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Antegrade Endobiliary Forceps Biopsy Improves Diagnosis of Klatskin Tumor Compared to Brush Biopsy

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Aim. To evaluate the safety and accuracy of percutaneous transhepatic biliary biopsy in patients with suspected Klatskin tumor.
Materials and methods. Between 2013–2020, percutaneous transhepatic biliary drainage (PTBD) was performed in 52 patients with Klatskin tumor, complicated by obstructive jaundice. After successful PTBD, the diagnosis was verified by antegrade access. 74 procedures were performed: brush (n = 36; 48.6 %) or forceps biopsies (n = 38; 51.4 %).
Results. There were no adverse events associated with a brush biopsy. Only grade I complications were after the forceps technique: 3 patients (7.9 %) developed hemobilia, which was corrected conservatively. Malignant lesions of the biliary tract were detected by forceps technique in 79.0 %, brush biopsy in 66.7 % (p >0,05). The degree of tumor differentiation was determined in 60.0 % (n = 18) vs 12.5 % (n = 3) (p < 0,01), respectively.
Sensitivity and specificity of forceps biopsy were slightly higher than in brush: 82.4 % and 75.0 % vs 73.3 % and 66.7 % (p >0,05).
Conclusions. Antegrade percutaneous transhepatic biliary biopsy is safe for both brush and forceps techniques. However, forceps biopsy has higher sensitivity and specificity in the diagnosis Klatskin tumor and better possibility of determining the degree of malignancy differentiation.
Keywords: cholangiocarcinoma, Klatskin tumor, brush biopsy, forceps biopsy, percutaneous transhepatic biliary drainage
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Антеградная эндобилиарная щипцовая биопсия улучшает диагностику опухоли Клацкина по сравнению с браш-биопсией

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Цель. Сравнить безопасность и морфологическую информативность щипцовой и браш-биопсии у пациентов с опухолью Клацкина.
Материалы и методы. За период 2013–2020 гг. чрескожное чреспеченочное холангиодренирование выполнено у 52 пациентов с опухолью Клацкина (27 женщин, 25 мужчин; средний возраст 59 лет). После этого антеградным доступом проведена верификация диагноза (74 процедуры): с 2013 по 2017 г. браш-биопсия (n =

36; 48,6 %) и с 2017 по 2020 г. щипцовая биопсия (n = 38; 51,4 %). Результаты биопсии были подтверждены последующим исследованием послеоперационного материала или клинико-рентгенологическими данными наблюдения пациентов.

Результаты. Нежелательных явлений, связанных с браш-биопсией, не было. Отмечены осложнения у пациентов, связанные со щипцовой биопсией: в трех случаях (7,9 %) развилась гемобилия, которая была купирована консервативными методами в течение 1 сут. После выполнения 74 процедур биопсий у 52 больных злокачественное поражение желчевыводящих путей было выявлено при щипцовой биопсии в 79,0 %, а при браш-биопсии в 66,7 % случаев. Степень дифференцировки опухоли была определена у 60,0 % (n = 18) против 12,5 % (n = 3) (p < 0,01) соответственно. Чувствительность и специфичность при щипцовой биопсии были выше, чем при браш-биопсии: 82,4 и 75,0 % против 73,3 и 66,7 % (p > 0,05).

Выводы. Эндобилиарная биопсия антеградным доступом является безопасной методикой как при браш-, так и при щипцовой методике. Однако при заборе материала щипцами увеличивается чувствительность и специфичность диагностики, возможность определения степени дифференцировки опухоли.

Ключевые слова: внепеченочная холангиокарцинома, опухоль Клацкина, браш-биопсия, щипцовая биопсия, холангиодренирование

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Introduction

Cholangiocellular cancer accounts for 3 % of cases of all malignant neoplasms of the digestive system and ranks second in frequency among patients with primary liver tumors [1, 2]. Cholangiocarcinomas are divided by anatomical location into intra- and extrahepatic, and the latter are detected much more often and in 50 % of cases localized in the area of the *porta hepatis* (Klatskin tumor). Moderate to low differentiation adenocarcinoma accounts for 90–95 % of cholangiocellular cancer cases [3–5].

Resection and liver transplantation allow to achieve the best result of treatment. About the bottom, operability is in the range of 20–27 % [6, 7], the median survival rate is 25–40 months, and the 5-year survival rate is about 25 % [2, 8, 9]. The median survival of patients with palliative treatment of a locally advanced tumor is 14–17 months, and in the presence of distant metastases 7–9 months [10].

Morphological verification of Klatskin tumor is complicated by the anatomical localization of the formation and, as a rule, the serious condition of patients. According to clinical guidelines [3], a biopsy is not necessary before surgery, but is necessary for the appointment of antitumor methods of treatment.

There are several methods of taking histological material from the bile ducts: percutaneous, aspiration, endobiliary forceps, puncture under endoscopic ultrasound guidance, brush biopsy. According to most authors, the specificity of intraductal biopsy is 100 %. At the same time, the sensitivity of brush and pinch biopsies are in a wide range: 0–87 % and 0–94 %, respectively [11, 12]. In the domestic literature, there are no publications devoted to this issue.

Given the ambiguous data obtained by different authors, it is necessary to improve the verification methods of extrahepatic cholangiocellular cancer.

The aim of the present study was to compare the safety and morphological information content of plucking and brush biopsy in patients with Klatskin’s tumor.

Materials and methods

For the period 2013–2020 in the Russian Scientific Center of Radiology and Surgical Technologies (RSCRST) named after academician A.M. Granov was admitted for additional examination and treatment of 128 patients with a preliminary diagnosis of extrahepatic cholangiocarcinoma. Percutaneous transhepatic cholangiodrainage was performed in 114 (89.0 %) before admission to our center, in 7 (5.5 %) in the RSCRST. Another 7 patients (5.5 %) had a tumor of the bile ducts with their expansion without hyperbilirubinemia.

Histological verification was carried out in other clinics in 35 patients. The degree of differentiation of adenocarcinoma was low in three (8.6 %) patients, moderate — in 7 (20.0 %), high — in one (2.8 %). Undifferentiated bile duct cancer was detected in 24 (68.6 %).

Histological examination was absent in 93 patients. Postoperative morphological conclusion was

obtained in 24 patients, histological verification was not performed due to the severity of the condition in 17, and the remaining 52 patients needed a biopsy to start specific therapy.

Material sampling was carried out by antegrade percutaneous percutaneous access in 52 patients (27 women, 25 men; mean age 59 years) with external-internal cholangiodrainages. 74 procedures were performed: from 2013 to 2017, a brush biopsy (n = 36; 48.6 %), and from 2017 to 2020, a pinch biopsy (n = 38; 51.4 %). In order to prevent complications associated with traumatization of the puncture canal, histological material was taken no earlier than in 5–7 days after primary cholangiodrainage placement. The safety, sensitivity and specificity of both methods were studied. The results of the Klatskin tumor biopsy were confirmed by a subsequent study of postoperative material or clinical and radiological data from patient observation.

Biopsy technique

The biopsy was performed under local anesthesia. The first step was to remove cholangiodrainage on the guidewire. Introducer 7–10 F was carried out in the bile ducts proximal to the site of obstruction and performed cholangiography with the introduction of a diluted 76 % contrast agent ("Ultravist", "Omnipaque", "Optiray"). The localization, extent and prevalence of tumor stricture were evaluated according to the Bismuth-Corlette classification.

For brush biopsy, a single endoscopic biliary cytological brush BC-202 D-2010 (Olympus, USA) with a diameter of 3.0 mm and a length of 10.0 mm was used. Through the introducer, parallel to the guidewire, the brush was installed to the site of obstruction of the bile ducts and two to three times it was carried throughout the stricture. The material was fixed in a test tube with formalin. The procedure was repeated three times, after which the material was installed sent for cytological examination (Fig. 1).

For forceps biopsy, radiopaque bending / rotating biopsy forceps Cordis BI-PAL 7 F (2.33 mm) with a length of 50 cm were used. According to the manufacturer's instructions, the main indication for their use is an endomyocardial biopsy, but it is indicated that it is permissible modification of the procedure. After getting acquainted with the characteristics of the forceps (length, diameter, stiffness, the possibility of changing the angle between the mating parts, the presence of cutting branches), we considered it possible to use them for biopsy of the bile ducts.

The sequence of manipulations was as follows. After diagnostic cholangiography, the guidewire was removed, since it did not allow the material to be optimally taken along the entire circumference of the stricture. Through the introducer, forceps were placed in the obstruction zone and the open branches rested on the wall of the bile duct affected by the tumor. The tongs closed tightly and pulled them outward at once. The material was taken four times from different sections of the stricture: three fragments for histological examination and one for cytological examination (Fig. 2).

The procedures ended with the installation of biliary drainage in the original position for adequate

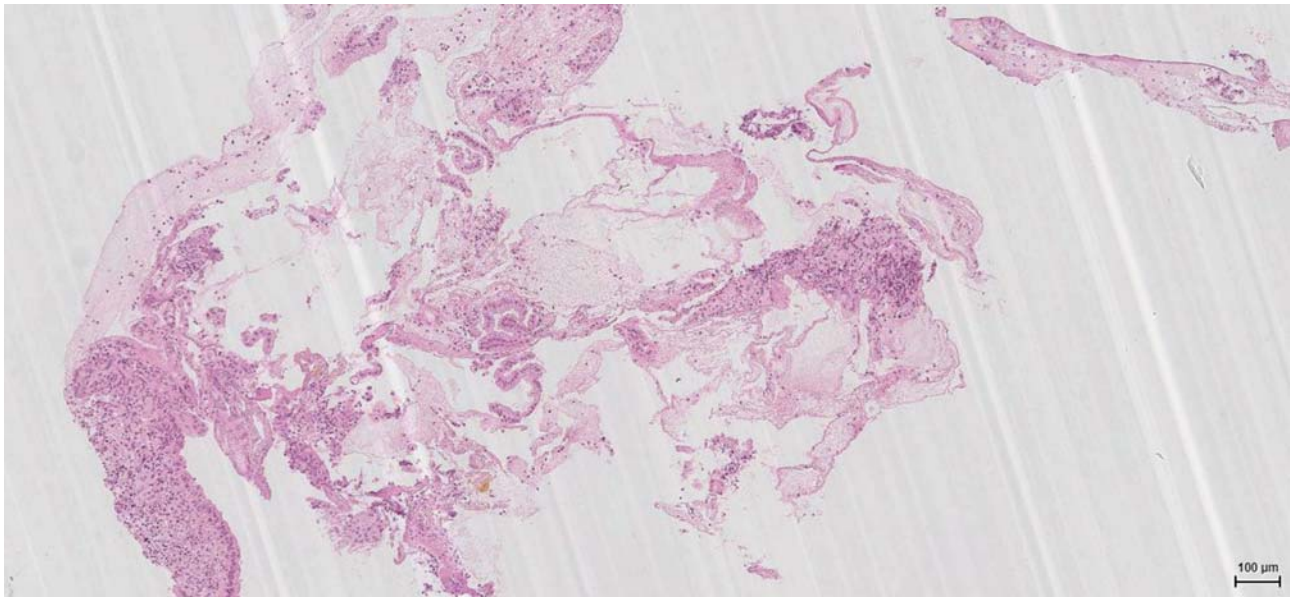
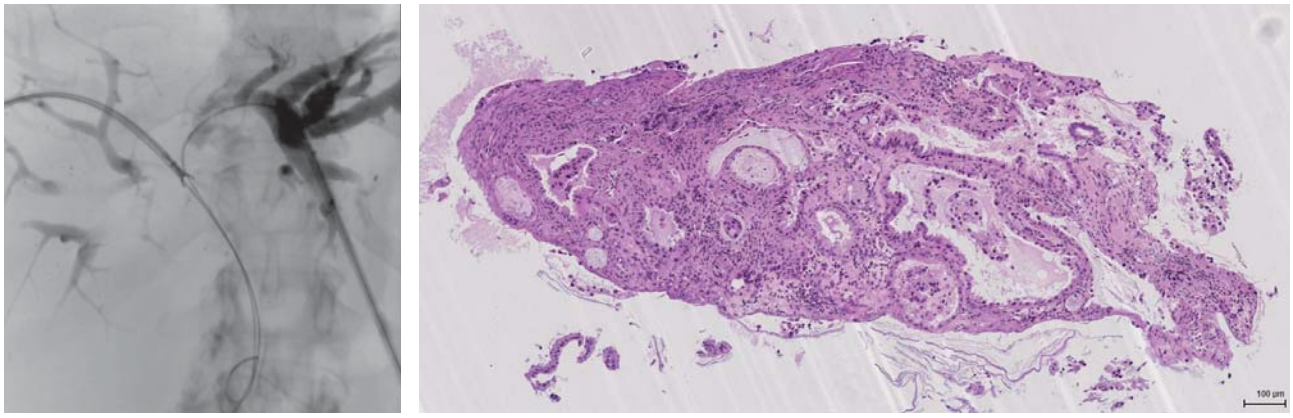


Fig. 1. Patient with Klatskin tumor, Bismuth III A. Fragment of the bile duct mucosa, scarified layers of the integumentary epithelium of the bile duct mucosa of typical structure (hematoxylin and eosin, ×4)



A B

Fig. 2. A patient with a Klatskin tumor, Bismuth IV. A — cholangiography followed by a pinch biopsy of a tumor of the common bile duct from the right access. The open branches of the forceps are visible; B — biopsy material. Fragment of the wall of the bile duct with the growth of highly differentiated adenocarcinoma (hematoxylin and eosin, ×6)

outflow of bile. After performing a biopsy, the material was sent for cytological and histological examination.

The conducted methods were approved (repeatedly) by the local ethical committee of the RSCRST (Minutes No. 03-04 / 2022 of 28.04.2022). Diagnostic and therapeutic procedures, data and material collection, as well as a survey were carried out after receiving voluntary written consent from patients.

To assess the reliability of the difference in indicators, Student's *t*-criterion was used. Sample fractions (relative frequencies) were used as the studied indicators. Confidence intervals for them were built according to the Fisher method. For special cases (0 and 100 %), the formula for the probability of the binomial distribution for events that do not occur was applied. All calculations were carried out in Microsoft Excel 2019.

Results

After performing 74 biopsies in 52 patients, malignant lesions of the biliary tract were detected: with a forceps technique in 79.0 %, with a brush biopsy in 66.7 % of cases. The degree of tumor differentiation was determined in 60.0 % (n = 18) versus 12.5 % (n = 3) (p < 0.01), respectively (Table 1).

The diagnosis of extrahepatic cholangiocarcinoma was not confirmed in 6 (11.5 %) patients with suspected Klatskin tumor. In these cases, 7 biopsy procedures were performed: three with a brush and four with forceps (in one patient, material was taken twice). During histological examination, tumor cells were not detected. After determining markers of autoimmune liver damage, performing magnetic resonance and computed tomography in dynamics, a diagnosis of sclerosing cholangitis was established in 5 patients, in another observation after studies of the surgical material revealed hemangioepithelioma of the liver. Thus, the sensitivity and specificity of forceps biopsy and brush biopsy were 82.4 % and 75.0 % versus 73.3 % and 66.7 % (p > 0.05), the difference did not reach statistical significance (Table 2).

There were no adverse events associated with brush biopsy. Only complications of the degree I according to the CIRSE classification (2017) [13] were noted in patients with a pinching technique that did not increase the duration of the usual postoperative period. In three cases (7.9 %), hemobilia developed, which was stopped by conservative methods within 1 day.

Discussion

The complexity of diagnosing Klatskin tumor in the early stages is associated with the absence of pathognomonic symptoms of the disease. Non-specific complaints characteristic of most cancer patients (fatigue, anorexia and weight loss) are noted in 56 % of observations. The first manifestation in 90 % of patients is jaundice, accompanied in 10 % by acute cholangitis [4]. Thus, complications of the underlying disease manifest themselves with a large tumor volume that can block the lumen of the bile duct [14].

According to the nature of growth, three subtypes of Klatskin's tumor are distinguished: sclerosing (≥70 %), nodular (20 %) and papillary (5–10 %). The first two, as a rule, dense structures are located in the area of the liver gate. The nodular and es-

Table 1. Histological results of 74 antegrade biopsy procedures in 52 patients with suspected Klatskin tumor

Histology	Brush biopsy (n = 36)	Forceps biopsy (n = 38)	Hazard Ratio (95 % confidence interval)	p-value
Degree of differentiation G1 G2 G3	 1 2 0	 5 8 5	0,176 (0,119–0,723)	0,4
Non differentiated cancer	21	12	1,847 (0,774–5,028)	0,01
No cancer	12	8	1,583 (0,614–4,169)	0,24

Table 2. Comparison brush and forceps biopsies

Parameter	Brush biopsy	Forceps biopsy
Procedures	36	38
Differentiation	12,5 %	60,0 %
Sensitivity	73,3 %	82,4 %
Specificity	66,7 %	75,0 %
Positive predictive value	91,7	96,6 %
Negative predictive value	33,3	33,3 %
Accuracy	72,2	81,6 %
Complications I degree	0	7,9 %

pecially sclerosing subtype are characterized by the development of a desmoplastic reaction: the tumor stimulates the radial or longitudinal proliferation of connective tissue with circular thickening of the bile duct. Stroma separates cancer cells from each other and leads to "low cellularity" of the tumor component. This reduces the likelihood of detecting adenocarcinoma in the biopsy material and increases the number of false-negative morphological conclusions [14].

On the other hand, sclerosing and nodular forms are characterized by early invasion of the periductal nerve and choroid plexuses, which leads to inflammation in this zone. Changes in epithelial cells are further exacerbated in the presence of biliary infection or concomitant primary sclerosing cholangitis. This also complicates the morphological examination of biopsy material and leads to false-positive conclusions, since reactive cells often mimic cancer cells [15].

At the time of diagnosis, the tumor of these two subtypes already grows into the surrounding liver parenchyma in 90–95 % of cases. Therefore, in almost all operable patients, it is necessary to perform a "extensive" resection such as hemihepatectomy. The third, papillary subtype of extrahepatic cholangiocellular cancer develops mainly in the distal part of the common biliary duct. The structure of neoplasms is soft, loose, often in the form of a mobile polypoid mass on a pronounced base, which expands, rather than compresses, the bile duct. Therefore, the papillary subtype rarely spreads to neighboring anatomical zones, which in most cases allows surgeons to limit themselves only to resection of the common biliary duct with a favorable prognosis of survival [9, 14, 16].

Klatskin tumor should be differentiated from benign strictures, other primary and metastatic neoplasms. In fragments resected during surgery, benign diseases are detected in 10–15 % of observations [4, 16, 17]. In our study, the diagnosis of cholangiocarcinoma was not confirmed in 6 patients (11.5 %): 5 had sclerosing cholangitis, one hemangioepithelioma of the liver.

With Klatskin tumor, the possibilities of percutaneous biopsy are limited to a remote anatomical location, many great vessels along the course of the alleged puncture, "creeping" tumor growth. In this regard, the main methods of tissue sampling are intraluminal manipulations.

Data on the use of endoscopic ultrasonography with biopsy are contradictory. Thus, according to

Table 3. Data on the sensitivity of antegrade biopsy in malignant tumors of the bile ducts

Author (year)	Patients	Brush biopsy, %	Forceps biopsy, %	Tandem procedure, %
Tapping (2012) [22]	31	87	94	-
Boots (2017) [12]	129	40,6	42,7	55,8
Tibana (2019) [19]	18	-	94,4	-
Augustin (2020) [18]	13	-	88,9	-
Chang (2020) [20]	79 - antegrade 38 - retrograde 41	- -	- -	86,7 77,1
РНЦРХТ (2021) own data	52 (74 biopsies)	73,3	82,4	-

the results of study D. Dondossola et al. (2020), the use of this technique is impossible in patients with surgical biliodigestive anastomoses, and the sensitivity directly depends on the anatomical location of the tumor [2]. This indicator decreases from 100 % in the case of damage to the distal bile ducts to 83 % with proximal spread, with a total specificity of 92–100 %. It is worth emphasizing that brush biopsy and fine-needle aspiration are accompanied by an increased risk of implantation metastasis. This applies primarily to the aspiration technique, since the biopsy needle penetrates the tumor through the wall of the duodenal bulb and the abdominal cavity. For the same reason, it is not recommended to perform percutaneous and laparoscopic biopsy of the hilar cholangiocarcinoma and its regional lymph nodes [9]. All these techniques are contraindicated before liver transplantation [2].

According to most authors, the specificity of intraductal biopsy is 100 %. This is explained by the fact that the detection of tumor cells in the biopsy material (especially when using forceps, which allows you to get a sufficient amount of tissue) indicates the presence of a malignant, not inflammatory process. At the same time, the sensitivity of brush and pinch biopsy is in the wide range from 0 % to 94 % [11, 12]. In our study, the sensitivity in these groups was 73.3 % and 82.4 %, which corresponds to the data of most authors (Table 3). At the same time, the specificity indicators were 67 % and 75 %, respectively. We associate three false positives (two with a brush biopsy and one with a pinch biopsy) with long-term recurrent cholangitis and the development of sclerosing changes in the bile ducts. The obtained material was not sufficiently informative and was interpreted in favor of a malignant process.

Brush biopsy has less sensitivity and accuracy. In cytological examination in most patients, it is impossible to assess the differentiation of the tumor process due to the collection of a small volume of tissue [18–20]. In our center, after brush biopsy, highly differentiated adenocarcinoma was found in one, moderately differentiated — in two cases, which was only 12.5 %. At the same time, this is a simple, safe and cheap technique that allows you to obtain material from the surface of the tumor stricture: the places of the greatest accumulation of cancer cells, which are easily picked up by the brush. Thus, a truly positive results can be quite high and reach 76 % [21]. However, brush biopsy is accompanied by a large number of false negative diagnoses: negative predictive value is about 20 % [22]. In our study, it was 33.3 %.

Most authors argue that percutaneous transhepatic pinching is one of the best methods for verifying tumors of the proximal bile ducts. So, according to Z. Li et al. (2016) [21], the frequency of true positive results was 88 %. The authors concluded that the invasion of the tumor into the wall of the bile duct allows forceps to easily take pathological material from the tumor, and significant dilation of the duct improves the technical possibility due to the large space above the stricture, allowing manipulation to be performed in full. Our study confirms these data. We did not face technical difficulties in performing the procedure, and the prognostication of a positive result was 91.7 %.

At the same time, J. Boos et al. (2017) obtained the same sensitivity of plucking and brush biopsy in cholangiocarcinoma: 34.5 % and 37.9 %, respectively; this figure was significantly higher with a combination of two methods (58.3 %) [12]. According to

the results of other authors, both methods have low values of negative predictive value (12.5–15.6 %) with a high rate of accuracy in the diagnosis of cholangiocarcinoma [22, 23].

The method of pinch biopsy is not perfect. For example, with the unchanged inner wall of the duct, it is necessary to perform a biopsy through the mucous membrane, which worsens the results of morphological examination [21]. The presence of a stent in the bile ducts makes it difficult to clearly identify the tumor zone and take a sufficient amount of histological material [24]. It is also not recommended to do balloon dilatation before biopsy and subsequent stenting, since the straightened stricture does not allow the forceps to cling to the pathological tissue (slippage occurs) and the material can be collected only in the distal part of the cholangiocarcinoma [19, 21].

We are cautious about stenting the bile ducts in patients with Klatskin's tumor. First, cholangiocarcinoma spreads quite quickly to the segmental ducts, which leads to inadequate stent function and the occurrence of a relapse of jaundice and cholangitis. Secondly, the presence of external-internal cholangiodrainages sometimes allows for the only possible method of antitumor treatment of patients with hyperbilirubinemia — intraductal photodynamic therapy.

Another disadvantage of plucking biopsy is the occurrence of "crushing artifacts", which occur in 8–9 % of cases due to damage to tissue samples by branches, which makes it technically impossible to histologically evaluate the material [12, 18, 22].

For a full histological analysis, it is necessary to obtain 4-5 fragments of biopsy material. A greater number of tests increases the risk of complications, of which the most frequent are hemobilia and biloma formation [19, 21]. We adhered to this rule and performed a pinch biopsy four times: three fragments for histological and one for cytological examination.

Intraductal sampling of histological material is a relatively safe procedure. H.-Y. Chang et al. (2020) compared the results of brush and pinch biopsy with transhepatic (n = 38) and endoscopic accesses (n = 41). Complications of moderate severity in the form of transient hemobilia and bile leakage were noted in 18 % and 17 % of patients, respectively, did not require surgical intervention and were cured for 3–5 days [20]. J. Boos et al. (2017) did not report serious complications in 232 biopsy procedures in 129 patients. One week after the intervention, various manipulations with cholangiodrainages (correction, exchange, additional drainage or stenting) were performed in 73 (32 %) cases [12]. Z. Li et al. (2016) analyzed the efficacy and safety of transient intraductal biopsy in 826 patients with mechanical jaundice of various etiologies. The study also did not show serious complications. Transient bilemia, bile leakage and mild hemobilia were noted in 5.7 %, 1.3 % and 3.4 %, respectively [21]. A. M. Augustin et al. (2020) reported complications in 2 out of 13 patients: one cholangitis, successfully managed conservatively, and one subcapsular hematoma requiring blood transfusion [18]. In study T. K. Tibana et al. (2019) complications were noted in 2 patients out of 18: in one case, hemobilia developed, in the other cholangitis [19].

In our study, the brush biopsy was not accompanied by complications. This was expected, since the manipulations associated with the collection of material with a brush from the bile ducts are low-traumatic and can be compared with the routine replacement of external-internal cholangiodrainage over the guidewire. At the same time, the use of the pinching technique leads to direct traumatization of the tumor with the risk of perforation and bleeding. With a sufficiently large number of observations (38) and four times taking the tissue of the bile ducts, we noted only three episodes of hemobilia (7.9 %), which were stopped during the day.

Conclusion

Endobiliary biopsy with antegrade access is a safe technique for both brush and pinching techniques. However, when taking material with forceps, the sensitivity and specificity of diagnosis increases, the ability to determine the degree of tumor differentiation increases.

The present work presents a separate fragment of the study, previously unpublished anywhere, and considers the diagnosis of Klatskin tumor in the original aspect of the study of the technique of intraductal biopsy. The results of the use of optical coherence tomography for navigation before a forceps biopsy are presented in another our publication [25].

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