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Prise en charge de la fuite chyleuse réfractaire post-pancréatectomie : résultats d'une enquête nationale française sur les pratiques et évaluation de l'intérêt de la lymphographie

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Liste des abréviations :

DPC : duodénopancréatectomie céphalique

PG : pancréatectomie gauche

NPE : nutrition parentérale exclusive

R-TCM : régime pauvre en triglycérides à chaîne moyenne

MCT-based diet : enteral or oral fat restricted or medium chain triglyceride enriched diet

CL : chyle leak

DP : distal pancreatectomy

ISGPS : International study group of pancreatic surgery

ICU : intensive care units

PD : pancreaticoduodenectomy

CG : conservative group

LG : lymphography group

BMI : body mass index

OR : odds ratio

POD : postoperative day

Résumé

Prise en charge de la fuite chyleuse réfractaire post-pancréatectomie : résultats d'une enquête nationale française sur les pratiques et évaluation de l'intérêt de la lymphographie

Introduction. La fuite chyleuse est une complication peu fréquente après pancréatectomie dont la prise en charge est peu codifiée. Notre étude vise à i) étudier les pratiques en France sur la gestion de la fuite chyleuse puis ii) étudier l'intérêt de la lymphographie dans le traitement des fuites chyleuses réfractaires post-pancréatectomie**.**

Méthodes. Un questionnaire détaillant la démarche diagnostique et thérapeutique, concernant la fuite chyleuse après pancréatectomie, a été envoyé à 25 chirurgiens issus de 25 centres Français experts. Un screening a été réalisé secondairement permettant l'identification des patients traités par lymphographie en France. Un deuxième groupe de patients présentant une fuite réfractaire fut défini par la présence d'une fuite chyleuse de grade B ou C ne répondant pas au régime diététique TCM.

Résultats. La prise en charge de la fuite chyleuse est hétérogène en France. 24 % des centres ont eu recours à la lymphographie. 33 patients traités par lymphographie (30,3% par voie bipédieuse, 69,7% par voie transnodale) et 23 patients par traitement conservateur ont été identifiés entre 2010 et mars 2023. Comparativement au traitement conservateur seul, les patients traités par lymphographie dans les 25 jours suivant la chirurgie (n=25) avaient significativement moins de collection abdominale (36 % vs 69,6%, p = 0,019), de drainage radiologique (20 % vs 60,9%, p = 0,007), et de réadmission pour récidive (0% vs 26,1 %, p = 0,008).

Conclusion. La lymphographie précoce pourrait avoir un impact positif sur les fuites chyleuses réfractaires post-pancréatectomie. Des études complémentaires sont nécessaires pour recommander cette approche en pratique courante.

Introduction :

Les résections pancréatiques sont variées en termes de voie d'abord, de dissection et de curage en fonction des indications opératoires. L'indication la plus fréquente, l'adénocarcinome pancréatique, a une incidence en augmentation depuis les années 80, représentant le cancer digestif au pronostic le plus défavorable. Il serait probablement en 2030 la 2ème cause de mortalité par cancer (1–4).

Alors que les techniques opératoires ont évolué permettant une épargne parenchymateuse ainsi que l'émergence des voies mini-invasives, les indications de résections ont été élargies à des tumeurs borderline et localement avancées encadrées par un traitement néoadjuvant. Ce traitement multimodal a permis d'augmenter la résécabilité des patients et leur survie (5). Après un traitement d'induction, il peut persister une infiltration périvasculaire, toutefois une réponse tumorale doit inciter à l'exploration chirurgicale (6). C'est ainsi que les curages sont plus étendus avec des résections vasculaires parfois associées.

Le curage ganglionnaire « élargi » pour l'adénocarcinome pancréatique implique une dissection circonférentielle du tronc cœliaque, et de l'artère mésentérique supérieure et la résection des ganglions latéro-aortiques(7), localisés à proximité immédiate de la citerne du chyle, la naissance du conduit thoracique et des voies lymphatiques intestinales.

En 1651 Jean Pecquet décrit la citerne de Pecquet, le canal thoracique et leur connexion avec les vaisseaux lymphatiques mésentériques (8). Les lymphatiques forment un système de transport des fluides et protéines (jusqu'à 8 à 12 litres / jour) en les collectant dans l'espace interstitiel et les acheminant dans la circulation sanguine, essentiels dans le maintien de la pression osmotique et hydrostatique, et transporteur des cellules de l'immunité (9).

La lymphe intestinale contient une quantité importante de graisses réabsorbées directement par le tube digestif, d'aspect trouble, laiteux, nommée chyle.

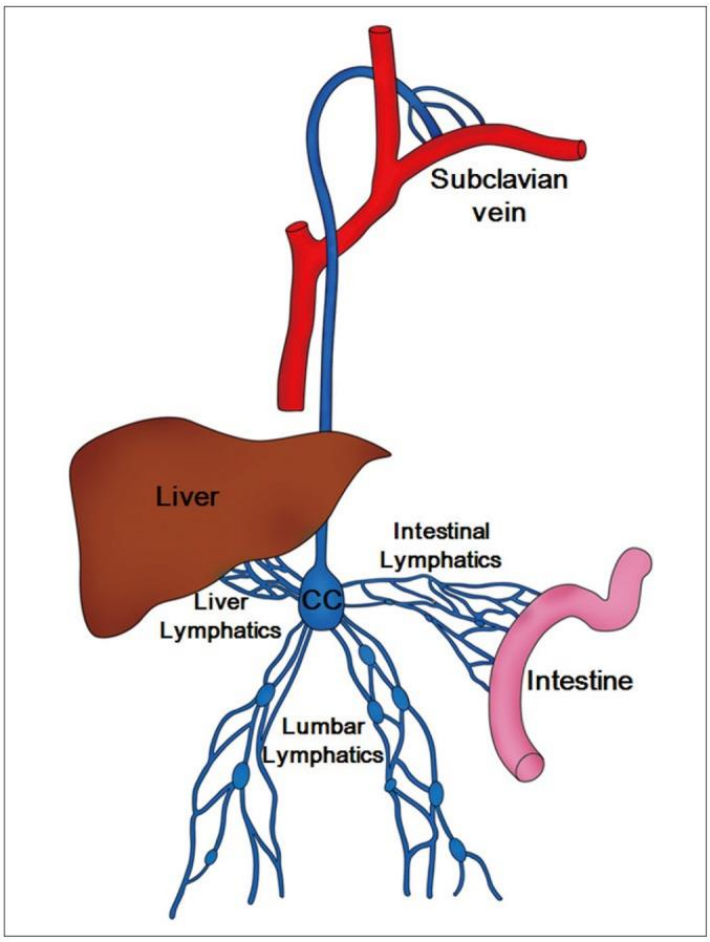


Image extraite de *Lymphangiography to Treat Postoperative Lymphatic Leakage: A Technical Review* (10)

La DPC représente entre 69 et 75 % des résections pancréatiques (11,12).

Après DPC, un dépistage précoce des complications postopératoires, dont l'incidence peut atteindre 64% (avec 4,2 à 31% de complications sévère Clavien-Dindo ≥ III) est primordial (13). Source de morbidité, elles peuvent induire un retard dans la prise en charge oncologique et réduire la probabilité de chimiothérapie adjuvante diminuant ainsi la survie des patients (14). De plus, la réhospitalisation à 6 mois après une résection pancréatique est d'environ 40% (12) et a un coût considérable pour la société.

Les complications les plus courantes de la chirurgie pancréatique sont la fistule pancréatique (environ 14 % des DPC (15), 20 % des pancréatectomies gauches (16)), la gastroparésie touchant 10 à 15% des patients (17,18), l'insuffisance pancréatique exocrine présente chez 38 à 93% des patients opérés d'une

DPC (19) et l'apparition ou la décompensation d'un diabète dans 14 à 30% des cas (20,21). La fuite chyleuse est une complication chirurgicale moins commune. Il est suggéré que son incidence pourrait augmenter en raison de l'augmentation des résections étendues (22).

Elle se résout souvent sans traitement ou par simple régime diététique. Néanmoins il arrive qu'une hospitalisation prolongée soit nécessaire avec plusieurs lignes de traitements devant une fuite réfractaire avec un impact significatif sur les suites du patient (collection postopératoire, dénutrition sévère chez des patients déjà dénutris en préopératoire, sepsis).

Synthétisé en 1901, le Lipiodol est un produit de contraste utilisé comme outil diagnostique depuis les années 1920 (23). L'efficacité de la lymphographie au Lipiodol a été démontrée notamment pour les chylothorax par l'accessibilité au conduit thoracique avec le développement de l'embolisation dans la prévention des fuites chyleuses (avec 92,4 % de succès clinique de l'embolisation du conduit thoracique dans une métanalyse coréenne (24)). Cette procédure diagnostique et thérapeutique est sûre et peu invasive (25).

Les mécanismes thérapeutiques sont peu connus, possiblement lié à un effet embolique due à sa viscosité ou par son extravasation induisant une réponse inflammatoire au niveau du site de la fuite (25).

Concernant l'application à l'ascite chyleuse, il n'y pas de technique standardisée étant donné la variété d'étiologies, et de localisations anatomiques (25). A cause des modalités de cette imagerie, seules les fuites sur l'axe du flux lymphatique entre les membres inférieurs et le conduit thoracique peuvent visualisées. Le système lymphatique mésentérique n'est pas exploré (9).

Des articles semblent montrer une efficacité de la lymphographie pour les ascites chyleuses, toutefois les séries comportent souvent des populations hétérogènes (associant chylothorax, lymphocèle, et ascites chyleuses). Nadolski et al. ont décrit dans leur série de 31 ascites chyleuses que la lymphographie ne révèle les fuites que chez 55% des patients (26). Les 45% restant surveillés ont

présenté une résolution spontanée ou un effet thérapeutique du Lipiodol avec 21% de guérison. 11 (65%) patients dont la fuite a été identifiée ont eu une embolisation à la glue et/ou coils avec résolution de la fuite chyleuse dans 82% des cas.

Revue de la littérature sur la fuite chyleuse post pancréatectomie :

Basés sur les principales études rétrospectives sur le sujet publiées sur les vingt dernières années (16 études rétrospectives de plus de 200 patients), voici un résumé de l'incidence de la fuite chyleuse, ses facteurs de risques et les traitements existants ainsi que leur efficacité décrite. Les séries publiées incluent principalement des DPC pour cancer.

Définition de la fuite chyleuse

Tout d'abord la définition de la fuite chyleuse varie selon les centres. Elle peut être exclusivement clinique par l'aspect des liquides de drainage ou associer un dosage biologique pour confirmer le diagnostic. La définition la plus utilisée est celle de l'ISGPS (International Study Group on Pancreatic Surgery) tenant compte de l'aspect laiteux du liquide de drainage, et biologiquement d'un niveau de triglycéride supérieur à 110 mg/dl ou 1.2 mmol/L sur l'analyse du liquide de drainage (22).

L'étude de *Strobel et al.*, publiée en 2016 (27), décrit que seulement 0.9% des fuites chyleuses étaient diagnostiquées sur le taux de triglycérides seul, suggérant que le diagnostic est cliniquement évident. Ainsi le diagnostic est posé typiquement à la reprise de l'alimentation orale ou entérale, entre le 3ième et 7ième jour (28), (29), (30).

D'autres auteurs ajoutent à la définition un seuil de débit de 100 ml (31,32) à 200 ml (33) ou de durée (7 jours pour *Tabchoury et al*. en 2016*)*

Incidence

Concernant l'incidence de la fuite chyleuse parmi 16 études rétrospectives, elle oscille entre 1.3% (*Assumpçao et al.*, incluant 3532 résections pancréatiques dont 47 cas de fuites chyleuses (29)) et 22,1% (*Shyr et al.*, comportant 451 résections dont 64 fuites chyleuses (34)).

Gradation de la fuite chyleuse

Ces recueils de patients sont réalisés tous grades de sévérité confondus. La sévérité de la fuite est rarement spécifiée, il est donc difficile d'estimer la proportion des fuites chyleuses cliniquement pertinentes. Pour la première fois dans leur étude publiée en 2008 (35), les auteurs de *Van der Gaag et al.* ont proposé une classification de la fuite chyleuse qui se rapproche de la classification du ISGPS publiée en 2016.

Classification de septembre 2016, ISGPS consensus definition and grading system for isolated chyle leak after pancreatic resection (22)

	Grade A	Grade B	Grade C
Therapeutic consequence	None or oral dietary restrictions	Nasoenteral nutrition with dietary restriction and /or TPN, percutaneous drainage by IR, maintenance of surgical drains, or drug (e.g. octreotide) treatment	Other invasive in-hospital treatment, admission to ICU and/ or mortality.
Discharge with (surgical) drain or readmission	No	Possibly	Possibly
Prolonged hospital stays	No	Yes	Yes
TPN, Total parenteral Nutrition; IR, Interventional Radiology			

La classification du ISGPS permet notamment de séparer les fuites chyleuses d'évolution spontanément favorables sans traitement ou avec régime oral seul (grade A), de celles qui requièrent une prise en charge plus complexe (nutrition entérale avec régime oral spécifique, nutrition parentale exclusive, ou octréotide), une hospitalisation prolongée, des drainages complémentaires ou des réadmissions secondaires (de grade B) et les fuites requérant une prise en charge invasive ou une admission en soins intensifs (grade C).

Dans la littérature, quatre études ont utilisé ce grade (27,36–38). Les incidences grade B et C confondus étaient respectivement de 3.5% (33 sur 945 résections, *Paiella et al.*), 7% (152 sur 2159 résections, *Augustinus et al*), 8.9% (297 sur 3324 résections, *Strobel et al*).

Les auteurs *Weniger et al.* ont publié en 2021 une série de 60 fuites chyleuses dont 45% des patients présentaient un grade A, 55 % un grade B. Une série néerlandaise multicentrique nationale (*Augustinus et al,* publiée en juillet 2022) décrivait une proportion de grades B et C, de 6.9% et 0.1%.

Les auteurs *Van der Gaag et al.* ont décrit un seuil minimal du débit des drains de 275 mL comme significatif pour trouver un bénéfice à toute prise en charge thérapeutique.

Facteurs de risques

Les facteurs de risque de fuite chyleuse, en tenant compte des analyses multivariées, étaient :

- Le curage extensif avec le nombre de ganglions prélevés (29,30),

Le nombre de ganglions prélevés n'était pas un facteur prédictif de fuite chyleuse dans l'étude multicentrique *d'Augustinus et al.*

- La manipulation de la zone para-aortique (31,39), de la racine de l'artère mésentérique supérieure (31),
- La résection vasculaire (OR de 8.25 selon l'étude d'*Assumpçao et al.*, 2.1 selon *Augustinus et al*),
- Le picking inter-aortico-cave (OR 6.26 selon *Tabchoury et al*),
- L'invasion rétropéritonéale (31,39),
- La pancréatite chronique calcifiante (31,35)
- Une initiation précoce de l'alimentation entérale (30,31,39) (OR 12.18 selon *Tabchoury et al*, OR 14.3 selon *Kuboki et al*). *Navez et al* ont reporté une incidence de fuite chyleuse de 10 %

en cas de nutrition entérale précoce vs 3% si tardive (p = 0.004) dans une étude multicentrique (40).

Les auteurs de l'étude de *Strobel et al*. décrivent également en analyse multivariée le diabète pré-existant, la résection pour cancer, la pancréatectomie caudale, une intervention de 180 minutes ou plus, une fistule pancréatique ou un abcès concomitant.

Concernant la voie d'abord, les auteurs *Augustinus et al* montrait une différence significative avec un OR à 3.5 (p =0.001) pour la voie ouverte en analyse multivariée (avec 20.4% de DPC mini-invasives). Toutefois il y avait des différences significatives entre les 2 groupes en termes de résécabilité, volume de l'hôpital, résections vasculaires. *Shyr et al.* ont également rapporté en 2020 une différence significative entre la voie robot-assistée et la voie ouverte pour DPC avec des lymphadénectomies étendues (57.9 vs 22.2%, p =0.016).

Des seuils de débit des modules de drainage autour de 330 ml ont également été proposés bien que la sensibilité et spécificité étaient inférieures à 80% (41,42).

Traitement conservateur

La prise en charge thérapeutique de la fuite chyleuse est très hétérogène, dépendant du chirurgien référent.

Le régime TCM (R-TCM) supprime l'apport des graisses absorbées par les entérocytes et transférées sous forme de chylomicrons (triglycérides à chaînes longues).

La somatostatine, hormone hypothalamique (ou son analogue de synthèse l'octréotide), est un peptide qui agit de façon endocrine et paracrine et exerce un effet inhibiteur sur plusieurs enzymes digestives : VIP, hormone de croissance, insuline, glucagon, gastrine. Elle permet une diminution à la fois de la pression veineuse portale, de l'absorption intestinale et du débit sanguin splanchnique. La posologie

habituelle de l'octréotide est de 100 µg par injection trois fois par jour, pouvant être majorée à 250 µg par injection (43).

Les auteurs de l'étude *Assumpçao et al.* décrivent 85% d'efficacité du traitement conservateur sur 47 cas de fuites chyleuses, avec pour les ascites chyleuses une durée médiane de nutrition parentérale de 15 jours. Les auteurs de l'étude *Tabchoury et al.* (15 cas de fuites chyleuses sur 614 résections) ont décrit 66.6% de succès du traitement conservateur.

L'efficacité de la NPE (nutrition parentérale exclusive) est décrite avec une médiane de tarissement de la fuite en 2 jours dans l'étude de *Kim et al.* (24 cas de fuites chyleuses sur 222 résections), un tarissement en moins de 7 jours dans la série de *Russel et al. (*17 fuites chyleuses sur 560 résections).

La durée médiane de la fuite était de 6 jours avec une NPE seule contre 24 heures avec l'adjonction d'octréotide dans l'étude de *Kuboki et al* (17 fuites sur 574 résections). Cette combinaison de traitements permettait une reprise plus rapide de l'alimentation orale, ainsi qu'un retrait plus précoce des drains.

Les durées médianes de tarissement de la fuite variaient de 2 à 13 jours, bien que certaines fuites chyleuses étaient réfractaires avec des résolutions plus tardives (29). Sur 346 fuites chyleuses dans l'étude de *Strobel et al.* publiée en 2016, le traitement conservateur semblait être efficace en 14 jours.

Un algorithme de prise en charge était parfois proposé par les auteurs qui était plus ou moins en concordance avec les recommandations de l'ISGPS, premièrement le régime TCM puis en cas d'échec la NPE (plus ou moins associée à l'octréotide). *Russel et al* et *Kuboki et al* proposaient d'emblée une NPE, et *Kim et al* en fonction du débit.

Il semble exister une différence significative entre les fuites contenues et les ascites chyleuses (5 jours de médiane VS 36 jours, *Assumpçao et al.*). Un débit des modules de drainage de plus de 2 litres

semble être pourvoyeur d'échec du traitement conservateur (35 % d'échec dans ce sous-groupe VS 5.2% si le débit est inférieur à 2 litres, *Strobel et al*.).

Prise en charge invasive, la lymphographie

Concernant la prise en charge invasive de la fuite chyleuse, la littérature fait l'état de 3 articles.

Dans l'étude *Assumpçao et al.,* 7 patients sur 47 présentaient un échec du traitement conservateur (dont 4 lymphoscintigraphies et 3 lymphographies). La fuite était documentée respectivement dans 33% et 25 % des cas. La durée médiane de tarissement était de 58 jours (au maximum 232 jours). Par ailleurs, la réintervention était toujours inefficace, le shunt péritonéo-veineux a été utilisé pour 2 patients et était associé à des complications notables.

Deux articles ont montré des résultats prometteurs de la lymphographie. Dans l'étude de *Tabchoury et al.* publiée en 2016, 5 patients ont eu une lymphographie bipédieuse, réalisée entre J17 et J55. Le tarissement s'est effectué en 2 jours pour 3 patients, et après 11 et 21 jours pour les deux autres, avec au total 100 % de succès de la lymphographie. Toutefois la fuite a été localisée que pour 2 patients. La sortie d'hospitalisation avait lieu en médiane 7 jours après la procédure. Les auteurs conseillent l'utilisation de cette procédure après 10 à 14 jours d'échec du traitement conservateur.

En septembre 2021, les auteurs de *Klotz et al.* (44) ont publié une étude rétrospective monocentrique allemande relatant 48 cas de lymphographie (67 % d'accès bipédieux, et 33% d'accès transnodal) en excluant 7 (12.7%) patients pour échec technique. L'hospitalisation moyenne était de 47 jours et le délai moyen de réalisation de la lymphographie était de 34 jours. 24% des patients ont été réadmis pour fuite chyleuse persistante. La localisation de la fuite chyleuse était authentifiée dans 11% des cas. En classant les 48 cas en 3 groupes en fonction de la diminution des débits des drains (>85%, entre 85 et 50%, et < de 50% de diminution), les auteurs décrivent un succès clinique global de la procédure (≥ 50% de baisse) de 48%, et complet (> 85%) de 19% (basé sur l'analyse de la diminution des débits

moyens calculés sur plusieurs jours consécutifs). Le débit initial des drains est décrit comme un facteur prédictif de succès (débit moyen de 723 ml/j dans le groupe succès complet, contre 1407 ml/j dans le groupe entre partiel et 1805 ml/j dans le groupe échec). Les modules de drainage étaient retirés significativement plus tôt dans le groupe succès complet (3.6 jours vs 6.4 jours si succès partiel) et la sortie d'hospitalisation était également significativement plus précoce (7.1 jours contre 12 jours dans le groupe succès partiel, et 19 jours en cas d'échec). Des complications mineures ont été rapportées pour 2 patients : défaut de cicatrisation locale de la zone de ponction et une petite rupture d'un vaisseau lymphatique. 5 patients ont eu un drainage radiologique complémentaire et 2 patients ont eu une reprise chirurgicale pour fuite persistante qui s'est avéré inefficace.

Sévérité de la fuite chyleuse

Enfin la morbidité induite par la fuite chyleuse n'était pas minime. 91% de dénutrition, 6.4% de péritonite, 12.8% de sepsis et 2.4% d'abcès postopératoire sont décrit dans l'étude d'*Assumpçao et al.* (29). Dans cette large série monocentrique rétrospective entre 1993 et 2008, les patients opérés d'un adénocarcinome pancréatique présentant un chylopéritoine (à l'inverse de la fuite chyleuse contenue) avaient une survie n'excédant pas 18 mois.

Dans l'étude de *Strobel et al*., la fuite chyleuse isolée de grade B et C était associée à hospitalisation prolongée (OR 2.8, $p < 0.001$) en analyse multivariée, et en cas de débit supérieur à 2 litres / jour à une hospitalisation allongée de 4 jours. La fuite chyleuse n'avait pas d'impact à long terme dans les procédures curatives mais un impact sur la survie des patients palliatifs si elle persistait plus de 14 jours (médiane de survie à 5.2 mois vs 16.4 mois en cas de résolution plus précoce).

L'hospitalisation médiane était entre 12 et 22 jours en fonction des séries.

L'étude de *Paiella et al*. estimait le coût moyen d'hospitalisation à 15 684 euros (± 473 euros) pour un grade C, 7 150 euros (± 4791 euros) contre 2 806 euros (± 1420 euros) pour un grade A ($p <0.01$).

Background

In recent years, there has been an increased focus on optimizing postoperative outcomes and quality of life for patients undergoing pancreatectomy. Pancreatic resection can introduce a spectrum of postoperative complications. One of such complication, the occurrence of chyle leak (CL), is less frequent for example than postoperative pancreatic leakage, delayed gastric emptying and diabetes decompensation. Although the incidence of CL can reach 22% in the literature (34).

This complication arises when chyle, a milky fluid, escapes into the abdominal cavity due to surgical disruptions in the lymphatic system (cisterna chyli or its main tributaries including the para-aortic lymphatic channels as well as portal and splanchnic lymphatics) (45).

The International Study Group of Pancreatic Surgery (ISGPS) defined a consensus-based definition for CL after pancreatic surgery, but no codification of the treatment currently exists for surgeons' practices. Refractory CL poses significant challenges due to its potential to lead to malnutrition, sepsis, prolonged hospital stays, and increased healthcare costs (36). Therefore, it becomes imperative to establish effective strategies for the early identification, and management.

Conservative approaches such as enteral or oral fat restricted or medium chain triglyceride enriched diet (MCT-based diet), total parenteral nutrition (TPN) and somatostatin analogues have interesting results in retrospective series. Although algorithms of strategy are proposed, no comparative study was made focused on the different treatment. Recent advancements in medical imaging techniques have sparked a renewed interest in the role of lymphangiography. The effectiveness of therapeutic lymphangiography, applying the oily contrast material Lipiodol, is largely known for chylothorax with the development of thoracic duct embolization (24). A few studies were undertaken in the post-

pancreatectomy setting on the role of lymphangiography as a diagnostic and therapeutic tool for CL (30,44).

First, this paper aims to provide an overview of the current state of knowledge and practices regarding CL after pancreatectomy, offering insights into multicentric approach in France throughout a nationwide survey.

Secondly, the principal issue of this paper was to evaluate the potential of lymphangiography as an asset in the multidisciplinary management of refractory CL.

Methods

First part nationwide survey

The survey was proposed on voluntary basis to 25 French University Hospital with high volume of pancreatic surgery (Lyon Croix Rousse, Bordeaux, Besançon, Rennes, Rouen, Strasbourg, Nantes, Nancy, Clermont-Ferrand, Dijon, Paoli-Calmettes Institute of Marseille, University Hospital of Marseille, Paris Cochin, Amiens, Lille, Nice, Reims, Toulouse, Montpellier, Paris Saint Antoine, Paris Beaujon, Paris Pitié Salpêtrière, Lyon Edouard Herriot, Tours, Grenoble).

The questionnaire was distributed digitally through Google Forms, sent to at least one expert surgeon from each center via e-mail. The form was composed by the authors and made of 20 questions on CL (incidence, well-known risks factors, the diagnostic approach, therapeutic strategies and finally the access and modality of lymphangiography). The survey was conducted over a period of 6 months between June and Novembre 2022.

Mostly the aim was to identify centers performing lymphangiography. Secondly, we investigate the surgical practices in the diagnostic and treatment of CL.

Second part: evaluation of lymphangiography as an effective option in the management of chyle leak

Study design

This study is an observational non interventional retrospective study composed by 2 groups.

After identifying both groups (lymphangiography vs conservative treatment), the aim of this multicenter study was to evaluate the benefits of therapeutic lymphography, applying the oily contrast material Lipiodol, on refractory CL after pancreatic resection compared to exclusive conservative treatment.

Definitions

The CL was defined according to the ISGPS as appearance of milky-colored fluid from drain fluids, or wound, after postoperative day (POD) 3, with a triglyceride content ≥110 mg/dL (≥1.2 mmol/L). Positive detection of chylomicrons was also accepted.

The recovery of the CL was defined as no milky appearance of the drain fluids and output of the drain less than 200 ml or specified by the surgeon; in the opposite it was considered as persistent chyle leak.

CL was considered as refractory if patient was considered as non-responder to MCT-based oral diet that could be combined with somatostatin analogue introduced from the first operative days.

Study population

We tend to identify the cases of lymphangiography and refractory CL between 2010 and mars 2023. All centers who had already performed lymphography (identified via the national survey) were secondary contacted to collect patients' data. Six centers had used at least once lymphangiography after pancreatic resection (University Hospital Center of Nantes, Rennes, Bordeaux, Clermont-Ferrand, Besançon and Lille). The patient lists were obtained thanks to radiology department register

of Rennes, Bordeaux, and Lille. For the University Hospital Center of Nantes, a surgical register on pancreatic resections provided cases of chylous ascites. All patients who had undergone therapeutic lymphography between 2010 and 2023 for the treatment of CL were retrospectively included. Patients with technically unsuccessful lymphography were excluded from lymphography group (LG). If a second attempt was performed and successful, the patient was included in the analysis.

Concerning conservative group (CG), University Hospital Center of Beaujon in Paris and of University Erasme Hospital in Brussels provided institutional prospective register on pancreatic resection, with specific mention about CL exclusively managed with conservative treatment. In addition, we included patients from the register of the Hospital Center of Nantes and from the Hospital Center of Lille. Thanks to Medical Information Department in Lille, following CCAM codes of surgical acts: HNFA001, HNFA002, HNFA004, HNFA005, HNFA006, HNFA007, HNFA008, HNFA010, HNFA011, HNFA013, HNFC001, HNFC002, HNFC028, were crossed with following complications: I898 or J940 of the CIM-10.

The inclusion criteria for CG were as follows: (1) patients diagnosed with postoperative CL between 2010 and mars 2023, (2) grade B or C according to the ISGPS, except to the patients (discharged or not with drain) who had at follow-up appointment complete clinical success with MCT oral diet (+/- combined with somatostatin analog introduced from the beginning), that were excluded.

Patients who had technical failure of lymphography were also incorporated in this group.

Retrospectives databases were created, and the information was collected namelessly for each center through Hospital computer software and papers-based archives.

Therapeutic lymphography

ISGPS consensus statement recommended lymphography for severe, refractory CL. The procedure was performed with two different approaches (transnodal and bipedal). Sclerotherapy could also be

combined with the procedure. In general, a maximum volume of 20 mL was respected to prevent fatal pulmonary embolization (described in literature), and the procedure was conducted by experienced interventional radiologists.

Technical success of lymphography was defined as successful injection of the contrast material and opacification beyond the site of punction with the intention to selectively visualize the lymphatic system under X-ray imaging (+/- followed by CT scan).

An optimal procedure was defined as opacification of the lymphatics extending beyond the site of the identified extravasation, or Pecquet cistern and thoracic duct.

Data collection and outcome parameters

Data collected included patients demographic and characteristics (age, sex, Body Mass Index, American Society of Anesthesiologist (ASA) status, pre-operative resectability status, surgical and medical history of diabetes, renal insufficiency, hepatopathy, or chronic calcific pancreatitis), preoperative nutritional status (albumin, prealbumin), treatments characteristics (neoadjuvant therapy and response to treatment, surgical approach and procedure, type of drainage, node dissection, type of vascular resection (veinous or arterial) and its respective reconstruction (wedge, end-to-end anastomosis, graft interposition, no reconstruction), duration of surgery, estimated blood loss), tumor characteristics (histologic diagnosis, tumor grade, tumor size, number of resected lymph nodes, pTNM tumor staging according to the AJCC, and resection margin), general post-operative outcomes (grade of pancreatic fistula, bile leak, hemorrhage, collection, new onset of diabetes or decompensation etc.), albuminemia before discharge.

Concerning the CL, we described the diagnostic modality, interval between the operative day and the diagnosis, initial output at diagnosis, average output at POD 7, 10, 14 and 30, and several treatments

that were undertaken. Different lines of conservative treatment were mentioned : MCT-based diet, TPN, or administration of somatostatin analog.

The main outcomes were radiologic or surgical additional drainage, prolonged drainage, 90-day readmission, readmission for CL recurrence, interval of time to hospital discharge and drain removal. We assessed the 90-days mortality and readmission, Clavien Dindo score > IIIa, surgical revision.

For the LG, we collected the interval of time to procedure (from operation date), the radiologic approach, the quality of the assessment (with opacification of the Pecquet cittern and thoracic duct), the location of the leak when it was identified, complications of the procedure and interval until the removal of the drains and hospital discharge. The average output at day 1, 5, 7 and 10 post-lymphangiography, the day before and the day of the procedure were gathered.

Statistical analysis

Concerning the survey, the responses were manually coded and quantitatively processed. The percentages were calculated by question over all the responses completed.

Descriptive statistics were performed, quantitative data were presented as mean ± standard deviation, while the continuous data were presented as count and percentage of the total. To compare groups, Fisher exact tests was used for categorial variables (because of the small sample size), while non-parametric Mann and Whitney test was performed for continuous variables.

Statistical analyses were performed using the IBM SPSS Statistics Software for Windows version 29. A p-value of below 0.05 was considered statistically significant.

Results

First part: Nationwide survey

In overall, 25 surgeons from 25 expert French centers completed the survey form.

As to surgeons, the estimated **incidence** of CL in their center oscillates between 1 and 20% (9 centers answered between 1 and 5 %, 7 centers between 5 and 10%, 7 centers between 10 and 20 %).

Risk factors were as consensus : extended node dissection for all the surgeons, and pancreaticoduodenectomy for almost 70% of them. The opinion about venous and arterial resection was mixed with 52% of approval for the venous resection and 60% for the arterial resection.

Most of the questioned surgeons don't consider chronic calcific pancreatitis as a predisposing factor (96%), as well as neoadjuvant chemotherapy (96%), radiotherapy (88%), left pancreatectomy (96%), and aortocaval lymph nodes sampling (88%).

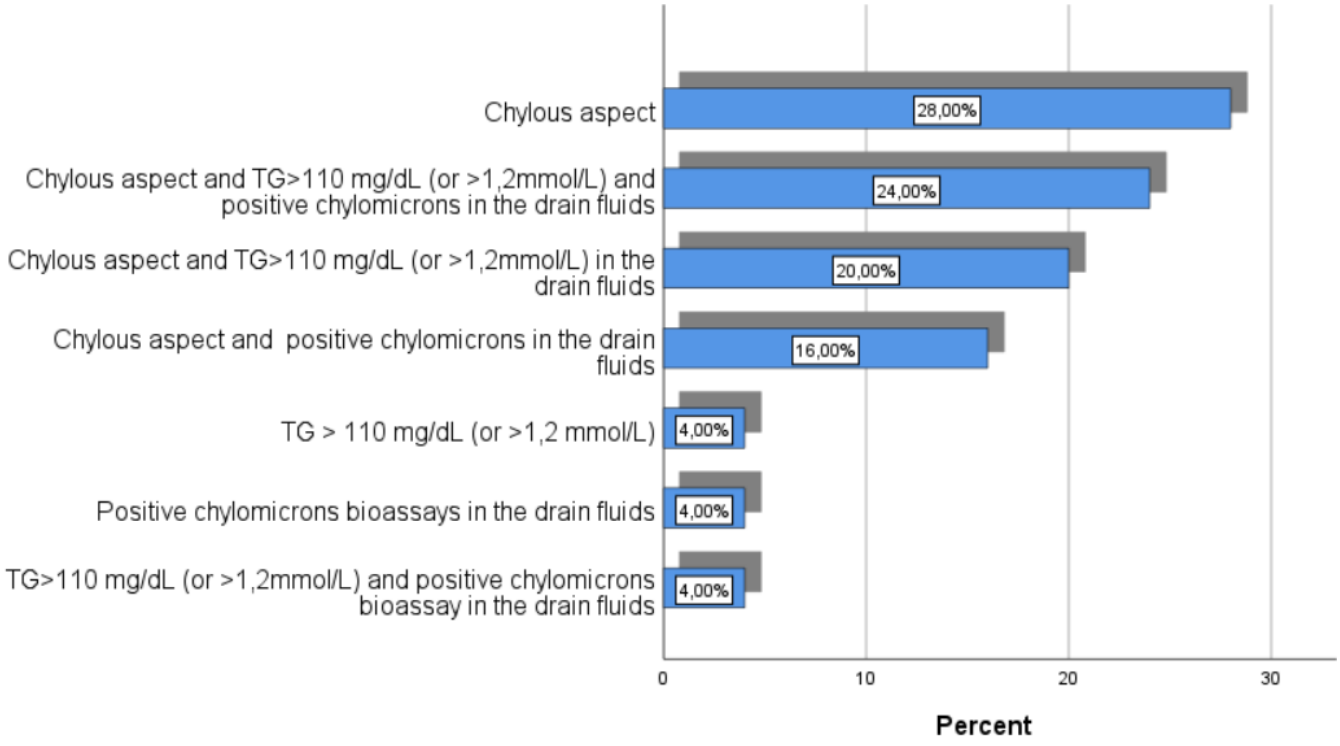


Figure 1: Various diagnostic definitions for CL

Concerning the **definition** (figure 1), heterogeneous modes of diagnosis are currently used nowadays. In this survey, 28% of the centers used exclusively clinic aspects of the drain, 20% used ISGPS definition and 24% of the centers add the positive bioassay of chylomicrons.

Interestingly, 16% didn't used TG bioassay but visual assessment and positive chylomicrons. Finally, 3 centers used exclusively biologic definition (either with TG level, or positive chylomicrons, or a combination of both).

Criteria to start the treatment were clinical. Figure 2 shows that 20% of the surgeons check out the output of the drain and the duration of CL (in days), 16% only the output and 12% of them either the output or the duration or the occurrence of complications.

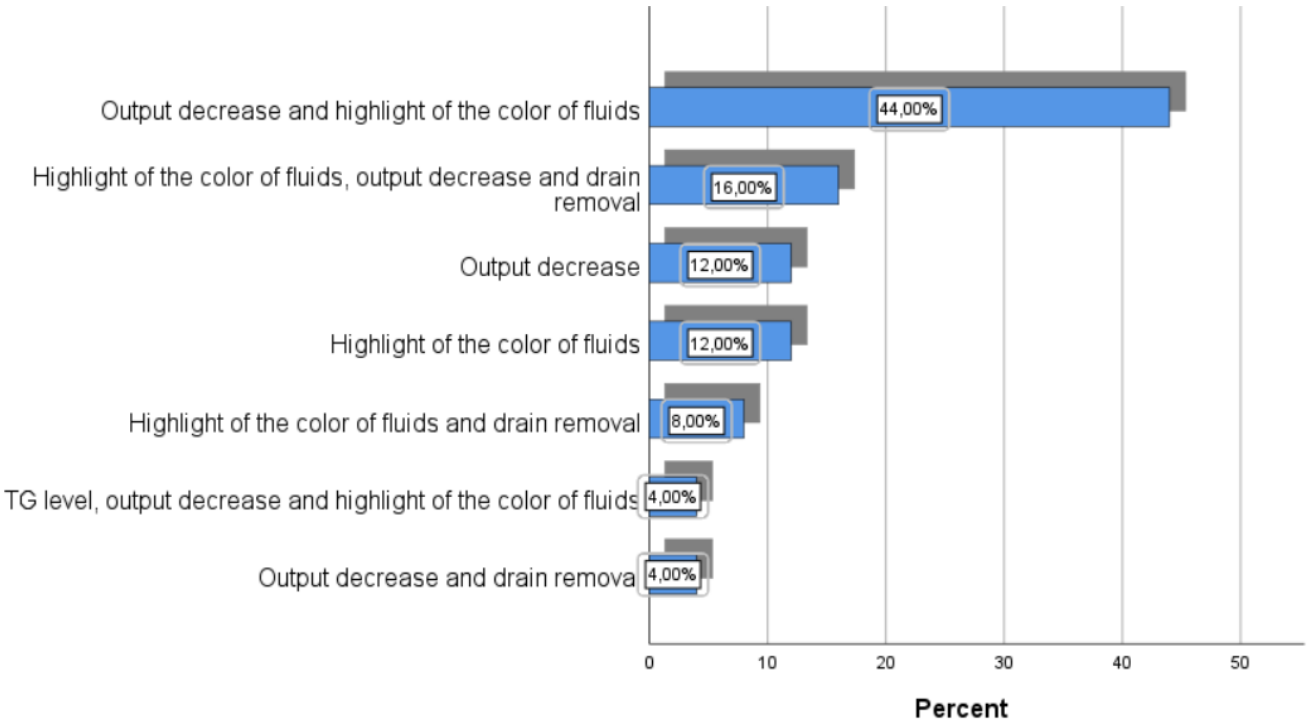


Figure 2: criteria of clinical success of the therapeutic strategy

Criteria of clinical success of the treatment are mentioned in the figure 3. 72% of the surgeons didn't consider drain removal as clinical success of the treatment and 16 centers mentioned a minimal output to start the therapy showed in the figure 3.

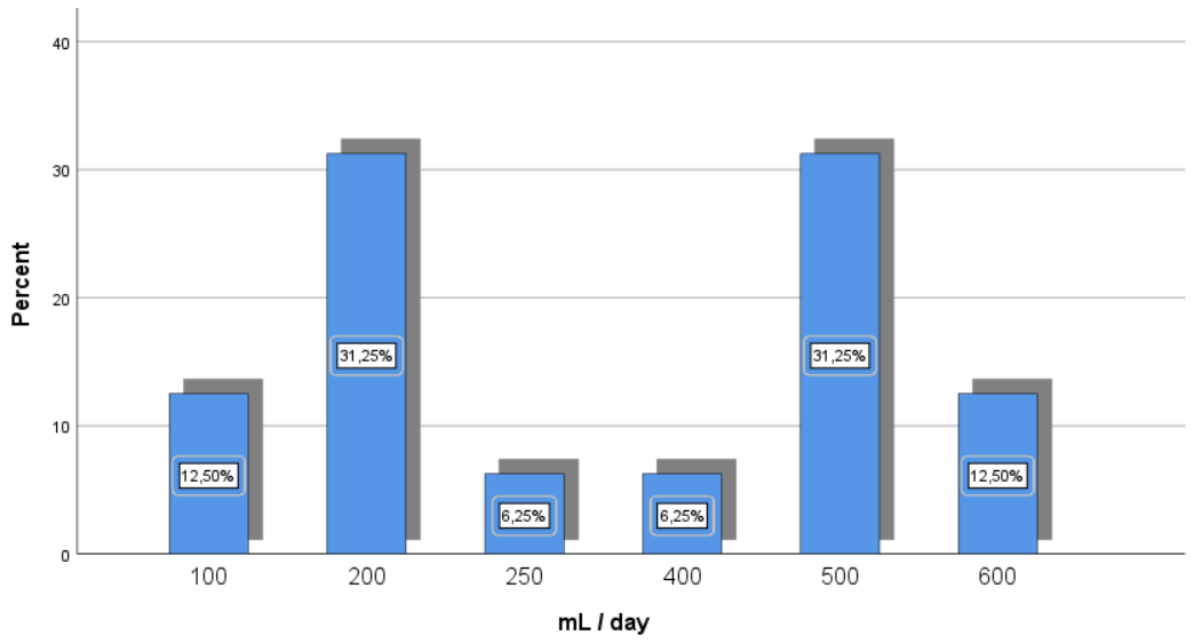


Figure 3: minimal output to start treatment

The management of CL is described in figures 4 and 5, representing the different **therapeutic line of conservative treatment** used by the different centers. Surgeons use mainly MCT diet in first line (+/- combined with octreotide), then either octreotide or TPN or a combination of both in second line. Only 8% recommend TPN at first line. One surgeon proposed an adjusted strategy according to the output of the drain (MCT diet in case of output < 500 ml, and parenteral nutrition if > 500 ml).

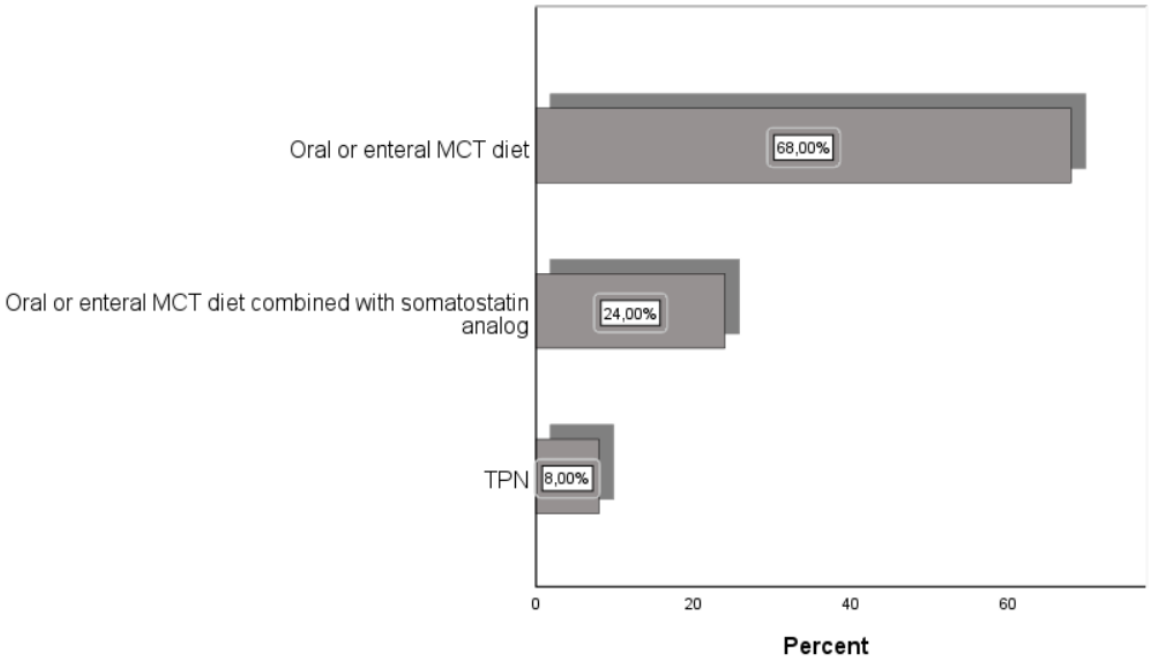
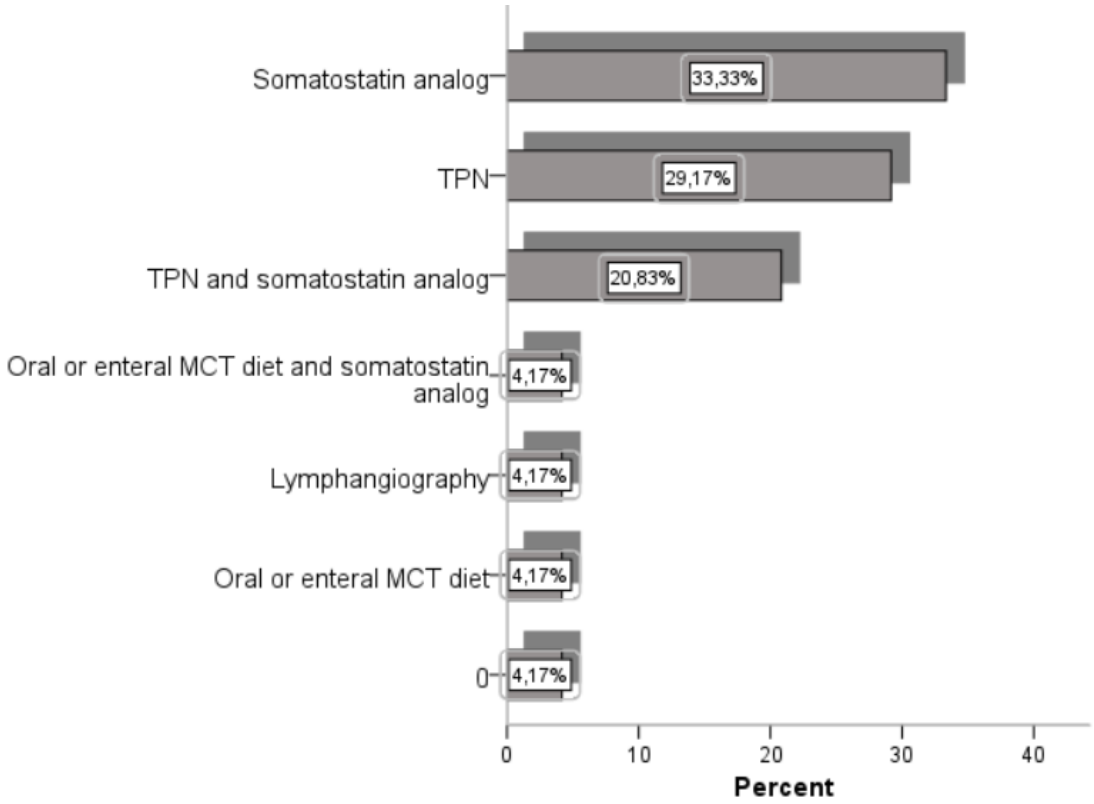


Figure 4: first therapeutic line



Figure

Figure 5: second therapeutic line

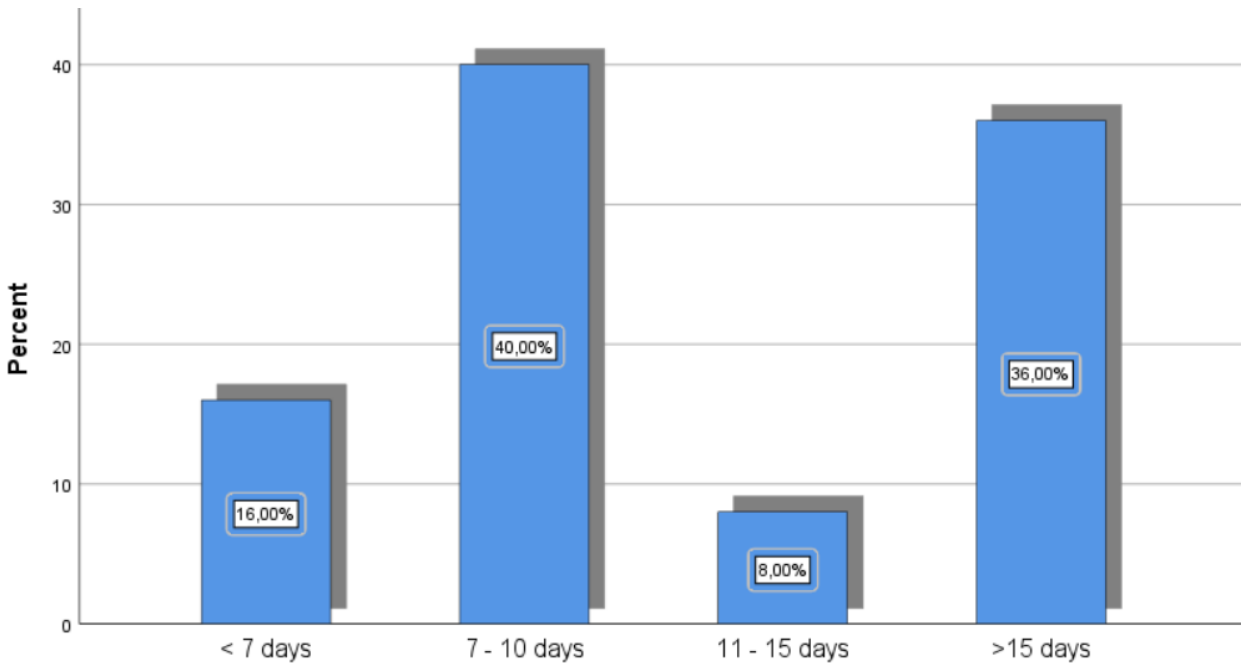


Figure 6: interval of time to conclude to clinical failure

The figure 6 represent the time in days before concluding to **clinical failure**. Forty percent of them evaluated the efficiency of treatment failure after 7 to 10 days, and 36% of them waited 2 weeks of treatment. Only 26% of the surgeons thought that an initial major output was a predictive factor of failure (with an output of at least 1000 ml for 16% of the surgeons).

Approximatively, half of surgeons disapproved prolonged drainage for refractory CL.

In the second part of the questionnaire, surgeons answered about the **use of lymphography** in their centers. To identify the patients who had the procedure in France, we renewed the question via e-mail to surgeons who gave a positive answer. Finally, we counted 5 centers besides Lille who have already used the procedure after a pancreatic resection.

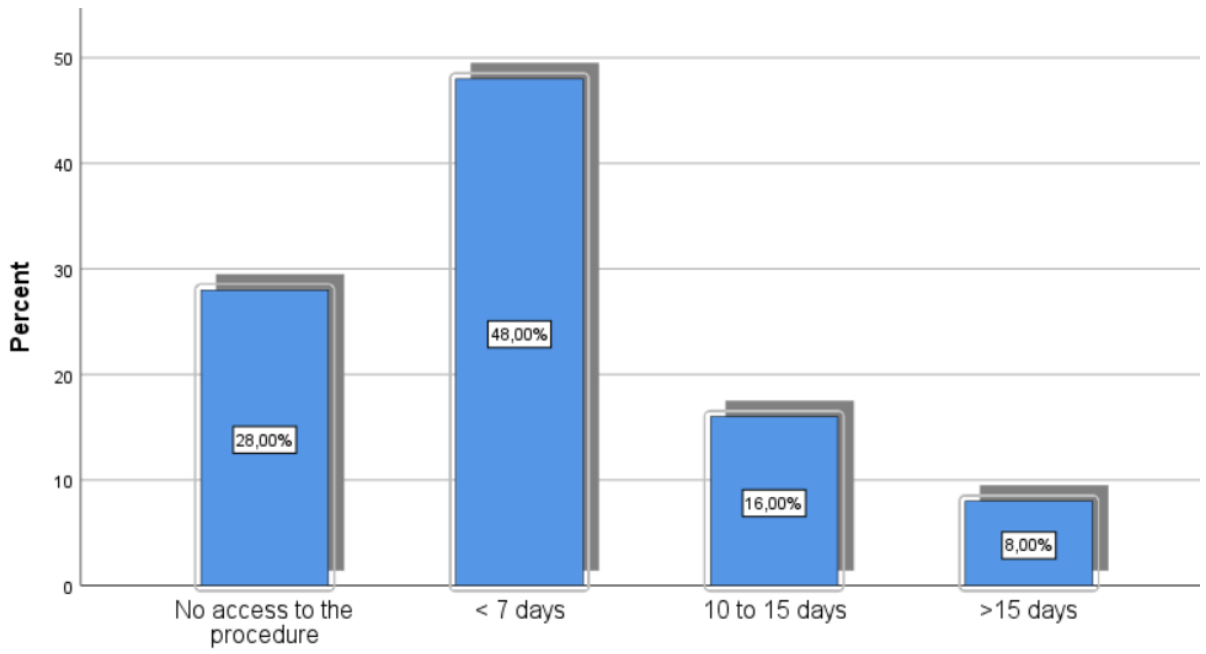


Figure 7: interval of time to access to lymphography in each center

Regarding lymphography, 28% of the pancreatic centers did not have any access to this procedure, whereas almost half of them can perform lymphography in less than a week.

About the success of lymphography, a quarter of expert surgeons estimated that most of the time the success was partial, and a quarter considered that it was complete.

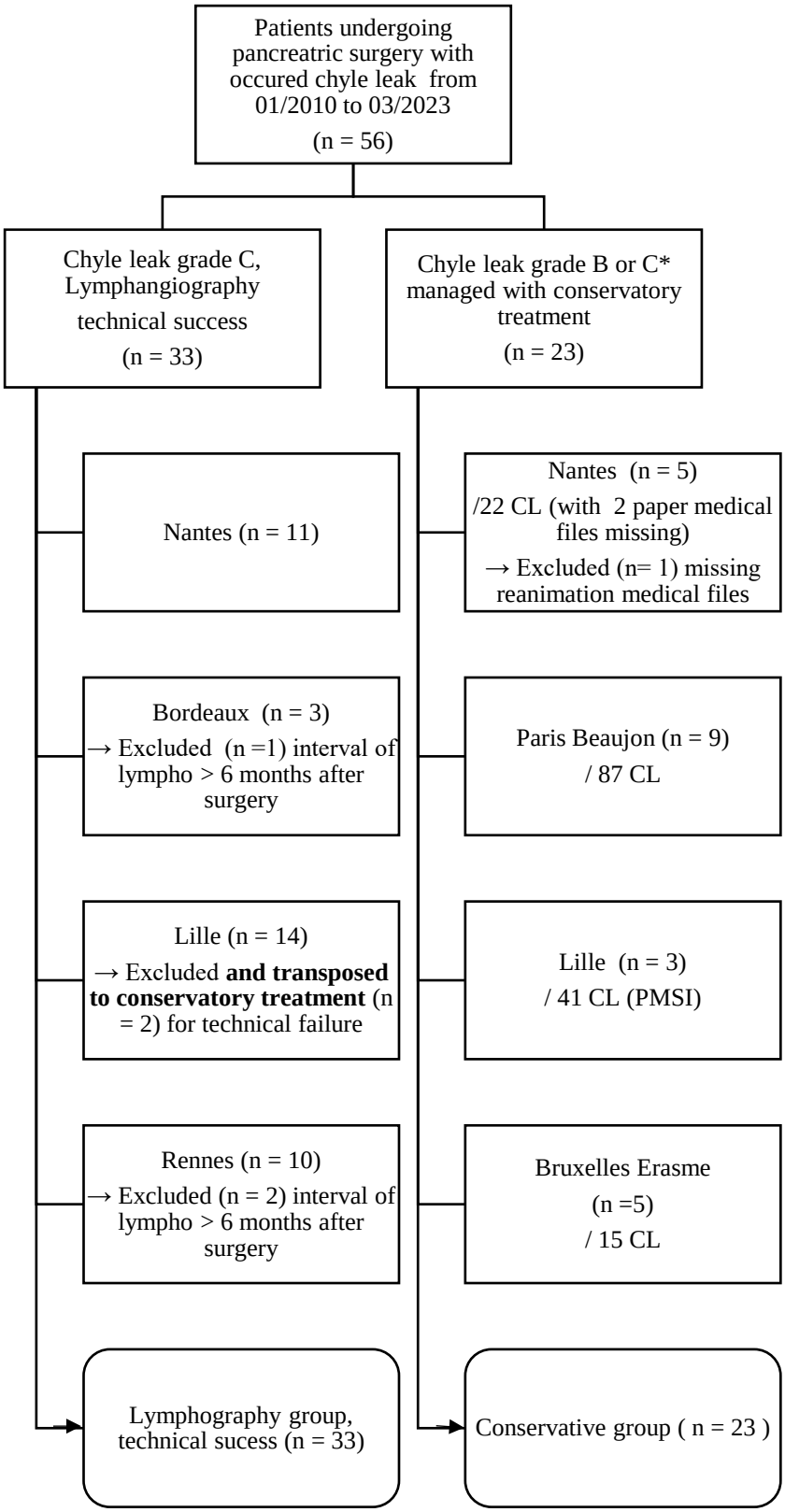
For the therapeutic strategy, 5 surgeons considered lymphangiography as an option after failure of a first line of conservatory treatment, and 10 surgeons after failure of a second line. Among surgeons who had already used lymphography, 4 approved an earlier lymphography in patients with a major output of the drain.

Finally, 40 % of the experts propose a second procedure of lymphography if the first failed to treat the CL.

Second part: Evaluation of lymphography a therapeutic tool in the management of chyle leak

Population

In overall, 56 patients with grade B or C were retrospectively identified. The repartition of patients between centers is depicted in the trial flow chart (figure 8). The lymphography group included 33 patients while the conservative treatment group included 23 patients.



*Refractory to MCT alone or combined with somatostatin analog

Figure 8: Flow chart

Baseline characteristics and operative details

Patient characteristics are shown in table 1. Groups are globally comparable except for age that was higher in LG (66 ± 13 vs 59 ± 12, p = 0.023).

Patients with locally advanced disease had more likely lymphography (21.2% vs 4.3 % p = 0.348). Furthermore, neoadjuvant treatment was mostly occurred in CG (34.8 vs 24.2, p = 0.549). Concerning the perioperative details, it seems more aorto-caval lymph nodes sampling was found in LG (45.5% vs 30.4 % p = 0.271). Two patients had multivisceral resection in the LG, and 4 in the CG. Regarding vascular resection, no arterial resection was performed in this study. The proportion of venous resection was similar in the two groups (33.3 % and 34.8 %). There was more active drainage in the LG, whereas passive or combined drainage was often used in the CG (p = 0.094).

About the tumor pathology, around a half of the patients in both groups had pancreatic cancer in both groups.

Table 1: Demographic characteristics, operative data, and histology

	Lymphography	**Conservative treatment**	p value
N	33	23	
Gender			1
Male	16 (48.5)	12 (52.2)	
Female	17 (51.5)	11 (47.8)	
Age (years)	66 ± 13	59 ± 12	**0.023**
BMI	23 ± 4	23 ± 5	0.677
Diabetes			0.866
No	19 (57.6)	14 (60.9)	
Insulin-dependent	6 (18.2)	5 (21.7)	
Non-insulin-dependent	8 (24.2)	4 (17.4)	
Calcific chronic pancreatitis			0.704
No	29 (87.9)	19 (82.6)	
Yes	4 (12.1)	4 (17.4)	
ASA Score			0.456
I	3 (9.1)	5 (21.7)	
II	22 (66.7)	12 (56.5)	

III	8 (24.2)	5(21.7)	
Albuminemia (g/L)	35.8 ± 7.8	37.6 ± 6.2	0.463
Tumor initial resectability			0.348
Primarily resectable disease	18 (54.5)	14 (60.9)	
Borderline resectable disease	4 (12.1)	6 (26.1)	
Locally advanced	7 (21.2)	1 (4.3)	
Not Applicable***	4 (12.1)	2 (8.7)	
Neoadjuvant chemotherapy			0.549
No	25 (75.8)	15 (65.2)	
Yes	8 (24.2)	8 (34.8)	
Neoadjuvant radiotherapy			0.331
No	28 (84.8)	17 (73.9)	
Yes	5 (15.2)	6 (26.1)	
Response to neoadjuvant therapy *			0.17
Complete response	0	0	
Partial response	4 (12.1)	6 (26.1)	
Stability	8 (24.2)	2 (8.7)	
Progression	0	0	
Type of Surgery**			0.521
PD	24 (72.7)	18 (78.3)	
Distal pancreatectomy	4 (12.1)	2 (8.7)	
Total pancreatectomy	2 (6.1)	1 (4.3)	
Exploration	2 (6.1)	0	
Other pancreatic resections	1 (3)	2 (8.7)	
Aorto-caval lymph nodes sampling			0.271
No	17 (51.5)	16 (69.6)	
Yes	15 (45.5)	7 (30.4)	
Missing	1 (3)	0	
Duration of surgery (min)	347 ± 108	390 ± 98	0.135
Intraoperative blood loss (ml)	674 ± 495.6	853.8 ± 544.4	0.245
Multivisceral resection			0.147
No	31 (93.9)	19 (82.6)	
Gastric resection	1 (3)	4 (17.4)	
Colic resection	1 (3)	0	
Venous resection			1
No	22 (66.7)	15 (65.2)	
Yes	11 (33.3)	8 (34.8)	
Type of venous reconstruction			0.636
Primary closure by suture	3 (9.1)	2 (8.7)	
Segmental resection, end-to-end anastomosis	7 (21.2)	3 (13)	
Interposition of venous conduit	1 (3)	1 (4.3)	
Peritoneal patch and longitudinal closure	0	2 (8.7)	
Arterial resection	0	0	
Type of peroperative drainage			0.094
Active	20 (60.6)	8 (34.8)	
Passive	12 (36.4)	11 (47.8)	
Combined	1 (3)	2 (8.7)	

No drain	0	2 (8.7)	
Number of resected lymph nodes	22 ± 11	22 ± 12	0.638
Histopathology			0.963
Pancreatic cancer	17 (51.5)	13 (56.5)	
Neuroendocrine tumor	3 (9.1)	1 (4.3)	
Pancreatitis	2 (6.1)	1 (4.3)	
Other	11 (33.3)	8 (34.8)	
T-Status			0.674
No residual tumor	0	1 (4.3)	
T1	6 (18.2)	3 (13)	
T2	9 (27.3)	6 (26.1)	
T3	7 (21.2)	6 (26.1)	
T4	2 (6.1)	0	
Not Applicable	9 (27.3)	7 (30.4)	
M-Status			0.279
M0	23 (69.7)	16 (69.6)	
M+	4 (12.1)	0	
Not Applicable	6 (18.2)	7 (30.4)	
R Classification			0.428
R0	20 (60.6)	18 (78.3)	
R1	7 (21.2)	3 (13)	
R2	0	0	
Not Applicable	6 (18.2)	2 (8.7)	

*	biochemical and radiographic response to neoadjuvant treatment
**	+/- splenectomy
***	Not applicable in non-malignant disease

Lymphography parameters

Among the 33 patients with technical success of lymphography, 28 (85%) underwent their first lymphography during immediate postoperative hospital stay. Five (15%) were discharged and readmitted due to persistent CL. The mean time between surgery and lymphography was 23 days (± 12) with a maximum of 58 days.

Two patients were excluded because of technically unsuccessful procedure due to failure of the puncture of the inguinal nodes (n = 1) or multiples extravasation of the contrast after several punctions without optimal opacification of the lymphatic vessels (n = 1).

Lymphography was mainly transnodal (69.6%). The leakage site was detected for 8 (24.2%) patients: L2-L3 for 4 patients, superior mesenteric artery area for one patient, inferior cave vein for 1 patient, the hepatic pedicle for 1 patient and localization wasn't determined for 1 patient.

The tables 2 shows the evolution of CL after lymphangiography procedure. As detailed in table 2, lymphography was associated with reduced mean of CL (1047 ± 1064 the day of the procedure vs 616 ± 614 at post-lymphography day 7).

In mean, patients were discharged 11 ± 9 days after the lymphography. In the same way, the drains were removed 11 ± 12 days after the procedure.

One patient (3%) had immediate lymph flow at the injection site after lymphography procedure, it spontaneously resolved.

Table 2: outcomes of the lymphography

	Lymphography
N	33
Delay between surgery and lymphography (days)	23 ± 12
Maximum	58
Lymphography approach	
Bipedal	10 (30.3)
Transnodal	20 (60.6)
Transnodal combined with sclerotherapy	1 (3)
Transnodal combined with punction of a collection of hepatic hilus	2 (6)
Volume of Lipiodol (ml)	15.5 ± 4.5
Maximum	25
Technical success of the lymphography	
Optimal	28 (84.8)
Under-optimal	3 (9.1)
Missing	2 (6.1)
Second attempt	
No	31 (93.9)
Yes	2 (6.1)
Criteria of technical success of the lymphography	
Pecquet opacification	
No	5 (15.2)
Yes	28 (84.8)
Thoracic duct opacification	

No	6 (18.2)
Yes	23 (69.7)
Missing	4 (12.1)
Identification of the chyle leak	
No	25 (75.8)
Yes	8 (24.2)
Site of the leak	
Near the SMA	1 (3)
At the level of L2-L3	4 (12)
In the front of ICV	1 (3)
Near the hepatic hilus	1 (3)
Missing	1 (3)
Average daily fluid output one day before the procedure (ml/d)	1268 ± 1076
Maximum	4980
Average daily fluid output the day of the procedure (ml/d)	1047 ± 1064
Maximum	4620
Average daily fluid output after the procedure (ml/d)	
At post-lymphography day 1	760 ± 998
Maximum	5000
At post-lymphography day 5	702 ± 899
Maximum	3200
At post-lymphography day 7	616 ± 614
Maximum	2100
At post-lymphography day 10	616 ± 543
Maximum	1410
Days between lymphography and hospital discharge?	11 ± 9
Maximum	43
Days between lymphography and drain removal	11 ± 12
Maximum	44
Complications of the procedure	
No	32 (97)
Yes	1 (3)

Comparative analysis

- **Postoperative complications**

In overall, no significant difference was found between the two groups regarding postoperative complications. Nevertheless, the conservative group was associated with higher rates of unplanned stay in intensive care unit (26.1% vs 9.1%, p = 0.139), abdominal collection (69.6 % vs 45.5 %, p =

0.057), radiologic drainage or paracentesis (52.2% vs 27.3%, p = 0.259), Clavien Dindo status > IIIa (26.1% vs 15.2%, p = 0.331), and reoperation (13% vs 3%, p = 0.295).

Furthermore, 90-day readmission was similar in the two groups (39.1% for CG and 39.4% for LG), as well as the length of stay (30 days for CG and 28 for LG). No 90-day mortality was reported.

Table 3: general complications and outcomes

	Lymphography (LG)	Conservative treatment (CG)	p value
N	33	23	
Surgical revision			0.295
No	32 (97)	20 (87)	
Yes	1 (3)	3 (13)	
Unplanned stay in intensive care unit			0.139
No	30 (90.9)	17 (73.9)	
Yes	3 (9.1)	6 (26.1)	
Postoperative pancreatic fistula			0.554
No	26 (78.8)	18 (78.3)	
Biologic fistula	5 (15.2)	5 (21.7)	
Grade B	2 (6.1)	0	
Postoperative biliary leak			1
No	32 (97)	23 (100)	
Yes	1 (3)	0	
Postoperative haemorrhage			1
No	29 (87.9)	20 (87)	
Grade A	2 (6.1)	2 (8.7)	
Grade B	2 (6.1)	1 (4.3)	
Postoperative abdominal collection			0.057
No	18 (54.5)	6 (26.1)	
Yes	15 (45.5)	16 (69.6)	
Missing		1 (4.3)	
Radiologic or surgical drain replacement			0.259
No	20 (60.6)	10 (43.5)	
Radiologic drainage or paracentesis	9 (27.3)	12 (52.2)	
Surgical drain replacement	3 (9.1)	1 (4.3)	
Endoscopic drainage	1 (3)	0	
90-days new onset diabetes or decompensation			0.79
No	14 (42.4)	11 (47.8)	
Yes	18 (54.5)	12 (52.2)	
Missing	1 (3)		
Portal hypertension *			0.753
No	26 (78.8)	17 (73.9)	

Yes	7 (21.2)	6 (26.1)	
Clavien Dindo status > III a			0.331
No	28 (84.8)	17 (73.9)	
Yes	5 (15.2)	6 (26.1)	
90-days mortality	0	0	
POD of discharge from hospital**	28 ± 12	30 ± 15	0.739
90-days readmission			1
No	20 (60.6)	14 (60.9)	
Yes	13 (39.4)	9 (39.1)	

* Due to mesenteric vein or portal vein stenosis or thrombosis

**** POD = postoperative day

- **Chyle leak management**

The diagnostic method was significantly different between the groups. In the two groups, diagnosis of CL was often based on clinical and biological data.

Moreover, first line of treatment was significantly different between two groups. MCT regimen with somatostatin analogues was the first treatment of CL in the Lymphography Group (54.5 % vs 8.7 % in CG, p <0.001).

Concerning the second line of treatment, 40% of patients in Conservative Group were treated by TPN (8.7% TPN alone, 21.7% combined with somatostatin analogs, 8.7% combined with MCT oral diet) vs 15 % in LG (p = 0.041). Somatostatin analogs were added to MCT-based diet for 15.2% of the patients in LG and 13% in the CG. Besides, 18,2% of the LG and 13 % of the CG had modified MCT-based diet as a second line, MCT enteral could be added or switched to MCT oral-diet. As third line of conservative treatment, 2 patients had TPN (associated to somatostatin analog for one patient), and one patient had somatostatin analog in CG.

The average daily fluid output at POD 14 was significantly higher in LG (1426 ± 1151 vs 702 ± 591, p = 0.01). Also, albuminemia before discharge was lower in the LG (23.4 ± 5 vs 27.5 ± 5.7, p = 0.013).

About the impact of chyle leak, 3 (9.1%) patients of the LG had concomitant chylothorax. Compared to Lymphography Group, Conservative Group had higher rates of radiologic drainage or paracentesis

(60.9% vs 39.4%, p = 0.174), prolonged drainage (95.7 % vs 78.8 %, p = 0.219), readmission for CL (26.1 % vs 15.2 %, p = 0,331), infected ascites (30.4 % vs 21.2 %, p = 0.535), prolonged parenteral nutrition (65.2 % vs 42.4%, p = 0.111). However, these differences were not significant. Similarly, there wasn't significant difference between two groups in time to drain removal between.

Table 4: management of CL and its outcomes

	Lymphography (LG)	Conservative treatment (CG)	P value
N	33	23	
Time until diagnosis of CL (days)	7	9	0.657
Diagnostic method			**0.016**
Clinical with appearance of drainage fluid (milky/white)	11 (33.3)	2 (8.7)	
Clinical and biological concentration in the fluid	22 (66.7)	19 (82.6)	
Biological only	0	2 (8.7)	
Assessment of the triglyceride concentration			0.069
No	12 (36.4)	3 (13)	
Yes	21 (63.6)	20 (87)	
Assessment of the chylomicrons concentration			0.089
No	25 (75.8)	12 (52.2)	
Yes	8 (23.5)	11 (50)	
First line of treatment			**<0001**
Oral/enteral MCT	15 (45.5)	19 (82.6)	
TPN combined with somatostatin analogs	0	2 (8.7)	
Oral/enteral MCT combined with somatostatin analogs	18 (54.5)	2 (8.7)	
Second line of treatment			**0.041**
Oral/enteral MCT	6 (18.2)	3 (13)	
TPN	5 (15.2)	2 (8.7)	
TPN combined with somatostatin analogs	0	5 (21.7)	
TPN combined with MCT-based diet	0	2 (8.7)	
Oral/enteral MCT combined with somatostatin analogs	5 (15.2)	3 (13)	
No second line	17 (51.5)	8 (34.8)	
Third line of treatment			
TPN associated with somatostatin analogs		1 (4.3)	
TPN combined with MCT-based diet		1 (4.3)	
Oral/enteral MCT combined with somatostatin analogs		1 (4.3)	
Average daily fluid output (ml/d) at diagnosis	1404 ± 714	1544 ± 1310	0.6
Maximum	3402	4800	
Average maximal daily fluid output (ml/d)	2363 ± 1537	3064 ± 2005	0.278
Maximum	8000	8000	

Average daily fluid output at POD 7 (ml/d)	1492 ± 1387	1273 ± 1054	0.473
Average daily fluid output at POD 10 (ml/d)	1462 ± 1429	1126 ± 863	0.877
Average daily fluid output at POD 14 (ml/d)	1426 ± 1151	702 ± 591	**0.01**
Average daily fluid output at POD 30 (ml/d)	823 ± 1159	1976 ± 2552	0.228
Albuminemia before the discharge (g/L)	23.4 ± 5	27.5 ± 5.7	**0.013**
Concomitant chylothorax			0.261
No	30 (90.9)	23 (100)	
Yes	3 (9.1)		
Radiologic drainage or paracentesis for CL			0.174
No	20 (60.6)	9 (39.1)	
Yes	13 (39.4)	14 (60.9)	
Surgical drain replacement for CL			0.688
No	28 (84.8)	21 (91.3)	
Yes	5 (15.2)	2 (8.7)	
Prolonged drainage			0.219
No	6 (18.2)	1 (4.3)	
Yes	26 (78.8)	22 (95.7)	
Missing	1 (3)		
Readmission for CL			0.331
No	28 (84.8)	17 (73.9)	
Yes	5 (15.2)	6 (26.1)	
Prolonged parenteral nutrition			0.111
No	19 (57.6)	8 (34.8)	
Yes	14 (42.4)	15 (65.2)	
Ongoing CL at time of discharge			1
No	17 (51.5)	12 (52.2)	
Yes	14 (42.4)	11 (47.8)	
Missing	2 (6.1)		
Infected ascites			0.535
No	26 (78.8)	16 (69.6)	
Yes	7 (21.2)	7 (30.4)	
Interval between surgery and drain removal (in days)	29 ± 16	34 ± 18	0.352

Most importantly, table 5 presents the results of main outcomes comparing patients who had early procedure (in the 25 postoperative days) to the Conservative treatment Group.

Patients who had early procedure had significantly less abdominal collection (36% vs 69.6%, p = 0.019), less radiologic drainage or paracentesis for CL (20% vs 60.9%, p = 0.007), less readmission for refractory CL (0% vs 26.1%, p = 0.008). There were less ascitic infection, Clavien Dindo > IIIa, 90-days readmission in general, and shorter interval to drain removal (25 ± 10 vs 34 ± 18, P = 0.099), yet it wasn't significant. No significant difference was found on the length of stay.

The mean average output at POD 14 was also significantly higher in the early lymphography subgroup similarly to. We didn't achieve significance on these outcomes for early procedure beyond 25 postoperative days.

Table 5: Comparison between early lymphography (≤25 days) and conservative treatment

	Early lymphography	Conservative treatment	p value
N	25	22	
Postoperative abdominal collection			**0.019**
No	16 (64)	6 (26.1)	
Yes	9 (36)	16 (69.6)	
Missing	0	1 (4.3)	
Radiologic or surgical drain replacement			**0.023**
No	18 (72)	10 (43.5)	
Radiologic drainage or paracentesis	4 (16)	12 (52.2)	
Surgical drain replacement	3 (12)	1 (4.3)	
Radiologic drainage or paracenthesis for CL			**0.007**
No	20 (80)	9 (39.1)	
Yes	5 (20)	14 (60.9)	
Readmission for CL			**0.008**
No	25 (100)	17 (73.9)	
Yes	0	6 (26.1)	
Infected ascites			0.068
No	23 (92)	16 (69.6)	
Yes	2 (8)	7 (30.4)	
Clavien Dindo > III a			0.279
No	22 (88)	17 (73.9)	
Yes	3 (12)	6 (26.1)	
90-days readmission			0.764
No	17 (68)	14 (60.9)	
Yes	8 (32)	9 (39.1)	
Interval to drain removal (in days)	25 ± 10	34 ± 18	0.099
POD of discharge from hospital	28 ± 11	30 ± 15	0.901

Discussion

This national survey gives a global overview of the heterogeneous management of CL in France. Contrarywise to some publications, most of the surgeons didn't consider major initial output as a predictor of clinical failure of the treatment. The most common treatment was a step-up approach with MCT-based diet followed in case of failure by TPN or somatostatin analog, or a combination of both. Concerning the lymphography, although most of the centers have access to the procedure, only 24% of them experienced it. The point of view of expert surgeons on the procedure success was controversial.

Data on invasive approaches in the management of refractory CL post-pancreatectomy is very poor in the literature. To our knowledge, this observational multicenter study is the first to compare lymphography and conservative treatment. Most of the previous studies were monocentric.

In line with precedent articles which described effectiveness of lymphography in the post-pancreatectomy setting (30,44), we found that early lymphography (≤ 25 postoperative days) might significantly reduce the incidence of abdominal collection, radiologic drainage, and readmission for refractory CL. Nevertheless, there were no significant difference between the groups on the length of stay and complications such as surgical revision, unscheduled admission in ICU and major complications (Clavien Dindo>IIIa).

About the diagnosis, lymphography provided accurate information on the leakage site only for 24 % of the patients, as it was previously described in the literature (30,44). In comparison with the recent study of *Rosa Klotz et al.* including 48 cases of lymphography, our cohort had more transnodal approach (70% vs 33%).

Besides, this cohort confirms the heterogeneity of the diagnostic assessment and therapeutic strategies with significant differences between the groups. It is important to mention that TPN was significantly more often used in CG (40%) than in the LG (15%) implying confounding factors. The effectiveness

of TPN is described in the literature and is increased by the adjunction of octreotide. It might explain the fact that patients were more likely to be undernourished in the LG just before discharge.

Even though refractory CL is rare, this article depicted the potential morbidity of refractory CL with unscheduled admission in ICU, abdominal collection that occurred for more than half of the patients, multiples radiologic drainage and prolonged parenteral nutrition required for half of the patient, 25% of infected ascites, 20% of readmission for this complication and increased length of hospital stay (with a maximal duration of 59 days). Therefore, diagnosis and appropriate treatment must be early undertaken for grade B.

About the risk factors, it is interesting to point out that no arterial resection was reported in the cohort that is in accordance with the outcomes of *Augustinus and al,* published in 2022 (37). Vascular resection was identified as significant predictor factor of CL, whereas in subgroups analyses arterial vascular resection was not. Our cohort include 34% of venous resection that is far more than the incidence in literature.

The findings of our study should be interpreted in light of several limitations. Contrariwise to previous publications, we didn't assess CL duration because no standardized definition was possible in the multicenter and retrospective design of the study. The evaluation of the recovery of CL was often at surgeon discretion at the follow-up appointment.

Although this cohort is among the largest in literature (considering grade B and C), statistically the sample size is quite small. Only 4 patients were excluded of the analysis, besides 3 of them had a very delayed lymphography (more than 6 months).

Because of the retrospective design of this study, we couldn't control for all confounding factors and data were missing mainly after hospital discharge (for the measurements of the output the days after the procedure).

Then, our data originated from prospective surgical registers, consequently there is a potential of underreporting CL. The surgical registers might not be exhaustive, and some data could be missing or filled out differently depending on the periods. This may probably be causing selection bias, as well as the fact that we include in conservative group patients coming from the same center as lymphography group. We can think that these patients didn't have the lymphography because they were responding to conservative treatment. Thereby, patients who had lymphography might have more severe leak. The higher output at POD 14 in the LG might reflect that.

By our approach, we tended to obtain large comparable groups. However, we faced the difficulty to find patients because no institutional prospective database on lymphangiography or CL after pancreatic resection currently exist. Very few French pancreatic centers defined CL as a monitored complication in their registers. In addition, grade B and C are rare with an incidence oscillating between 3,5 and 8,9% if we consider the main studies which used ISGPS classification. In Hospital of Beaujon Register, around 2750 pancreatic resections were performed between 2012 and 2023 including 9 refractory CL on 87 cases all grades confounded, representing around 0,3 % of the total population.

Our population is quite different from other published series. Excluding grade A and grade B that reply to MCT diet (+/- combined with somatostatin analogs), we intentionally decide to define refractory CL that makes more sense in clinical practice and was necessary to have a comparable group to LG.

We didn't assess pancreatic exocrine insufficiency that is leading to potential weight of loss and undernutrition (45). Also, we collected BMI that is a poor tool for assessing nutritional status, though that malnutrition has a real impact on readmission and postoperative infection.

Outcome parameters such as interval of time to drain removal and length of hospital stay might be influenced by concurrent complications other than chyle leak, even if pancreatic fistula was infrequent in our population. Postoperative portal hypertension may have induced a bias of confusion and increase readmission rate, even if the groups were comparable on that variable.

Considering the infrequency of refractory CL, additional randomized trials on the different therapeutics' strategies are unlikely (22). Further largest studies are needed to conclude to the benefit of early lymphangiography on refractory CL. Moreover, multicentric prospective studies should be focused on the outcomes of different conservative measures to create new guidelines for the management of CL, and predictors of failure to conservative treatment. Moreover, adherence to adjuvant chemotherapy and survival should be explored.

Conclusion

Early lymphography might have positive impact in the management of refractory chyle leak. Conservative treatment is currently the gold standard to improve patient outcomes and quality of life. Nevertheless, the conservative management of CL is heterogeneous and further studies should be undertaken to recommend this approach in surgeon practice.

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Annexes:

Table 6: Purposes of unscheduled stay in intensive care units

	LG	CG
N	3 (9.1)	6 (26.1)
Purpose of unscheduled stay in intensive care unite		
Hyponatremia and confusion due to CL	1 (3)	
Infected ascites and pneumopathy		1 (4.3)
Anasarca with infected CL, multiple organs failure		1 (4.3)
Infected CL		1 (4.3)
Infected ascites at POD 1		1 (4.3)
Thrombosis of mesenteric vein anastomosis		1 (4.3)
Haemorrhage	1 (3)	1 (4.3)
Iliac stent thrombosis	1 (3)	

Clavien Dindo score :

APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
	Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

AUTEURE : Nom : RAJAONARISON **Prénom : Hélène**

Date de soutenance : Le 20 octobre à 16 heures

Titre de la thèse : Prise en charge de la fuite chyleuse réfractaire post-pancréatectomie : résultats d'une enquête nationale française sur les pratiques et évaluation de l'intérêt de la lymphographie

Thèse - Médecine - Lille 2023

Cadre de classement : *Médecine*

DES + FST/option : *Chirurgie Viscérale et Digestive*

Mots-clés : Pancréas fuite chyleuse pancréatectomie lymphographie

Introduction. La fuite chyleuse est une complication peu fréquente après pancréatectomie dont la prise en charge est peu codifiée. Notre étude vise à i) étudier les pratiques en France sur la gestion de la fuite chyleuse puis ii) étudier l'intérêt de la lymphographie dans le traitement des fuites chyleuses réfractaires post-pancréatectomie.
Méthodes. Un questionnaire détaillant la démarche diagnostique et thérapeutique, concernant la fuite chyleuse après pancréatectomie, a été envoyé à 25 chirurgiens issus de 25 centres Français experts. Un screening a été réalisé secondairement permettant l'identification des patients traités par lymphographie en France. Un deuxième groupe de patients présentant une fuite réfractaire fut défini par la présence d'une fuite chyleuse de grade B ou C ne répondant pas au régime diététique TCM.
Résultats. La prise en charge de la fuite chyleuse est hétérogène en France. 24 % des centres ont eu recours à la lymphographie. 33 patients traités par lymphographie (30,3% par voie bipédieuse, 69,7% par voie transnodale) et 23 patients par traitement conservateur ont été identifiés entre 2010 et mars 2023. Comparativement au traitement conservateur seul, les patients traités par lymphographie dans les 25 jours suivant la chirurgie (n=25) avaient significativement moins de collection abdominale (36 % vs 69,6%, p = 0,019), de drainage radiologique (20 % vs 60,9%, p = 0,007), et de réadmission pour récidive (0% vs 26,1 %, p = 0,008).
Conclusion. La lymphographie précoce pourrait avoir un impact positif sur les fuites chyleuses réfractaires post-pancréatectomie. Des études complémentaires sont nécessaires pour recommander cette approche en pratique courante.

Composition du Jury :

Présidente :

Madame la Professeure *Stéphanie TRUANT*

Assesseurs :

Madame la Docteur *Mathilde VERMERSCH*

Monsieur le Docteur *Julien BOURRY*

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