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Bile Ducts Stones After Pancreatoduodenal Resection: Risk Factors and Treatment

Vasiliy I. Egorov[1,2]

[1] *Kazan State Medical University, Kazan, Russian Federation*
[2] *Republican Clinical Oncological Dispensary, Kazan, Russian Federation*

Pancreaticoduodenectomy (PDR) is the primary surgical treatment for periampullary malignancies. Late complications after PDR occur in 31.5 % of cases. The most serious of these are biliary anastomotic strictures and bile duct stone formation (biliary complications), which can occur in up to 10.2 %.
Aim: to analyze the literature concerning the causes of biliary complications, particularly stone formation in the bile ducts after PDR, and the treatment methods for these patients.
Key points. Predisposing factors for stone formation after PDR include bile stasis (due to anastomotic stricture), remnants of suture material or clips, infection, and reflux of intestinal contents into the bile ducts. The choice of a minimally invasive treatment method for patients with bile duct stones after PDR depends on the qualifications of specialists and the technical resources of the medical institution. The endoscopic approach is characterized by rapid clinical success and shorter hospitalization but has a lower technical success rate due to altered anatomy. Percutaneous access is a highly effective minimally invasive treatment for late biliary complications, which can be used as a first-line option or in cases where endoscopic intervention has failed. The use of absorbable suture material, minimizing the number of anastomotic sutures, various hepaticoplasty techniques, and avoiding excessive bile duct mobilization may help prevent stone formation after pancreaticoduodenectomy.
Conclusion. Bile duct stones as a complication of the late postoperative period of PDR require highly qualified surgical care, including minimally invasive techniques. Further research is needed to identify possible ways to prevent and improve treatment methods for biliary complications of postpartum biliary reflux.
Keywords: pancreatoduodenectomy, bile duct stones, cholangitis, biliodigestive anastomosis stricture, mechanical jaundice, pancreatic head cancer
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Камни в желчных протоках после панкреатодуоденальной резекции: причины и лечение

В.И. Егоров[1,2]

[1] *ФГБОУ ВО «Казанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Казань, Российская Федерация*
[2] *ГАУЗ «Республиканский клинический онкологический диспансер» Министерства здравоохранения Республики Татарстан, Казань, Российская Федерация*

Панкреатодуоденальная резекция (ПДР) является основным методом хирургического лечения злокачественных новообразований периампулярной зоны. Поздние осложнения после ПДР встречаются в 31,5 % случаев. Наиболее серьезными из них являются стриктуры билиодигестивного анастомоза и образование камней в желчных протоках (билиарные осложнения), частота которых может достигать 10,2 %.
Цель данного обзора — анализ литературы, посвященной причинам развития билиарных осложнений, включая образование камней в желчных протоках после ПДР, и методам лечения таких пациентов.
Основные положения. К предрасполагающим факторам камнеобразования после ПДР относятся застой желчи (вследствие стриктуры анастомоза), остатки шовного материала или клипс, инфекция и рефлюкс кишечного содержимого в желчные протоки. Выбор малоинвазивного метода лечения пациентов с камнями желчных протоков после ПДР зависит от квалификации специалистов и технической оснащенности медицинского учреждения. Эндоскопический доступ характеризуется быстрым достижением клинического успеха и меньшей продолжительностью госпитализации, однако обладает более низкой частотой технического успеха в условиях измененной анатомии. Чрескожный доступ представляет собой высокоэффективный метод малоинвазивного лечения поздних билиарных осложнений, может применяться в качестве первого этапа или у пациентов после неудачного эндоскопического вмешательства. Использование рассасывающегося

шовного материала, минимизация количества швов при формировании анастомоза, применение различных вариантов гепатикопластики и предотвращение излишней мобилизации желчного протока могут служить мерами профилактики камнеобразования после панкреатодуоденальной резекции.
Заключение. Камни желчных протоков как осложнение позднего послеоперационного периода ПДР требуют оказания высококвалифицированной хирургической помощи, в том числе малоинвазивной. Необходимы дальнейшие исследования с целью поиска возможных путей профилактики и совершенствования методов лечения билиарных осложнений ПДР.
Ключевые слова: панкреатодуоденальная резекция, камни желчных протоков, холангит, стриктуры билиодигестивного анастомоза, механическая желтуха, рак головки поджелудочной железы
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Introduction

Pancreatoduodenectomy (PDR) is the primary surgical method for treating malignant neoplasms of the periampullary region [1]. This operation is highly invasive and is associated with a significant rate of postoperative complications and mortality — up to 63 % and 2–6 %, respectively [2, 3].

Early postoperative complications hinder the administration of adjuvant chemotherapy or significantly delay its initiation, thereby worsening long-term treatment outcomes [4].

Complications following PDR can occur not only in the early but also in the late postoperative period. Late complications of PDR are observed in up to 31.5 % of cases and are often associated with functional impairments characteristic of this surgery — namely, exocrine and endocrine pancreatic insufficiency [5, 6].

Among the most serious late complications of PDR are biliary complications (strictures of the biliodigestive anastomosis, formation of bile duct stones), the incidence of which can reach 10.2 % [7–9].

Management of patients with bile duct stones after PDR is the prerogative of specialized centers, as significant anatomical alterations in the pancreatoduodenal zone following this surgery can pose serious challenges for performing minimally invasive procedures and surgical interventions [10, 11].

To date, very few studies have been published on the treatment methods for patients with bile duct stones after PDR, and there are no established guidelines on this issue.

The aim of this review is to analyze the literature concerning the causes of biliary complications, specifically stone formation in the bile ducts after PDR, and the treatment approaches for this patient category.

Incidence and risk factors for bile duct stone formation after PDR

Bile duct stones represent a rare complication of the late postoperative period after PDR. The relevance of studying this issue is also underscored by the recent expansion of indications for PDR for various tumors and improved patient survival. Understanding the causes of bile duct stone formation after PDR may form the basis for potential prevention. The pathogenesis of biliary stone formation after PDR is not yet fully understood; however, it is believed that the triggering mechanism is a stricture of the biliodigestive anastomosis [12–14]. Against the background of anastomotic stricture, the incidence of stone formation in the bile ducts can reach 81 % [15].

T. Ito et al. (2018) demonstrated that biliary complications developed in 3.8 % (28/732) of patients who underwent PDR, at a median time of 23.4 (0.7–98.9) months. Among these, stones in the bile ducts were identified in 11 (39.2 %). Risk factor analysis revealed that patients with a common hepatic duct (CHD) diameter of < 4 mm developed biliary complications significantly more often than those with a diameter ≥ 4 mm (27.6 % vs. 1.3 %; $p < 0.001$). It was also noted that biliary complications occurred significantly more frequently after PDR for duodenal tumors ($p < 0.001$) [7]. A high incidence of biliary complications in patients after PDR for duodenal tumors was also reported in another study [16]. It was established that adjuvant chemotherapy and radiotherapy, as well as the presence of biliodigestive anastomotic leakage, did not affect the risk of developing cholangitis and hepaticolithiasis in the late postoperative period. The authors concluded that patients with a CHD diameter of less than 4 mm should be informed about the

possibility of developing bile duct stones and anastomotic strictures [7].

H. Zhan et al. (2016) showed that stone formation occurs in 1.2 % (6/489) of patients in the late postoperative period after PDR. As in the previous study, the primary tumor location leading to surgery was the duodenum — 66.7 % (4/6). Chills and fever were noted in 100 % of patients, whereas jaundice developed in only three (50 %). The mean time to detect stones after PDR was 47.3 ± 27.8 months [16].

A. Henry et al. (2024) found that biliary complications developed in 10.3 % (93/900) of patients who underwent PDR. The incidence of bile duct stone formation was 3.2 % of the total number operated on. A significant risk factor for the development of late biliary complications was the presence of biliodigestive anastomotic leakage in the early postoperative period (odds ratio (OR) — 2.56; 95% confidence interval (CI): 1.42–4.62; $p = 0.018$). The median time to the first episode of cholangitis was 8 months (4–16) after surgery. In 44 (47.3 %) patients, attacks recurred more than twice, and 83 (89.2 %) patients required hospitalization [9].

In the study by M. Hiyoshi et al. (2016), late biliary complications occurred in 8.1 % (13/161) of patients after surgery. It was found that an independent factor for the development of biliary complications was the ratio of the postoperative bile duct diameter to its preoperative diameter, expressed as a percentage. This ratio was significantly lower in the group of patients with late biliary complications compared to the group without complications (48.2 % vs. 63.5 %; $p = 0.0028$). The authors investigated the impact of hepatoplasty during the primary surgery (expansion of the common hepatic duct via a longitudinal incision along its left wall for 5–10 mm). The left-sided incision location was explained by an anatomical feature: the left hepatic duct joins at an acute angle, which may create additional conditions for bile stasis. Hepatoplasty was performed overall in 27.3 % (44/161) of patients. It was shown that a longer incision during hepatoplasty reduced the rate of decrease in bile duct diameter ($p < 0.0001$), thereby helping to prevent complications; however, the authors did not provide a threshold value for the required incision length, citing only its mean value of 6.1 ± 1.2 mm. In the group of patients who underwent hepatoplasty, late biliary complications did not occur, unlike in patients without hepatoplasty, although the difference did not reach statistical significance (0 % vs. 5 %; $p = 0.08$) [8].

T. Orii et al. (2014) studied the role of technical aspects of hepaticojejunostomy formation in the risk of biliary complications. The authors established that the number of sutures and the placement of a stent during hepaticojejunostomy formation significantly influence the risk of late biliary complications. Thus, it was shown that in the group of patients with 33.2 ± 8.4 sutures, biliary complications were observed more frequently compared to patients with 14.0 ± 2.3 sutures (9.4 % vs. 2.9 %; $p < 0.05$, respectively). According to the authors, an excessive number of sutures at the anastomosis creates more pronounced ischemia, which leads to the development of strictures and duct stones [17].

S. Kobayashi et al. (2024) determined that independent risk factors for biliary complications after PDR are a bile duct diameter of less than 8.8 mm (OR = 7.51; 95% CI: 1.75–52.40; $p = 0.005$) and male sex (OR = 4.05; 95% CI: 1.10–19.49; $p = 0.034$) [18].

Predisposing factors for stone formation after PDR include bile stasis (due to anastomotic stricture), residual suture material or clips, infection, and reflux of intestinal contents into the bile ducts [19, 20]. Anatomical changes after PDR contribute to the development of reflux and recurrent infections. Anastomotic narrowing, infection, and stone formation are closely interrelated processes [21]. Cases of bile duct stone formation around foreign bodies, such as fish bones, are also known [22, 23]. Furthermore, causes of biliary complications can include stasis due to impaired peristalsis of the afferent loop of the small intestine [24].

Analysis of the influence of interrupted and continuous sutures in the formation of biliodigestive anastomosis on the incidence of biliary complications after PDR did not reveal statistically significant differences between them (2.7 % vs. 4.0 %; $p = 0.581$) [7].

One cause of biliodigestive anastomotic stricture may be ischemia of the anastomosed bile duct stump. It is believed that the mobilization of the duct stump should not exceed 5 mm to preserve adequate blood supply [16].

It has been shown that elevated alkaline phosphatase levels (OR = 3.81; 95% CI: 1.519–9.553; $p = 0.004$) directly correlate with late biliary complications and serve as an indicator thereof. A threshold alkaline phosphatase value above 410 IU/L was a significant indicator of late biliary complication ($p = 0.041$). The authors established that alkaline phosphatase levels were more frequently elevated in patients with pneumobilia. Based on this, it was concluded that careful monitoring of alkaline phosphatase levels is necessary in the presence of pneumobilia [25].

Treatment options for bile duct stones after PDR using minimally invasive techniques

Treatment of patients with bile duct stones is comprehensive and includes conservative methods

(antibiotic therapy, detoxification, anti-inflammatory therapy), minimally invasive interventions, and surgical methods [7].

Repeat surgical interventions are associated with a high complication rate, and their performance is fraught with technical difficulties due to adhesions and altered anatomy following the previous surgery, which is why preference is given to minimally invasive treatment methods [16].

Minimally invasive methods can be performed via percutaneous and endoscopic approaches. The goal in both cases is stone removal and anastomotic dilation [26].

The percutaneous approach is performed in interventional radiology departments by experienced specialists. The first stage involves percutaneous transhepatic cholangiostomy, after which a dilatation catheter is advanced through the biliodigestive anastomosis. Subsequently, stepwise dilation of the created fistula tract is performed to allow for the insertion of a cholangioscope. Stone fragmentation is achieved using electrohydraulic or laser lithotripsy under direct visual control via the cholangioscope. The fragmented stone pieces are pushed through the anastomosis into the intestinal lumen; the procedure is repeated until the bile duct cavity is completely cleared of stones. Following this, the cholangiostomy tube is replaced with a smaller diameter drain, drainage is prolonged for several days, and a control cholangiography is performed before its removal [26, 27].

If necessary, the percutaneous approach can be combined with balloon dilation of the anastomosis or duct in several stages. The efficacy of the combined approach for complete strictures can reach 87 % [28, 29].

The undeniable advantages of the percutaneous approach are considered to be the possibility of precise navigation under direct visual control via the cholangioscope along the bile ducts to the calculus and the anastomosis [24], as well as the ability to utilize the created fistula tract until complete stone removal [18, 26]. The percutaneous approach creates technical conditions for removing residual suture material or clips that may have served as a nidus for stone formation [30, 31].

Disadvantages of the percutaneous approach include the multistage nature of the procedure, which increases the likelihood of complications and prolongs the duration of hospitalization. For instance, J.H. Lee et al. showed that the number of sessions required for complete stone removal ranged from two to four in 48.6 % of patients. Complications were observed in 51.5 % (17/33), and the median hospitalization duration was 14 days [32].

It has been shown that technical success with the percutaneous approach reaches 100 %, and stricture recurrence occurs in 38 % of patients [27].

The endoscopic approach is initially performed transorally. The endoscope is advanced to the site of the biliodigestive anastomosis, after which it is cannulated with a tapered catheter followed by dilation of the lumen. For impacted stones, shockwave lithotripsy may be performed. After complete stone clearance, cholangiography is performed for control [26].

The endoscopic approach is a more complex method due to the necessity of performing it in the setting of altered postoperative anatomy, which requires high physician skill and specific technical characteristics of the endoscopes (length, etc.) [33, 34]. Furthermore, in cases of complete anastomotic stricture where duct cannulation is technically impossible, the application of the endoscopic method becomes unfeasible. Advantages of this approach include less pronounced pain, a shorter time to complete stone removal, and shorter hospitalization compared to the percutaneous approach [26].

Results of forming a magnetic compression anastomosis by combining percutaneous and endoscopic approaches in cases where neither method alone was successful for complete strictures are known [15].

K. Tsutsumi et al. (2017) conducted a comparative study of the results of using percutaneous and endoscopic approaches (double-balloon enteroscope) for treating bile duct stones after previously formed hepaticojejunostomy in 40 patients. Technical success with the percutaneous approach was 100 % (8/8), and with the endoscopic approach — 91 % (29/32). Three patients for whom endoscopic intervention was initially unsuccessful underwent successful percutaneous access. The results showed that adverse events were less frequent with the endoscopic approach (10 % vs. 45 %; $p = 0.025$). The median duration of inpatient treatment until complete stone removal was also shorter in the group of patients after the endoscopic approach (10 vs. 35 days; $p < 0.001$). In 32.5 % (13/40) of patients, recurrence of bile duct stone formation was observed in the long term after stone removal [26].

S. Kobayashi et al. (2024) showed that biliary complications after PDR occurred between 3.3 and 70.9 months postoperatively. In 92.3 % of patients, complications were successfully resolved using the endoscopic approach. In the remaining cases, percutaneous techniques were used in combination with the endoscopic approach via a rendezvous technique. Balloon dilation alone was sufficient for four patients, while nine patients underwent duct and biliodigestive anastomosis stenting. None of the patients required repeat surgery [18].

T. Ito et al. (2018) demonstrated that in 82.1 % (23/28) of patients, the biliodigestive anastomosis site was reached endoscopically, and technical and clinical success was achieved in 21 (75 %). In the

Table. Prevalence, risk factors for biliary complications in the late postoperative period and treatment effectiveness
Таблица. Распространенность, факторы риска билиарных осложнений в позднем послеоперационном периоде и эффективность лечения

Authors ***Авторы***	**Type of study** ***Тип исследования***	***n***	***Frequency of biliary complications*** **Частота билиарных осложнений** ***n* (%)**	**Risk factors** ***Факторы риска***	**Type of treatment EA/PA/RO** ***Вид лечения ЭД/ЧД/ПО* (%)**	**Technical success EA/PA/RO** ***Технический успех ЭД/ЧД/ПО* (%)**	**Recurrence rate** ***Частота рецидивов* (%)**
Orii T. et al. (2014)	Retrospective *Ретроспективный*	67	–	Number of sutures, biliary stent *Количество швов, билиарный стент*	–	–	–
Ito T. et al. (2018)	Retrospective *Ретроспективный*	732	28 (3.8 %)	CHD diameter < 4 mm, duodenal tumors *Диаметр ОПП < 4 мм, опухоли ДПК*	75/25/0	100/100/-	–
Zhan H. et al. (2016)	Retrospective *Ретроспективный*	489	6 (1.2 %)	Duodenal tumors *Опухоли ДПК*	0/0/100	–/–/100	–
Hiyoshi M. et al. (2016)	Retrospective *Ретроспективный*	161	13 (8.1 %)	CBD ≤ 15 mm Ratio of CHD before and after surgery *Диаметр ОЖП ≤ 15 мм, Соотношение диаметра ОПП до и после операции*	–	–	–
Henry A. et al. (2024)	Retrospective *Ретроспективный*	900	93 (10.3 %)	BDA failure *Несостоятельность БДА*	–	–	–
Kobayashi S. et al. (2024)	Retrospective *Ретроспективный*	175	13	Male gender, CHD diameter ≤ 8.8 mm *Мужской пол, диаметр ОПП ≤ 8,8 мм*	100/0/0	92,3/–/–	0 (1.5 years) *0 (1,5 года)*
Ito Y. et al. (2018)	Retrospective *Ретроспективный*	133	28 (21.1 %)	ALP – 401 IU/L, pneumobilia *ЩФ – 401 МЕ/л, пневмобилия*	–	–	–
Lee J. et al. (2013)	Retrospective *Ретроспективный*	443	34 (7.8 %)	–	0/100/0	–/100/–	–
Tsutsumi K. et al. (2017)	Retrospective *Ретроспективный*	40	–	–	8/32/0	91/100/–	32.5 %
Itokawa F. et al. (2014)	Retrospective *Ретроспективный*	28	–	–	100/0/0	92.8/–/–	–
Duconseil P. et al. (2014)	Retrospective *Ретроспективный*	397	17 (4.3 %)	CHD diameter ≤ 4 mm *Диаметр ОПП ≤ 4 мм*	59/35/0	70/50/–	–
House M.G. et al. (2006)	Retrospective *Ретроспективный*	1595	42 (2.6 %)	Biliary stent *Билиарный стент*	0/95/5	–/100/100	9 %

Note: *CHD – common hepatic duct, CBD – common bile duct, BDA – biliodigestive anastomosis, ALP – alkaline phosphatase, EA – endoscopic access, PA – percutaneous access, RO – reoperation.*
Примечание: *ОПП – общий печеночный проток, ДПК – двенадцатиперстная кишка, ОЖП – общий желчный проток, БДА – билиодигестивный анастомоз, ЩФ – щелочная фосфатаза, ЭД – эндоскопический доступ, ЧД – чрескожный доступ, ПО – повторная операция.*

remaining seven (25 %) patients, the percutaneous approach was successfully used. Thus, no cases required open reoperation [7].

The Table presents summarized data from studies dedicated to late postoperative biliary complications.

Conclusion

In conclusion, it should be noted that bile duct stones are a rare complication of the late postoperative period following pancreatoduodenectomy, but one that requires the provision of highly skilled minimally invasive or surgical care. The choice of minimally invasive treatment method for patients with bile duct stones after pancreatoduodenectomy depends on the expertise of specialists and the technical equipment of the medical institution.

The endoscopic approach is characterized by rapid achievement of clinical success, a lower complication rate, and shorter hospitalization duration; however, it has a lower technical success rate in the setting of altered anatomy.

The percutaneous approach is a highly effective method for the minimally invasive treatment of late biliary complications after pancreatoduodenectomy, which can be used as a first-line option or in patients after failed endoscopic intervention. In cases of complete anastomotic stricture, a combination of these two approaches is possible as an alternative to repeat open surgery.

The use of absorbable suture material, minimizing the number of sutures during biliodigestive anastomosis formation, employing hepatoplasty, and preventing excessive mobilization of the bile duct may serve as preventive measures against hepatolithiasis after pancreatoduodenectomy.

Further detailed study of this issue is necessary to identify potential preventive strategies and improve treatment methods for this rare complication.

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Information about the author

Vasiliy I. Egorov – Cand. Sci. (Med.), Teaching Assistant of the Department of Oncology, Radiation Therapy, Kazan State Medical University; Oncologist, Republican Clinical Oncology Dispensary.
Contact information: drvasiliy21@gmail.com;
420000, Kazan, Butlerova str., 49.
ORCID: https://orcid.org/0000-0002-6603-1390

Сведения об авторе

Егоров Василий Иванович – кандидат медицинских наук, ассистент кафедры онкологии, лучевой диагностики и лучевой терапии, ФГБОУ ВО «Казанский государственный медицинский университет» Министерства здравоохранения Российской Федерации; врач-онколог, ГАУЗ «Республиканский клинический онкологический диспансер» Министерства здравоохранения Республики Татарстан.
Контактная информация: drvasiliy21@gmail.com;
420021, г. Казань, ул. Бутлерова, 49.
ORCID: https://orcid.org/0000-0002-6603-1390

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