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Combined treatment of nonresectable cholangiocarcinoma complicated by obstructive jaundice

A.A. Shiryaev[a], G.Kh. Musaev[a], V.V. Levkin[a], I.V. Reshetov[a], M.V. Loshchenov[b], P.M. Alekseeva[b,c,*], V.V. Volkov[b], K.G. Linkov[b], V.I. Makarov[b], I.O. Shchekoturov[a], A.V. Borodkin[b], V.B Loschenov[b,c]

[a] Oncology Center, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of the Russian Federation, University Clinical Hospital no. 1, Bolshaya Pirogovskaya str., 6, Moscow, 119435, Russia
[b] Prokhorov General Physics Institute of the Russian Academy of Sciences, Vavilov str., 38, Moscow, 119991, Russia
[c] National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), Kashirskoye sh., 31, Moscow, 115409, Russia

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ABSTRACT

Background: The five-year survival rate for successful surgical treatment of cholangiocellular cancer is only 20–40%, and in the case of an unresectable tumor, the life expectancy does not usually exceed 6 months. Survival decreases with the presence of jaundice, due to the spread of the tumor process along the bile ducts, leading to their obstruction.

We report outcomes of patients with nonresectable bile duct carcinoma complicated by obstructive jaundice treated with Photodynamic Therapy (PDT).

Methods: Combined diagnosis and treatment included percutaneous cholangiostomy, intraductal video fluorescence diagnostics, photodynamic therapy, and bile duct stenting. All patients were treated at the Sechenov University Oncology Center in Moscow. The results of treatment of 33 patients have been presented. The intraductal diagnosis of malignant bile duct lesions was performed after cholangiostomy using the endovideofluorescence module for minimally invasive surgery and endoscopy. With the use of this method, it is the first time in Russia that it has become possible to obtain a videofluorescent image of the tumor and to determine the high level of photosensitizer accumulation in all cholangiocarcinoma patients. The preparations Photolon, Radachlorin, and Photosens were employed as photosensitizers (PS). Intraductal photodynamic therapy was used to achieve the antitumor effect. Laser power density was about 200 mW/cm^2.

Results: We present initial results, improved the diagnostic possibilities in this difficult localization of carcinoma, and demonstrated the feasibility of prolongation of life without significant deterioration of its quality. The average survival time in the treatment group is 9.5 months.

Conclusion: The treatment of patients with nonresectable cholangiocarcinoma with Photodynamic Therapy should be an available option.

In this context, the additional use of intraductal endovideofluorescence diagnostics is a highly specific technique that allows reliable detection of the photosensitizer accumulation predominantly by the tumor tissue and appears promising.

As shown by our experience, flourescent localization followed by Photodynamic Therapy, enabled us to improve diagnostic techniques and treat the tumor with improved outcome.

1. Introduction

Bile duct carcinoma (cholangiocellular carcinoma) is a rare disease characterized by slow growth, late metastatic involvement, and, regrettably, poor prognosis [1,2]. The main cause is late diagnosis. It is for this reason that cholangiocarcinoma is one of the most challenging

* Corresponding author at: Prokhorov General Physics Institute of the Russian Academy of Sciences, Vavilov str., 38, Moscow, 119991, Russia.
E-mail addresses: artemdoc@mail.ru (A.A. Shiryaev), gasiyav@mail.ru (G.K. Musaev), doctor-levkin@mail.ru (V.V. Levkin), reshetoviv@mail.ru (I.V. Reshetov), maxvl2000@gmail.com (M.V. Loshchenov), alekseeva.polina2012@mail.ru (P.M. Alekseeva), vlvlvolkov@yandex.ru (V.V. Volkov), rkir@mail.ru (K.G. Linkov), vi.makarov@physics.msu.ru (V.I. Makarov), samaramail@bk.ru (I.O. Shchekoturov), borodkin.aleksandr@gmail.com (A.V. Borodkin), loschenov@mail.ru (V.B. Loschenov).

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problems of present-day oncology. As a rule, its first clinical symptom is pain-free obstructive jaundice, which is the most common cause of hospital admissions [1].

Unfortunately, the appearance of obstructive jaundice gives evidence of the disease stage at which radical surgical treatment is not normally feasible [7]. The mainstay of treatment of these patients is cholangiostomy, whose variants may be antegrade (US- and fluoroscopy-guided) or retrograde endoscopic cholangiostomy [3–6,8,11–13].

According to different data, radical operative intervention is possible in approximately 20–30% of cholangiocarcinoma patients. This is accounted for by both the extent of the process and the presence of associated diseases and blood clotting disorders making the risk of radical operations extremely high [2–5,24]. Not infrequently, these factors coincide. In the case of surgical treatment, the five-year survival rate varies according to different authors between 20 and 40% [2]. In nonresectable cholangiocarcinoma, the survival rarely exceeds one year, and the survival rate of victimized patients is reduced when they develop obstructive jaundice [2,4,5].

Cholangiocarcinoma is usually diagnosed on the basis of clinical and instrumental findings (MSCT, ultrasonography, MRI, and cholangiography).

However, the morphological verification of the diagnosis of cholangiocarcinoma is difficult, because the acquisition of biopsy material from the bile duct tumor for histological examination poses major problems, or the material provides little information [10–12].

From the point of view of the quality of life of a patient, the most preferable method for percutaneous cholangiostomy is bile duct stenting [6,14]. However, the involvement of uncovered stent by the tumor or the spread of infiltration beyond its boundaries remains the area of particular concern. This results in recurrent obstructive jaundice [6,9,23]. In such a situation, the contemporary possibilities of influencing the tumor directly in order to stabilize the process or, at least, to slow down its progression are limited.

A principally new approach to diagnosis and treatment of malignant tumors is fluorescence diagnostics (FD) and photodynamic therapy (PDT). The capacity of photosensitizers for selective accumulation in the tumor tissues underlies these methods. On local exposure, laser radiation at a certain wavelength is capable of inducing fluorescence, which can be recorded with spectrometers or even visually using special highly sensitive endoscopes [15,17,20]. When the PS-accumulating tissue is irradiated at a wavelength corresponding to the PS peak absorption, a photochemical reaction takes place with the formation of active oxygen species (singlet oxygen) and free radicals resulting in the cytotoxic effect.

PDT is possibly advantageously superior to conventional antitumor radiation and pharmacological therapy being distinguished for high tumor lesion selectivity, the absence of severe local and systemic complications, and the possibility of repetition of the therapeutic procedure. The depth of the effect on the tumor may attain several millimeters depending on the laser wavelength and the photosensitizer used. Undoubtedly, the possibility of combining both the treatment and fluorescence diagnostics of the tumor process in one procedure is an advantage of the method. Moreover, obstructive jaundice, unlike for chemotherapy, is not a contraindication for FD and PDT [16].

FD and PDT methods have found wide application in the diagnostics and treatment of skin cancer, bladder cancer, and cervical cancer and allow recanalization in esophageal infiltration by the tumor, etc. [15,17,19,20]. However, it is noteworthy that only a few works devoted to fluorescence (spectral, video) diagnostics and PDT of cholangiocellular carcinoma are available today.

2. Objective

To improve the methods of diagnosis and treatment of nonresectable and functionally inoperable cholangiocarcinoma complicated by obstructive jaundice using a combination approach: cholangiostomy with fluorescence diagnostics (FD) and photodynamic therapy (PDT).

3. Materials and methods

The study group included 33 patients (19 men and 14 women) with nonresectable cholangiocarcinoma complicated by obstructive jaundice. The mean age was 69 ± 11 years. Lesions in the common bile duct were detected in 9 patients. Twenty patients had hilar cholangiocarcinoma involving the confluence and lobar ducts. Note that in four patients, the tumor involved the right lobar duct; three patients had a stricture of the left lobar duct; the remaining 13 patients had a stricture of the right or left lobar ducts with their complete or partial block. In four patients, cholangiocarcinoma was localized in the proximal division of the common bile duct; in one of them, the tumor infiltrated the cystic duct.

It is notable that more than 50% of patients were found to have metastases (in the liver, regional lymph nodes, and the lungs).

Obstructive jaundice aggravated the patients' severe condition. The total blood level of bilirubin was 161–492 μmol/L; the direct bilirubin level varied between 99 and 380 μmol/L.

All the patients underwent US examination of the hepatopancreatoduodenal zone using color Doppler mapping, MSCT with intravenous contrasting and DICOM-image processing with 3D reconstruction of the liver; in the absence of convincing findings in favor of the neoplastic process or in diagnostically difficult cases, MRI with MR-cholangiography were used (Fig. 1).

Radical treatment was not given due to the spread of the tumor process, distant metastases, or the functional state of a patient (Fig. 2).

At the first stage, all the patients were subjected to US- and fluoroscopy-guided cholangiostomy.

The following variants of cholangiostomy are distinguished: external cholangiostoma (11 patients) and cholangiostomy with placement of a drainage tube more distally than the stricture (22 patients). Fluorescence diagnostics and photodynamic therapy of the tumor-associated stricture were performed under fluoroscopic control. The final variant of cholangiostomy in all the patients of this group was bile duct stenting.

In order to carry out fluorescence diagnostics and photodynamic therapy, we used the following intravenous photosensitizers: sulfonated aluminum phthalocyanines — Photosens (3 patients), which was injected 24 h before the procedure at a dose of 0.5 mg/kg, chlorin-based drugs — Radachlorin (7 patients) or Photolon (23 patients) at a dose of 1.0 mg/kg intravenously 3–5 h before surgery.

The choice of Photosens is determined by the fact that it has a long-term skin phototoxicity due to which it was more often used in the autumn-winter period. Photolon and Radachlorin were predominantly used in spring and summer. No significant difference in the photodynamic effect on this type of tumor tissue was noted (obviously, due to insufficiency of observations). However, based on the experimental results, its was established that Photosens has a higher photodynamic activity due to a higher quantum yield of singlet oxygen generation and a more uniform interstitial accumulation not only in vessel wall, as it occurs with the chlorin series drugs, but also in the tumor cells. Patients, for whom repeat PDT procedure was indicated, were injected Photosens capable of being accumulated in tissues for a long time (up to 30% of the maximal values is determined for a week after intravenous administration), which allows us to hold no less than 5–7 therapy sessions during this period with radiation dose adjustment.

Fluorescence diagnosis was made using the videofluorescence module for endoscopy and minimally invasive surgery (OOO Biospek, Fig. 3) and a Karl Storz 2.8 mm cholangioscope. The module was introduced into bile ducts via the 9Fr (3 mm) introducer. Both visual assessment and examination in the fluorescent mode were carried out.

The average laser radiation power for fluorescence diagnostics was 2 mW; the density of local laser radiation energy did not exceed 0.02 J/

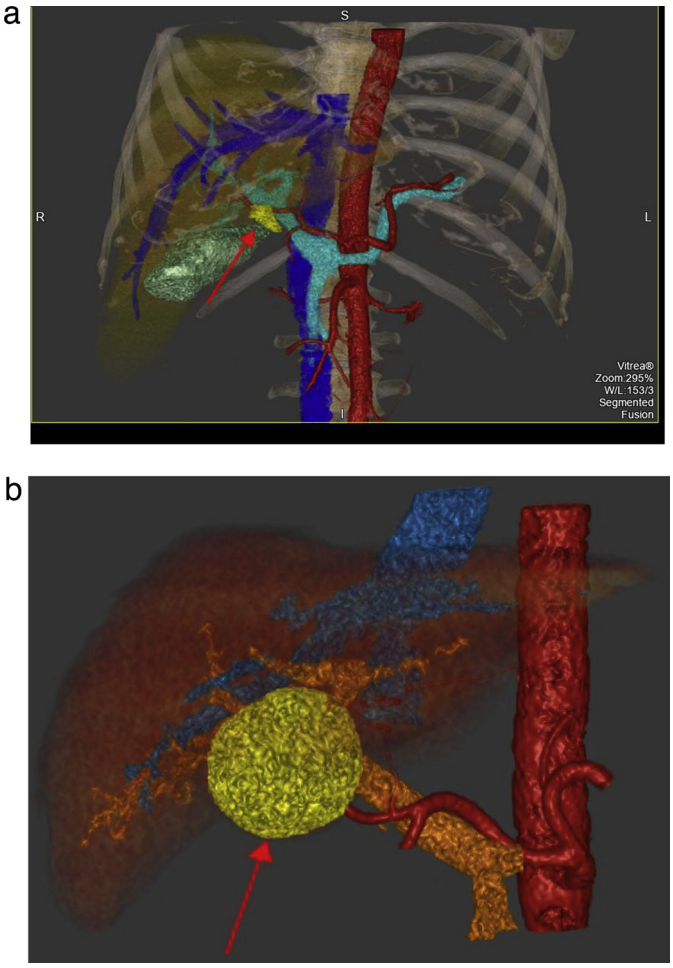

Fig. 1. MSCT, 3D reconstruction. **a**. The arrow shows type II Klatskin tumor according to Bismuth-Corlett classification. **b**.The arrow shows type IIIA hilar cholangiocarcinoma according to Bismuth-Corlett classification.

cm^2.

Contact (local) spectroscopy was performed with a fiberoptic spectral analyzer by irradiating the hepatopancreatoduodenal zone with low-intensity radiation at a specific wavelength (LESA-01-BIOSPEK, OOO Biospek, wavelength 633 nm). For this purpose, a flexible fiberoptic probe was passed through the introducer under fluoroscopic control.

We made an attempt to take biopsy material from the region of the tumor-associated stricture using biopsy forceps through the cholangioscope or with the brush biopsy technique from all the patients. The biopsy material was then sent for morphological examination.

Photodynamic therapy was administered after video fluorescence diagnostics and the confirmation of photosensitizer accumulation by the tumor tissue. The fiberoptic system with a cylindrical 10–20-mm irradiator at the distal end (Biospek) was used. All the patients were administered PDT through the introducer whose distal end was fixed in the region of stricture under fluoroscopy control. In 23 patients, the irradiator was passed through a 6 F (2 mm) drainage tube. Ten patients received PDT using a balloon catheter developed on the collaboration basis with Biospek. The main lumen is intended for manipulation performance; the other is used to keep the balloon distended at the distal tip of the catheter. A flexible light guide was placed in the main sheath, with the cylindrical irradiator being fixed in the region of the balloon portion of the catheter. The balloon was enlarged by introducing lipofundin solution into the second catheter sheath. The size of the balloon portion of the catheter varied between 1 and 4 cm. The power of the LFT-675-01-BIOSPEK radiation laser system (active for all the photosensitizers used) with a wavelength of 698 nm was equal to 1.5 W, which allowed us to attain a laser power density of about 200 mW/cm^2. The laser wavelength allowed us to successfully cause a photodynamic effect for both aluminum phthalocyanine and chlorin derivatives. The average exposure time was 12 ± 2 min.

To prevent photodermatosis, all the patients adhered to the light regimen for 48 h after the injection of chlorin-based photosensitizers (radachlorin and photolon) and for two weeks after the use of photosens.

As the final method of cholangiostomy, endoprosthetic replacement was performed for all the patients. A self-expanding nitinol stent was fixed in the stricture region so that its edges would be proximally and distally 1–2 cm apart from the stricture boundaries. Depending on the tumor site, covered and uncovered stents were used. Thirteen patients had covered stents placed. With a high block, when the tumor spread infiltrating the confluence and/or lobar ducts, stenting was carried out with uncovered stents (n = 20). Ten patients had several (two or three) stents placed with the formation of bifurcation of the lobar ducts (Fig. 4).

4. Results

Unfortunately, the choice of therapeutic modalities of nonresectable cholangiocelluar carcinoma is limited. High doses of radiotherapy of cholangiocarcinoma carry the potential risk of complications in the form of damage to the surrounding tissues and organs both in the course of treatment and in the follow-up period [1]. The use of chemotherapy is limited by jaundice and hepatic failure. Moreover, chemotherapy is known to be inefficacious as an independent method for cholangiocarcinoma [1,18,21].

In our study, the combined use of the methods for diagnostics and minimally invasive treatment was tried on 33 patients with nonresectable cholangiocarcinoma complicated by obstructive jaundice.

We succeeded in morphologically verifying the diagnosis of cholangiocellular carcinoma in 25 of 33 patients. But we failed technically to obtain the biopsy material form eight patients with Klatskin tumors. Other authors also faced the difficulties in taking biopsy material from the tumor of this localization [9,23].

In twenty-two patients, cholangiostomy was performed with drainage tube placement more distally than the stricture and followed by stenting after FD and PDT. Eleven patients underwent external cholangiostomy at the first stage. Of them, 8 patients had a complete block of the common bile duct contrasting during fistulography with the involvement of the confluence and lobar ducts. Multiple attempts to pass the instrument beyond the tumor-associated stricture were unsuccessful. On the third day after PDT, thread-like bile duct contrasting in the distal direction of the stricture was noted in these patients during fistulography, and on the fifth day, we observed partial recanalization of the bile duct lumens when the contrast medium freely entered the intestine. This allowed us to repeat PDT session with irradiation of the extent of the tumor. Treatment was completed with bile duct stenting.

Thus, we have obtained the videofluorescent images of the bile duct tumors in all study group patients. The measurement of the level of sensitizer accumulation in the hepatopancreatoduodenal zone makes it possible to suggest the nature of lesion at the stage of imaging (Figs. 5a, and b).

Unfortunately, local fluorescence spectroscopy has significant limitations for analysis of bile duct fluorescence related to the presence and continuous production of bile whose intense fluorescence often surpasses photosensitizer fluorescence. In addition, the peculiarities of the bile duct structure make the passage of an uncontrolled fiberoptic probe difficult. As a result, we succeeded in measuring the PS fluorescence spectra in the tumorous tissue in several patients. Note that of these measurements, the most successful were those made only in two patients whose bile had been washed off. Therefore, the study was focused on video fluorescence, which yielded more contrast images, especially

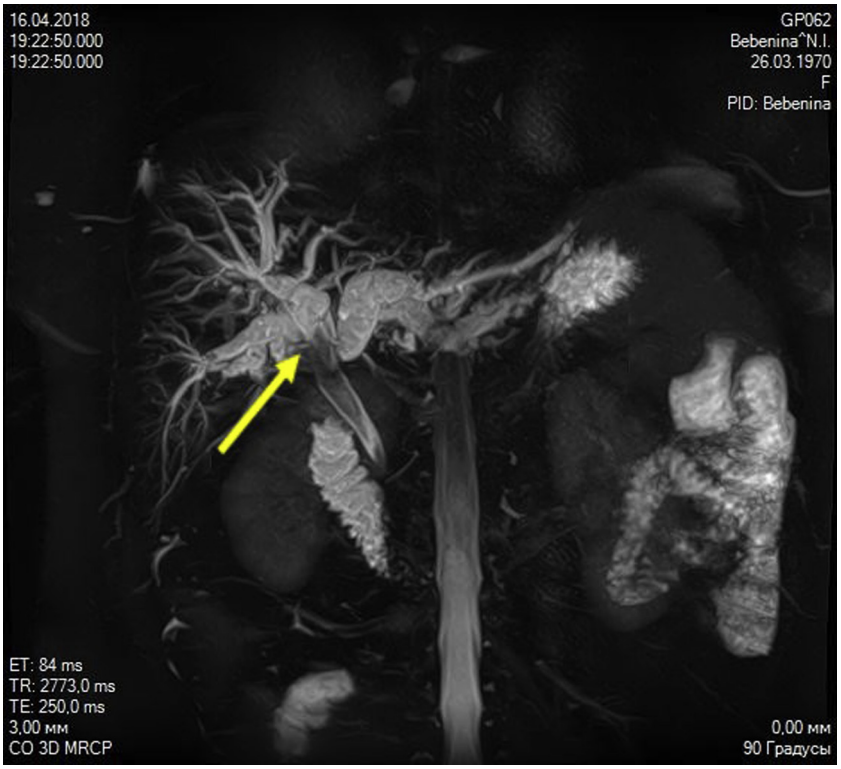

Fig. 2. MR-cholangiography, frontal view. Arrow: hilar cholangiocarcinoma.

Fig. 3. Photo. Endovideofluorescence module for minimally invasive surgery and endoscopy.

in the dynamic (video) versus static mode (photo). However, due to the presence of bile, the quantitation of interstitial PS concentration appears to be difficult.

The data obtained during intraductal videofluorescence diagnostics were compared with the results of local fluorescence spectroscopy, which confirmed the predominant quantitative accumulation of the photosensitizer by the tumor rather than by normal tissues (Figs. 5c, and d). Note a twofold and greater increase in the amount of the photosensitizer accumulated by the tumor compared with normal tissues.

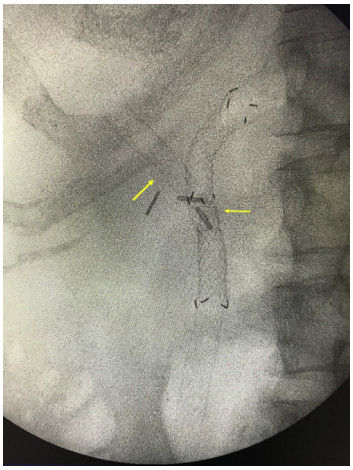

Fig. 4. X-ray. Bile duct stenting. The arrows show the stents placed in the Y-shaped fashion with the formation of the lobar duct confluence.

We also succeeded in clinically proving the efficacy of photodynamic therapy in bile duct malignancy, which allowed tumor recanalization.

It should be noted that the use of the introducer through which the optic system is delivered to the lumen of the bile ducts may be considered to be optimal, because its two-sheath design allows the surgeons to irrigate bile ducts and to remove bile in the visual field, which interferes with examination and may supply false information.

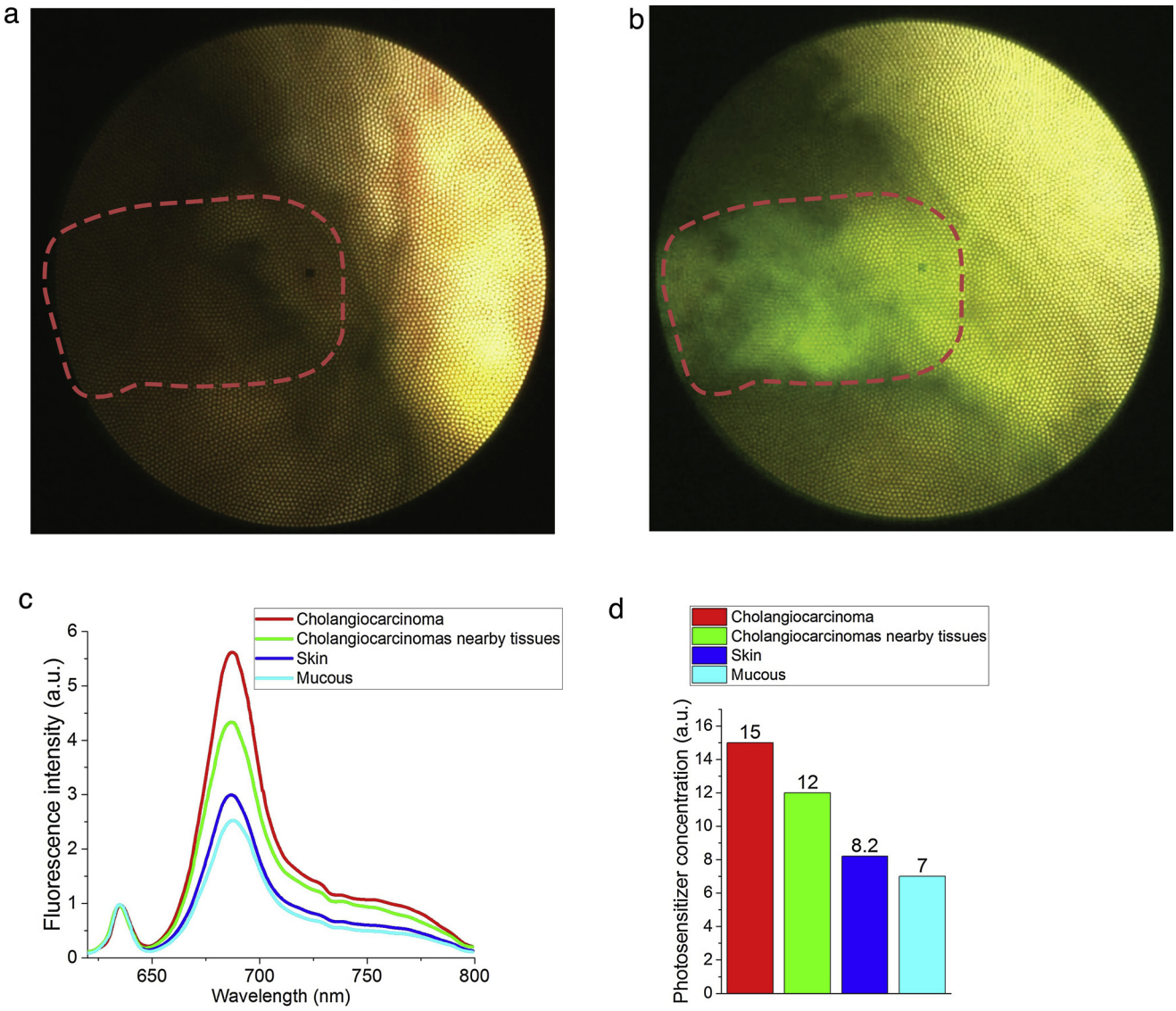

Fig. 5. Cholangioscopy. **a**. The image before injection of photosensitizer (the broken line indicates tumor tissue). **b**. Video fluorescent image. The tumor is designated with an arrow (the broken line indicates tumor tissue). **c**. The fluorescence spectra (right) of aluminum phthalocyanine in the tumor and in surrounding normal tissues. The fluorescence spectra (690 nm) are normalized to the reflected laser radiation (633 nm) from studied tissue. **d**. The diagram quantifies the accumulation of the photosensitizer by the tumor and normal tissues.

5. Discussion

PDT uses a flexible fiberoptic light guide with a cylindrical irradiator at the distal end. To rule out the risk of its being scorched to contact tissues, it is expedient to use a balloon catheter with a two-sheath structure. The main sheath is used for light guide placement in the catheter; the other sheath [channel] is additional and used for the distal part of the balloon to be distended. Lipofundin solution (1%) used for expanding the balloon part of the catheter, owing to its scattering properties, enables us to achieve a uniform power of the light field acting on the tumor. Such a system allows continuous PDT performance, because the optic fiber is protected against possible scorching and fractures.

The stents were placed depending on the localization and extent of stricture. Most patients (n = 20) had an uncovered self-expanding nitinol stent placed. In these patients, the tumor stricture was localized in the region of the confluence and lobar ducts. Placement of a covered stent in this case caused the risk of block of segmental ducts by the stent. This is a least-evil measure, as it is known that the uncovered stent may quickly be obturated by the tumor, thus requiring recurrent cholangiostomy [9,22]. However, PDT reduces these risks, which is evidenced by the results obtained by us: the jaundice-free period is prolonged; the life span is lengthened; and the risk of stent obliteration by the tumor is reduced.

Proceeding from the clinical observations, the duration of the jaundice-free period in bile duct stenting without PDT is usually no more than six months. The combination of stenting and PDT results in the jaundice-free period lasting a lifetime. The lethal outcomes resulted from the complications unrelated to duct obstruction. Two patients had recurrent bile hypertension following FDT and placement of uncovered nitinol stents in the area of the common bile duct stricture after six and nine months, respectively. The cause of obstructive jaundice was linked to the spread of tumorous infiltration beyond the stent with the formation of a common bile duct stricture, with the stent lumens in the region of PDT remaining unclogged for the passage of the contrast medium in both patients. The patients had repeat PDT administered and their bile ducts restented. After treatment, the patients survived for seven and twelve months, respectively, maintaining their working and social activity.

Thirteen patients with a tumorous stricture localized below the

confluence had covered self-expanding nitinol stents placed. Such a position of the stent poses a high risk of obturation of the cystic duct with the development of the clinical picture of cholecystitis. Six patients had a history of cholecystectomy; in one patient, tumor-associated stricture infiltrated the cystic duct. In two patients, the covered stent blocked the cystic duct, which subsequently required percutaneous mucoclasis of the gallbladder.

On the first postoperative day, eleven patients presented with the clinical picture of cholangitis that was counteracted conservatively over 24 h. If the light regimen was observed (limitation of direct sunlight and room light), no phototoxic reactions were noted.

The efficacy of treatment was assessed based on the life span of the patients. Note that the outcomes were initially encouraging. According to the literature data, the average survival time of patients with non-resectable cholangiocarcinoma constitutes six months [2,4,7]. In our group, the longest survival time was 32 months. The average life span in the group was 14 ± 5 months; 12 patients were dynamically followed up for 6–19 months. Five patients died within 3 ± 1 months after treatment, and initially they all had multiple distant metastases, with their state on admission being assessed as 20–40 according to Karnofsky score.

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