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ORIGINAL ARTICLE

Perioperative application of somatostatin analogs for pancreatic surgery—current status in Germany

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Abstract
Background The most common major complication after pancreatic resection is the postoperative pancreatic fistula (POPF). Somatostatin analogs can reduce POPF, but the use of somatostatin analogs is still controversial. The aim of this study was to assess treatment algorithms for pancreatic surgery in Germany with a special focus on the application of somatostatin analogs.
Methods A questionnaire evaluating the perioperative management–especially the use of somatostatin analogs—and postoperative complications after pancreatic surgery was developed and sent to 209 German hospitals performing >12 pancreatoduodenectomies per year (the requirement for certification as a pancreas center). Statistical analysis was carried out using SPSS 21.
Results The final response rate was 77 % (160/209), 14.5 % of hospitals never, 37 % always, and 45 % occasionally apply somatostatin analogs after pancreatic surgery. A (standard) drug of choice was defined in 64 % of hospitals. When standard and occasional usage was analyzed, it appeared that hospitals favored somatostatin (69 %) > sandostatin (50 %) > pasireotide (5 %). A relation between the usage of the different somatostatin analogs and morbidity (POPF) or mortality (84 and 16 % of hospitals reported <5 and 5–10 %, respectively) was not seen. Eighty-seven percent of hospitals were interested in participating in future studies analyzing somatostatin use.
Conclusion This is the first national survey in Germany evaluating the perioperative application of somatostatin analogs for pancreatic surgery. Despite controversial results in the literature, the majority of German pancreas surgeons apply somatostatin analogs perioperatively. The ideal drug to reduce POPF is still unclear. This uncertainty has aroused significant interest and prompted surgeons to participate in future studies in order to elucidate this issue.

Keywords Pancreas surgery · Postoperative pancreatic fistula · Somatostatin · Pasireotide

Abbreviations

DKG	Deutsche Krebsgesellschaft (German Cancer Association)
DGAV	Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (German Association for General and Visceral Surgery)
POPF	Postoperative pancreatic fistula

Introduction

Pancreatic resections for benign or malignant diseases are among the most technically challenging gastrointestinal operations. The literature reveals that due to perioperative and technical advancements, there are decreased mortality rates of approximately 5 % in high-volume centers. Recent data from a nationwide study in Germany showed an overall hospital mortality rate of 10 %, assuming that the perioperative mortality is higher than anticipated from previous studies [1]. The operative morbidity has remained between 30 and 50 % [2–5]. The most common major

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complication after pancreatic resection is the postoperative pancreatic fistula (POPF) with reported rates between 10 and 28 % [6, 7]. In central pancreatectomies, the rate of POPF goes up to 60 % due to the creation of two pancreatic remnants and subsequently two potential sites for fistula formation [8]. POPF can cause significant morbidity, such as life-threatening postpancreatectomy hemorrhage (PPH) or sepsis. The potentially serious and even life-threatening event of a pancreatic fistula may prolong the hospital stay with increased costs and doubles the risk of death [9, 10].

The International Study Group on Pancreatic Fistula (ISGPF) and the International Study Group of Pancreatic Surgery have published a definition for pancreatic fistulas and a system for recording and reporting clinical data during pancreatoenterostomy [11, 12].

A large variety of studies analyzing different factors for reduction of POPF has been conducted in the past. Several authors focused on the treatment of somatostatin analogs to reduce the risk of fistula formation [13, 14]. Somatostatin inhibits pancreatic exocrine, biliary, and small-bowel secretions and increases the net absorption of water [15]. One possible disadvantage of somatostatin is the short half-life period with approximately 2 min [16]. Synthetic analogs of somatostatin with longer half-lives, such as octreotide, have been developed and have been used in pancreatic surgery [17]. The use of somatostatin or somatostatin analogs have been studied in several trials with different results. Yeo et al. conducted a prospective trial in patients undergoing pancreaticoduodenectomy, in which patients were randomized to a control (saline) or octreotide group; each drug was given before surgery and continued for 7 days postoperatively [18]. POPFs were seen in 9 and 11 % in the control and octreotide groups, respectively, not demonstrating *benefits* for octreotide treatment. A French multicenter prospective trial in patients undergoing pancreatectomy with randomization to octreotide treatment versus no treatment showed a lower incidence of intraabdominal complications in patients receiving octreotide; however, effects were not statistically significant [19]. A recent meta-analysis reported that somatostatin or pasireotide only resulted in decreased POPF rates, while octreotide did not seem to be effective [20].

Recently, a single-center, prospective, and double-blind trial using the long-acting somatostatin analog pasireotide in patients undergoing pancreaticoduodenectomy or distal pancreatectomy demonstrated a significantly reduced risk of POPF in patients treated with pasireotide [13]. Nevertheless, the use of somatostatin analogs remains controversial. Thus, we aimed to evaluate the use of somatostatin analogs in surgical departments in Germany and their influence on morbidity and mortality.

Methods

Questionnaire

A questionnaire was developed consisting of eight main question blocks with a combined total of 33 parameters to evaluate general aspects of participating hospitals and their strategy for carrying out pancreatic resections (Fig. 1). The questionnaire was created using the present literature and our own clinical experience [12, 21].

Contacted hospitals

An online database (white list/www.weisse-liste.de) was used to identify German hospitals that were subsequently contacted and sent the questionnaire. Search items were surgeries by specific codes (OPS code), 5–52 (pancreatic operations), 5–524 (partial resection of the pancreas), and 5–525 (total

	Parameter	Answering Options
1	Name and city of hospital	Free text
	Head of dept.	Free text
	Specialized dept. for pancreatic surgery	Yes/No
	Head of pancreatic surgery	Free text
2	Pancreatic surgeries per year	<12; >12; >20; >50; >100
	Pancreatic head resections per year	<12; >12; >20; >50; >100
	Pancreatic enucleations per year	<12;>12; >20; >50; > 100
	Other pancreatic surgeries per year	<12; >12; >20; >50; >100
3	DGAV certified	Yes/No
	DKG (OnkoZert) certified	Yes/No
4	Use of abdominal drain	Yes/No
	Postoperative evaluation (A/L)of drain fluids	Yes/No
	Standardized evaluation	Yes/No
	Evaluation (A/L) of drain fluids	Yes/No/Both
5	Always somatostatin analogues	Yes/No
	Always at risk (soft tissue, small duct)	Yes/No
	Sometimes	Yes/No
	Never	Yes/No
	Evaluation of pancreatic tissue	No/Surgeon/CT
6	Use of somatostatin	Yes/No/Occasionally
	Use of sandostatin	Yes/No/Occasionally
	Use of octreotide	Yes/No/Occasionally
	Use of pasireotide	Yes/No/Occasionally
	Standard for somatostatin analogue	Yes/No
	If yes, which drug do you use	Free text
	Application	s.c./i.m./i.v.
	Standard for duration of application	Yes/No
7	Grade A fistula	5%; >5%; >10%; >20%
	Grade B fistula	5%; >5%; >10%; >20%
	Grade C fistula	5%; >5%; >10%; >20%
8	Mortality of pancreatic head resections	<5%/ >5%/ >10%/ > 20%
	Mortality of pancreatic resections	<5%/ >5%/ >10%/ > 20%
9	Interest in a multicenter trial	Yes/No/Maybe

Fig. 1 Display of the questionnaire with questions and answering options. Parameters are grouped by blocks (1) hospital data, (2) pancreatic procedures, (3) certification status, (4) standard drain strategy, (5) use of somatostatin analogs, (6) drug of choice, (7) complications, (8) mortality, and (9) interest in a multicenter trial

pancreatectomy). Of the hospitals identified by these terms, 209 reported a case load of >12 pancreatoduodenectomies per year, one of the requirements for certification as a pancreas center. These hospitals were sent the questionnaire in June 2015. After 6 weeks, an identical questionnaire was sent to all hospitals that did not reply. The contacted hospitals comprised 31 university hospitals, 33 maximum care hospitals (hospitals with complete service/departments but no university), 68 tertiary hospitals (hospitals with extended service; however, some services/departments (such as neurosurgery) are missing and 28 basic care hospitals (hospitals with primary care, generally offering internal medicine, surgery, gynecology).

Statistics

Data analysis was performed using SPSS Statistics 21 (IBM). The chi-squared test and the Fisher's exact test were utilized for contingency tables. The Mann-Whitney *U* test and the Spearman's test were used for nonparametric testing. Incompletely or faultily filled out questionnaires were excluded from analysis for the unanswered questions. All tests were two sided and considered significant at $P < 0.05$.

Results

Response rate

The response rate after the first mailing was 50 % (104/209 hospitals) and increased to 77 % (160/209 hospitals) after the second mailing. The composition of contacted and responding hospitals was similar. Most nonresponding hospitals were basic care providers; all university hospitals returned the questionnaire.

General results

Surgery

The majority of the responding hospitals (47 %) perform more than 20 pancreatic procedures per year. Twenty-two (14.8 %) and 4 (2.7 %) hospitals display a caseload of more than 50 and 100 pancreatic head resections, respectively. Enucleation of pancreatic tumors is widely accepted (82 % of hospitals); however, numbers are limited (majority <12 cases/year; Fig. 2).

Certification

Only 18 % of all responding hospitals were certified by the German Association for General and Visceral Surgery (DGAV), and 43 % were certified by the German Cancer Association (DKG).

Specific results

Use of somatostatin analogs

Almost 15 % of the hospitals never use somatostatin analogs; however, the majority of hospitals (85 %) apply somatostatin analogs during pancreatic resections (Fig. 3), 35 % always, 62.6 % occasionally (depending on the pancreatic tissue or the diameter of the pancreatic duct), and 14.7 % never use somatostatin analogs.

The length of application demonstrates heterogeneity; many hospitals do not have a defined standard for how many days the drug is administered. However, 24 % of hospitals apply drugs for 7 days postoperatively, 23 % for 5 days, and 8 % for 3 days.

A drug of choice (standard) was defined by 64 % of the hospitals. Concerning standard and occasional usage,

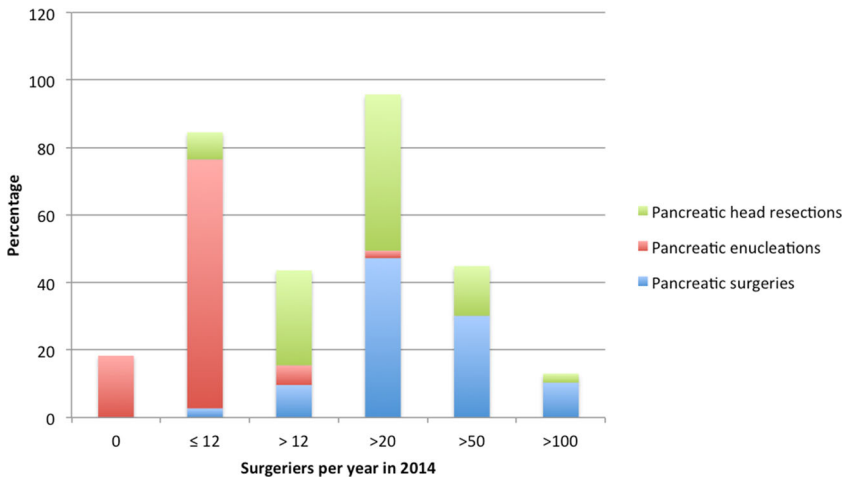

Fig. 2 Number of pancreatic resections in total, pancreatic head resections, and pancreatic enucleations

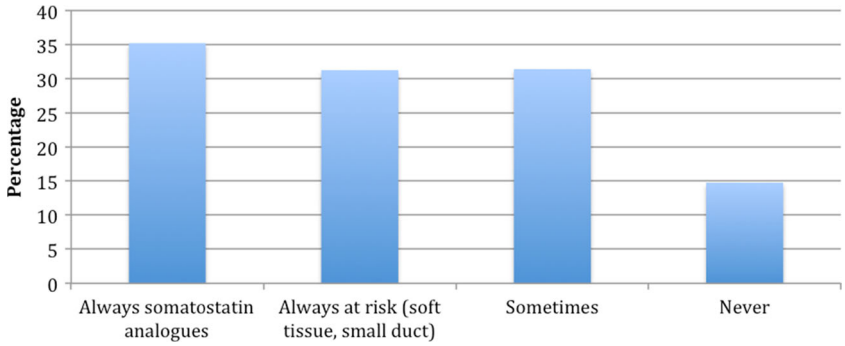

Fig. 3 Use of somatostatin analogs. The majority of hospitals administer somatostatin analogs in a risk-adjusted fashion

hospitals favored somatostatin (69 %) > sandostatin (50 %) > pasireotide (5 %; Fig. 4).

Drains and drain fluid assessment

The routine use of intraoperatively placed drains in pancreatic surgery is reported by the vast majority of participating hospitals (99.4 %).

Monitoring of pancreas enzyme levels in drain fluids was carried out by most of the hospitals (86 %). Interestingly, the assessment of enzyme levels is not standardized in many of the responding pancreatic centers; 58 % of hospitals displayed a standardized evaluation of drain fluids, with 44 % assessing both enzyme levels (amylase and lipase).

Morbidity and mortality

Analyzing the reported fistula rates of all hospitals, the majority of hospitals reported low fistula rates; 55, 82, and 93 % of hospitals reported their grade A, B, and C fistula rates to be below 10 %, respectively (Table 1).

Mortality rates were reported to be below 5 in 84 % of hospitals and between 5 and 10 % in 16 % of hospitals. No mortality above 10 % was stated.

The analysis of a potential correlation between POPF and use of somatostatin analogs did not show any significance for the analyzed subgroups: (a) use of somatostatin analogs ("always", "always at risk," and/or "sometimes") and (b) surgery ("pancreatic surgeries," "pancreatic head resections," and "pancreatic enucleations"). There were no significant correlations between the fistula rate and somatostatin use (Fig. 5).

In addition, significant correlations between hospital case load, hospital capacity level, or hospital certification status were not identified.

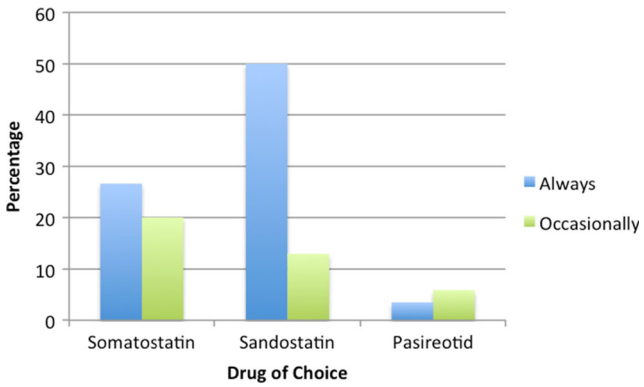

Fig. 4 Drug of choice. Sandostatin (87 %) and somatostatin (32 %) are frequently used, while pasireotide (5 %) is used by a few hospitals and only infrequently

Discussion

Postoperative pancreatic leakage (POPF) is the most common and challenging complication in pancreatic surgery. Despite technical advancements in the perioperative setting, the incidence of POPF still represents a significant problem. One of the major determinants of POPF is the consistency of the pancreatic parenchyma. Nowadays, indications for pancreatic surgery, including cystic neoplasms with a soft tissue, may lead to a higher risk of fistula formation. There have been several attempts to reduce POPF. Beside operative strategies, several studies focused on the treatment of somatostatin analogs to reduce the risk of fistula formation [13, 14]. The use of somatostatin analogs is still discussed controversially, and a consensus regarding a specific pathway does not exist. Because of these uncertainties in treatment algorithms for pancreatic surgery, we conducted a national survey to evaluate the currently favored treatment approaches in order to (1) disseminate knowledge of the de facto standard and (2) identify relevant issues for further investigation.

The high response rate of 77 % reflects the interest of German surgeons in POPF and the topicality of the subject. The survey could not address all anticipated questions; it was

Table 1 Reported fistula rates of all hospitals

Fistula grade (ISGPF)	<5 %	5–10 %	11–20 %	>20 %
Grade A	25 %	30 %	35 %	10 %
Grade B	45.3 %	36.5 %	17.5 %	0.7 %
Grade C	77.5 %	15.3 %	7.2 %	0 %

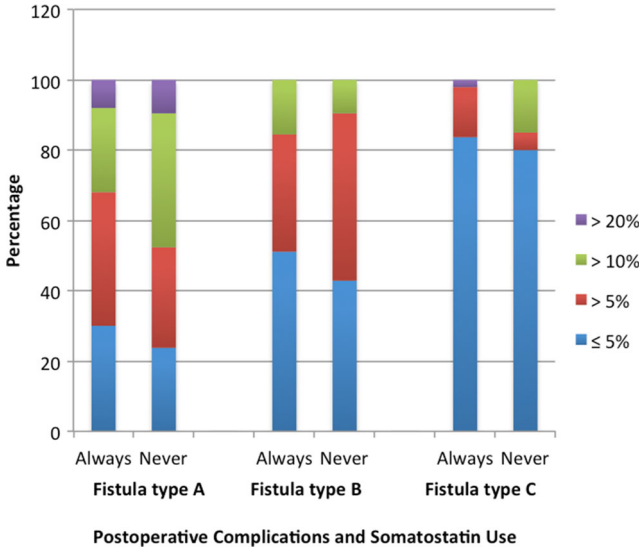

Fig. 5 Correlations between fistula rate and use of somatostatin analogs. Display of POPF rates (grade A–C) in relation to use (*always*) or absence (never) of somatostatin analogs

kept simple in order to achieve a high response rate and obtain representative results. However, the presented data supplies an accurate picture of the current surgical routine and reveal correlations.

When the numbers of pancreatic resections were evaluated, the data showed that most hospitals performed more than 20 pancreatic resections per year. Interestingly, most hospitals (82 %) perform enucleations; however, the numbers are limited (74 % <12/a, 6 %12–20/a, 2 % >20/a).

One possible explanation could be the increasing amount of resected benign lesions, such as cystic and neuroendocrine tumors, due to better diagnostic regimen and surgical knowledge. In addition, positive study results of pancreatic enucleations [22–26] demonstrating the feasibility with favorable outcomes might explain the popularity and increasing numbers. In terms of general morbidity as well as the incidence of postoperative diabetes mellitus and exocrine dysfunction, enucleations seem to be superior to standard resections.

The majority of hospitals reported the routine use of abdominal drains with monitoring of pancreas enzyme levels. In 1992, a study by Jeekel et al. reported that abdominal drainage after pancreaticoduodenectomy could be abandoned [27]. Since then, several trials found a higher complication rate in the routine use of abdominal drains compared with patients without abdominal drains (no drainage group). All authors suggested that a prophylactic drainage after pancreatic surgery could be omitted [28–32]. A recent Cochrane Database from Peng et al. showed no significant reduction in the incidence of postoperative complications in the routine use of abdominal drains after pancreatic surgery [33]. Most recently, the not published data of the PANDRA trail (ISRCTN04937707) have been presented at the 136th Annual Meeting of the American Surgical Association. This randomized controlled study concluded that drains during routine pancreatic head resections cannot be recommended because omission of drains results in decreased postoperative reinterventions and POPF rates.

In contrast with these findings, Van Buren et al. found that pancreaticoduodenectomy without drain use was associated with an increased morbidity and mortality [34]; however, the study has to be interpreted carefully because the study was aborted prematurely and might be underpowered. Similar results were found in a study from Nitsche et al. [35]. Both authors concluded that the insertion of abdominal drainage is recommended. These different findings indicate the ongoing debate about drain use in pancreatic surgery.

Our results show that the majority of German surgeons use abdominal drains and do not seem to be convinced about omitting abdominal drains in pancreatic surgery.

In our department, we suggest the routine use of abdominal drains during pancreatic surgery with subsequent monitoring of pancreas enzyme levels. Our strategy is an early removal of the drain on the third postoperative day if enzymes in the drain fluid have increased less than tenfold compared with serum levels [36].

The results of the monitoring of enzyme levels in abdominal drain fluids are also interesting; the majority of the responding hospitals analyze enzyme levels (amylase/lipase) in the drain fluid to assess POPF. Only about 50 % have a standardized protocol to determine pancreatic enzymes in drain fluids, and most of the responding hospitals evaluate both enzymes. Whereas the content of drain lipase is widely accepted as a tool for predicting pancreatic fistula, the content of drain amylase in the days immediately after major pancreatic resection has been investigated as a predictor of POPF in the recent literature [37–39]. Some authors suggest drain amylase on the first postoperative day [38, 39], others on the third day [37] as a possible predictor for pancreatic fistula. An ideal time point for the evaluation of the content of drain activity is not completely known. In addition, the enzyme of choice (amylase or lipase) is an ongoing debate.

The use of somatostatin analogs may reduce the risk of pancreatic leakage, as somatostatin inhibits pancreatic and exocrine secretions with an increase of net absorption of water [15, 40]. More than 80 % of German hospitals use somatostatin analogs, but the drug of choice is not yet known. In a large review identifying 21 trials with 2348 patients, Gurusamy et al. recommended somatostatin and its analogs for routine use in people undergoing pancreatic resection [41]. A study by Allen et al. even showed that treatment with pasireotide in the perioperative period significantly reduces the risk of clinically relevant postoperative pancreatic fistula. Moreover, the risk of overall pancreatic complications was also reduced with pasireotide [13].

Other studies showed that octreotide prophylaxis after pancreatic surgery has no beneficial effect on the clinical severity of POPF [42, 43]. A recent study by Paye et al. on patients undergoing distal pancreatectomy (normally associated with a higher fistula rate than, e.g., pancreatic head resections) showed that the prophylactic use of somatostatin analogs was not associated with a lower rate of pancreatic fistula [44]. These different results reveal the ongoing discussion about the use of somatostatin analogs. Furthermore, the drug of choice seems to be unknown.

In the case of pasireotide (Signifor ®), it is noteworthy that pasireotide is not approved for the treatment of pancreatic fistulas in Germany. The German Pharmaceuticals Act (Deutsches Arzneimittelgesetz) allows pasireotide to be used only for the treatment of Cushing's disease. The application of pasireotide is still an off-label use in Germany. Additionally, pasireotide is significantly more expensive compared with sandostatin [45]. In general, somatostatin is administered intravenously (3.5 μg/kg/h) for 7 days with total costs of approximately €360 for a standard patient with 70-kg body weight. Sandostatin (octreotide) and pasireotide are given subcutaneously for 7 days with dosages and costs of 100 μg three times per day for approximately €420 and 0.9 mg two times per day for approximately €900.

The current literature from specialized centers and experienced surgeons with above-average outcomes reports POPF rates between 5 and 15 % [46]. Corresponding to this, a recent randomized controlled trial by Keck et al. involving 320 patients treated at 14 German high-volume academic centers for pancreatic surgery revealed a rate of 21 % of grade B/C fistulas [47]. Interestingly, our data shows considerably lower POPF rates than described in the literature; only 24.7 % of the responding hospitals displayed more than 10 % grade B/C fistulas. The decreased fistula rate—as well as any other data—reported in our study could be biased by the surgeon filling out the questionnaire. The answers could have been subjectively influenced. This represents a typical weak point of survey-based studies.

In our study, the majority of hospitals reported low fistula rates with POPF grade A and B below 10 % in 82% and 93% of patients, respectively. Corresponding to the low morbidity, mortality rates were reported to be below 5 in 84 % of hospitals and between 5 and 10 in 16 % of hospitals. In contrast with the most recent study of Nimptsch et al. [1], our data did not reveal mortality rates above 10 %. A possible explanation for the low morbidity and mortality rates could be the surgeon bias. The answers in our questionnaire could have been subjectively influenced and not based on a thorough review of the current clinical data. Thus, the results of our survey are interesting, because it is possible that the survey data might often underestimate reality and might need to be evaluated even more carefully.

Limitations of the study

As discussed previously, the data presented in this study is based on statements of the responding surgeons. The accuracy of our data cannot be verified or guaranteed and represents an important drawback of our study and many other questionnaire-based studies.

In addition, our study does not include a cost benefit analysis that would have been interesting to assess potential economic benefits of somatostatin analogs.

Conclusion

This is the first national survey in Germany to evaluate the perioperative application of somatostatin analogs in pancreatic surgery. While there is an ongoing debate about the use of somatostatin analogs in the literature, most German pancreas surgeons apply somatostatin analogs. The ideal drug to reduce POPF remains unclear.

The data emphasizes the significant interest of surgeons in participating in future studies to elucidate this issue.

Author contributions Andreas Volk: study design, data acquisition, data analysis, data interpretation, drafting of the manuscript.

Philipp Nitschke: study design, data acquisition, data analysis, data interpretation, manuscript revision.

Franziska Johnscher: data analysis, data interpretation, manuscript revision.

Nuh Rahbari: data acquisition, data analysis, manuscript revision.

Thilo Welsch: study design, data interpretation, manuscript revision.

Christoph Reissfelder: study design, data interpretation, manuscript revision.

Juergen Weitz: study design, data interpretation, manuscript revision.

Marius Distler: study design, data analysis, data interpretation, drafting of the manuscript.

Soeren Torge Mees: study design, data acquisition, data analysis, data interpretation, drafting of the manuscript.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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