cm (6)                                    | Chemotherapy           | -                                                    | -          | -                        | Yes                  |
| 7           | 39  | M   | ICC, intraductal growth, <1 cm (7)                                  | Right hepatectomy, segmentectomy 7 | Invasive IPNB (7)                                   | Yes        | Yes                      | No                   |
| 8           | 31  | M   | ICC, mass-forming, 2.1 cm (8)                                       | Right hepatectomy, resection of extra hepatic bile duct | Moderately differentiated papillary adenocarcinoma (8) | Yes        | Yes                      | Yes                  |
| 9_1         | 34  | M   | ICC, intraductal growth, 1.5 cm (9a)                                | Extended left hepatectomy | Invasive IPNB (9a)                                  | Yes        | Yes                      | No                   |
| 9_2         | 36  | M   | Distal ECC, papillar, <1 cm (9b)                                    | Resection of extra hepatic bile duct S8 partial hepatectomy" | Invasive IPNB (9b)                                  | Yes        | Yes                      | No                   |
| 9_3         | 37  | M   | ICC, mass-forming, 2.5 cm (9c)                                      | S6 and S7 partial hepatectomy | Moderately differentiated tubular adenocarcinoma (9c) | Yes        | ND                       | No                   |
| 10          | 48  | M   | Distal ECC, diffusely infiltrating, NM (10)                         | Pancreaticoduodenectomy | Moderately differentiated tubular adenocarcinoma (10) | ND         | ND                       | Yes                  |

ICC, intrahepatic cholangiocarcinoma; ECC, extrhepatic cholangiocarcinoma; <1 cm, diameter less than 1 cm; NM, diameter could not be determined because intraepithelial cancerous spread could not be measured on macroscopic examination; BilIN, biliary intraepithelial neoplasia; IPNB, intraductal papillary neoplasm of the bile duct; ND, not determined. Patient no. 9 is classified and defined as follows, 9-1) at the first surgery, 9-2) at the second surgery, and 9-3) at the third surgery.
operations). In 3 surgical specimens (patient nos. 3, 9 [the third operation], and 10), the presence of IPNB could not be evaluated sufficiently because of the presence of small numbers of non-cancerous large bile ducts. Of the 4 patients, lymph node metastasis in the hepatoduodenal ligament and/or peripancreatic region was diagnosed by pathological examination in 2 (patient nos. 3 and 8) and by diagnostic imaging alone in 2 (patient nos. 4 and 6).

Findings of FDG-PET imaging

Abnormal FDG uptake was observed in 8 main tumors (tumor nos. 1, 3, 4, 5a, 8, 9a, 9c, and 10) among the 14 main lesions (Table 2, Figure 1a). The SUVmax values ranged from 2.9 to 11.0 (Table 3). Of 6 tumors that were not detected on FDG-PET (false negative), 4 (tumor nos. 2b, 6, 7, and 9b) showed a longest diameter of less than 1 cm, 1 (tumor no. 2a) showed a longest diameter of 1.7 cm, and 1 (tumor no. 5b) showed intraepithelial cancerous spread without mass formation. Thus, the sensitivity was 57.1% (Table 3). On the other hand, in patient no. 9 at the third surgery, although...
Thus, the specificity was calculated as 93.3% (Table 3). In all 4 patients who had lymph node metastasis, abnormal FDG uptake was observed in each metastatic lymph node with high SUVmax values ranging from 3.8 to 14.2 (Table 2, Figure 1b), and the sensitivity and specificity were both 100% (Table 3). All of the BilIN-2/3 lesions were not found to have abnormal marrow uptake on FDG-PET imaging (Table 2, Figure 2a, 2b). IPNB lesions without any invasion in 5 surgical specimens (patient nos. 2, 5, 7, 8, and 9 [the first and second operations]) were not detected on FDG-PET imaging (Table 2, Figure 2a, 2c). However, 2 (tumor nos. 5a and 9a) of 4 tumors with invasive IPNB as the main lesion showed abnormal marrow uptake on FDG-PET imaging (SUVmax 4.1 and 3.8, respectively) (Table 2, Figure 3a, 3b).

### Discussion

Our previous studies reported that elevated serum gamma-glutamyl transpeptidase activities, regional dilatation of the intrahepatic bile ducts without tumor-induced obstruction and biliary findings similar to those indicating the appearance of PSC (Vitellas et al., 2000) on diagnostic imaging, a papillary proliferating tumor, presence of precancerous or early cancerous lesions, such as BilIN and IPNB, and non-specific bile duct injuries, such as fibrosis, are characteristics of patients with occupational cholangiocarcinoma (Kubo et al., 2014; Kubo et al., 2014; Kinoshita et al., 2016). Furthermore, a carcinogenic process consisting of chronic bile duct injury with DNA damage within various sites in the large bile ducts, the induction of pre or early cancerous lesions, such as BilIN and IPNB, and the development of invasive carcinoma with high frequency of somatic mutations, has been proposed (Kinoshita et al., 2016; Mimaki et al., 2016). Although it is sometimes difficult to perform curative resection for such multicentric carcinogenesis of occupational cholangiocarcinoma, aggressive treatment, including repeated resections, may be considered as effective through analyses of postoperative outcomes (Kubo et al., 2016). Therefore, accurate and efficient diagnostic imaging and the evaluation of the extent of carcinoma are important for treatment.

Although normal hepatic tissues displayed a relatively high glucose uptake, there was usually an intense FDG uptake in ICCs, indicating high metabolic activity with a consequently much greater tumor-to-normal liver tissue ratio (Kim et al., 2003; Lee et al., 2008; Jiang et al., 2016). However, the present study showed that the sensitivity of FDG-PET for occupational cholangiocarcinoma was not high (57.1%). A previous study suggested that the ICC size was significantly correlated with FDG uptake, and perihilar cholangiocarcinoma tended to lower FDG uptake because of symptoms involving the obstruction of the large bile duct by small tumors (Jiang et al., 2016). Actually, in the present study, all tumors less than 1 cm in the longest diameter and 1 of 2 lesions showing intraepithelial cancerous spread (without mass formation) were not found to have abnormal marrow uptake on FDG-PET. In patients with occupational cholangiocarcinoma, cholangiocarcinoma was detected by further examination after the identification of abnormal findings in a regular health examination (Kubo et al., 2014; Kubo et al., 2014; Kubo et al., 2016), and the main tumor was detected to be small without any symptoms. In addition, small carcinomas were sometimes detected through macroscopic and microscopic examinations of operative specimens because a multicentric carcinogenic process was noted at various sites of the bile ducts (Kubo et al., 2014; Kubo et al., 2014; Kinoshita et al., 2016). Because of these reasons, although FDG-PET is generally useful for the diagnosis of main lesions in patients with occupational cholangiocarcinoma, accurate detection of the carcinoma may be sometimes difficult with FDG-PET, especially when the tumor is small. On the other hand, all of the lymph node metastases showed abnormal FDG uptake on FDG-PET imaging. Some previous studies reported that FDG-PET has higher specificity (91.7-100%) and similar or superior sensitivity (43-70%) in the detection of lymph node metastases for patients with cholangiocarcinoma compared with computed tomography or magnetic resonance imaging (Itatsu et al., 2007; Jiang et al., 2016). In this study, the sensitivity and the specificity were 100% in the detection of lymph node metastases. Although the sensitivity of FDG-PET seemed to be higher in patients with occupational cholangiocarcinoma than in those with non-occupational cholangiocarcinoma, it was difficult to compare the usefulness of FDG-PET in the detection of lymph node metastases in patients with occupational cholangiocarcinoma because of a small number of patients with occupational cholangiocarcinoma. The distribution of the metastatic lymph nodes were similar in both patients with occupational cholangiocarcinoma and with non-occupational cholangiocarcinoma.

BilIN and IPNB are currently regarded as precancerous or early cancerous lesions according to the World Health Organization’s classification of cholangiocarcinoma (Nakanuma et al., 2010), and they are considered to be involved in the multistep carcinogenesis of cholangiocarcinoma in patients with hepatolithiasis or PSC (Chen et al., 2001; Itatsu et al., 2007; Zen et al., 2007; Nakanuma et al., 2010).
Papillary or invasive carcinoma, precancerous or early cancerous lesions, such as BilIN and IPNB, and non-specific bile duct injuries, such as fibrosis, are reportedly pathological characteristics of occupational cholangiocarcinoma (Kubo et al., 2014; Kubo et al., 2014; Kubo et al., 2016). In addition, high frequency of BilIN and/or IPNB and wide distribution of such lesions were considered to be characteristics of patients with occupational cholangiocarcinoma in comparison to patients with hepatolithiasis or PSC (Kinoshita et al., 2016). There are no reports about FDG-PET of BilIN lesions. Our present study showed that BilIN-2/3 lesions were not detected on FDG-PET in patients with occupational cholangiocarcinoma. Thus, the diagnosis and surveillance of BilIN lesions may be difficult with FDG-PET. On the other hand, FDG-PET findings of IPNB have been rarely reported, including case reports (Takanami et al., 2010; Takanami et al., 2011; Dong et al., 2012; Watanabe et al., 2013). These previous reports showed that an invasive IPNB with a large mural nodule may show increased FDG uptake and that FDG uptake was higher for a larger IPNB with high-grade dysplasia than for a small IPNB with low-grade dysplasia (Takanami et al., 2010; Takanami et al., 2011; Dong et al., 2012; Watanabe et al., 2013). In this study, although invasive IPNB was detected as abnormal marrow uptake on FDG-PET imaging with a sensitivity of 50%, IPNB without any invasion was not detected. Thus, although an invasive IPNB may be detected on FDG-PET, this approach is not an efficient diagnostic tool for IPNB without invasion.

This study has some limitations. This study included a few subjects because the number of patients with occupational cholangiocarcinoma is originally small. The pathological examination was performed using surgical specimens in 8 patients and it was impossible to examine pathologically using the whole liver. However, the results in this study provide an important information for the diagnosis of occupational cholangiocarcinoma.

In conclusion, although FDG-PET may be useful for assessing tumor progression, including progression of main tumors and lymph node metastasis, it cannot accurately detect precancerous lesions such as BilIN and IPNB without invasive carcinoma.

Author contribution
Study design: M. Kinoshita and SK designed the study
Acquisition of data: M. Kinoshita, YN, YS, S. Takemura, S. Tanaka, GH, TI, M. Koda, TA, SN, AA, TY, HT, and SK. Pathological aspect of the study: YN and YS analyzed pathological findings. Data analysis: M. Kinoshita, S. Takemura, S. Tanaka, GH, TI, M. Koda, TA, TM, and SK. Manuscript drafted by MK and SK. All authors reviewed the manuscript.

Conflicts of interest
No potential conflicts of interest were disclosed.

Acknowledgments
This study was supported in part by Health and Labor Sciences Research Grants for Research on Occupational Safety and Health (epidemiological and cause-investigated study of cholangiocarcinoma in printing company workers) and by Industrial Disease Clinical Research Grants (establishment of diagnostic methods for occupational cholangiocarcinoma; 14040101-01). This work was also supported in part by the Japan Society for the Promotion of Science KAKENHI Grant Number 26245678 (clinicopathological and molecular biological analysis of carcinogenesis of intrahepatic cholangiocarcinoma by chemicals). We thank Drs. S. Marubashi and M. Kaji for their assistance with data collection.

References
Albazaz R, Patel CN, Chowdhury FU, Scarsbrook AF (2013). Clinical impact of FDG PET-CT on management decisions for patients with primary biliary tumours. Insights Imaging, 4, 691–700.
Benbrahim-Talaia L, Lauby-Secretan B, Loomis D, et al (2014). Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sulfone. Lancet Oncol, 15, 924–5.
Chen TC, Nakanuma Y, Zen Y, et al (2001). Intraductal papillary neoplasia of the liver associated with hepatolithiasis. HEPATOLOGY, 34, 651–8.
Dong A, Dong H, Zhang L, Zuo C (2012). F-18 FDG uptake in borderline intraductal papillary neoplasms of the bile duct. Ann Nucl Med, 26, 594–8.
Hamano G, Kubo S, Takemura S, et al (2016). Comparison of clinicopathological characteristics between patients with occupational and non-occupational intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Sci, 23, 389–96.
Itatsu K, Zen Y, Ohira S, et al (2007). Immunohistochemical analysis of the progression of flat and papillary preneoplastic lesions in intrahepatic cholangiocarcinogenesis in hepatolithiasis. Liver Int, 27, 1174–84.
Japanese Ministry of Health, Labour and Welfare (2013). Occupational biliary tract cancer cases in Japan. http://www.mhlw.go.jp/english/policy/employ-labour/labour-standards/Occupational.html.
Jiang L, Tan H, Panje CM, et al (2016). Role of 18F-FDG PET/CT Imaging in Intrahepatic Cholangiocarcinoma. Clin Nucl Med, 41, 1–7.
Keidar Z, Haim N, Guralnik L, et al (2004). PET/CT using 18F-FDG in suspected lung cancer recurrence: diagnostic value and impact on patient management. J Nucl Med, 45, 1640–6.
Kim YJ, Yun M, Lee WJ, Kim KS, Lee JD (2003). Usefulness of 18F-FDG PET in intrahepatic cholangiocarcinoma. Eur J Nucl Med Mol Imaging, 30, 1467–72.
Kinoshita M, Kubo S, Nakanuma Y, et al (2016). Pathological spectrum of bile duct lesions from chronic bile duct injury to invasive cholangiocarcinoma corresponding to bile duct imaging findings of occupational cholangiocarcinoma. J Hepatobiliary Pancreat Sci, 23, 92–101.
Koyama K, Kubo S, Ueki A, et al (2017). MR imaging and MR cholangiopancreatography of cholangiocarcinoma developing in printing company workers. Jpn J Radiol, 35, 233–41.
Kubo S, Kinoshita M, Takemura S, et al (2014). Characteristics of printing company workers newly diagnosed with occupational cholangiocarcinoma. J Hepatobiliary Pancreat.
Asian Pacific Journal of Cancer Prevention, Vol 19

FDG-PET in Occupational Cholangiocarcinoma

Sci, 21, 809–17.
Kubo S, Nakanuma Y, Takemura S, et al (2014). Case series of 17 patients with cholangiocarcinoma among young adult workers of a printing company in Japan. J Hepatobiliary Pancreat Sci, 21, 479–88.
Kubo S, Takemura S, Sakata C, et al (2014). Changes in laboratory test results and diagnostic imaging presentation before the detection of occupational cholangiocarcinoma. J Occup Health, 56, 317–22.
Kubo S, Takemura S, Tanaka S, et al (2016). Outcomes after resection of occupational cholangiocarcinoma. J Hepatobiliary Pancreat Sci, 23, 556–64.
Kubo S, Takemura S, Tanaka S, et al (2016). Screening and surveillance for occupational cholangiocarcinoma in workers exposed to organic solvents. Surg Today, 46, 705–12.
Kumagai S, Kurumatani N, Arimoto A, Ichihara G (2013). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med, 70, 508–10.
Lee JD, Kang WJ, Yun M (2008). Primary cancer of the liver and biliary duct. PET Clin, 3, 169–86.
Mimaki S, Totsuka Y, Suzuki Y, et al (2016). Hypermutation and unique mutational signatures of occupational cholangiocarcinoma in printing workers exposed to haloalkanes. Carcinogenesis, 37, 817–26.
Nakanuma Y, Curado MP, Franceschi S, et al (2010). WHO classification of tumors of the digestive system. In “Intrahepatic cholangiocarcinoma”, Eds Bosman FT, Carneiro F, Hruban RH, Theise ND. IARC Press, Lyon, pp 217–24.
Nakanuma Y, Tsutsui A, Ren XS (2014). What are the precursor and early lesions of peripheral intrahepatic cholangiocarcinoma?. Int J Hepatol, 2014, Article ID; 805973, 9 pages.
Pang YY (2000). The Brisbane 2000 terminology of liver anatomy and resections. HPB, 2, 333–9. HPB (Oxford) 2002;4:99; author reply pp 99–100.
Seo S, Hatano E, Higashi T, et al (2008). Fluorine-18 fluorodeoxyglucose positron emission tomography predicts lymph node metastasis, P-glycoprotein expression, and recurrence after resection in mass-forming intrahepatic cholangiocarcinoma. Surgery, 6, 769–77.
Takanami K, Hiraide T, Kaneta T, et al (2010). FDG PET/CT findings in malignant intraductal papillary mucinous neoplasm of the bile ducts. Clin Nucl Med, 35, 83–5.
Takanami K, Yamada T, Tsuda M, et al (2011). Intraductal papillary mucinous neoplasm of the bile ducts: multimodality assessment with pathologic correlation. Abdom Imaging, 36, 447–56.
Vitellas KM, Keogan MT, Freed KS, et al (2000). Radiologic manifestations of sclerosing cholangitis with emphasis on MR cholangiopancreatography. Radiographics, 20, 959–75.
Votrubaova J, Belohlavek O, Jaruskova M, et al (2006). The role of FDG-PET/CT in the detection of recurrent colorectal cancer. Eur J Nucl Med Mol Imaging, 33, 779–84.
Watanabe A, Suzuki H, Kubo N, et al (2013). An oncocytic variant of intraductal papillary neoplasm of the bile duct that formed a giant hepatic cyst. Rare Tumors, 5, e30.
Zen Y, Adsay NV, Bardadin K, et al (2007). Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. Mod Pathol, 20, 701–9.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.