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# The pancreatic lymphatic drainage network in the human fetus: diffuse, rich and borderless

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| Abstract: | Purpose: Pancreatic neoplasms are one of the most frequent causes of death by cancer worldwide. Lymph node (LN) involvement directly impacts the survival rate of patients with surgically resected pancreatic ductal adenocarcinoma. Although the patterns of lymph node metastatic spread are somewhat well described, the anatomy of pancreatic lymphatic system itself is complex and poorly understood. The aim of the study was to study precisely the lymphatic drainage of the pancreas in order to find an anatomic basis for lymphadenectomies in oncological surgical procedure. Methods: Using computer-assisted anatomic dissection (CAAD), we studied the duodeno-pancreato-splenic area of three human fetuses aged from 18 to 34 weeks of gestation. Results: We observed that pancreatic lymphatic drainage is a diffuse, rich and boundless network. We did not find any structural pattern to the lymphatic pathways either on the retro-portal lamina or the fatty tissue surrounding the caudal pancreas. Conclusion: According to our findings and compared to the anatomical definition of "meso", the term "meso-pancreas" doesn't appear to be a distinct anatomic entity and |

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# The pancreatic lymphatic drainage network in the human fetus: diffuse, rich and borderless


**Abstract:**

Purpose: Pancreatic neoplasms are one of the most frequent causes of death by cancer worldwide. Lymph node (LN) involvement directly impacts the survival rate of patients with surgically resected pancreatic ductal adenocarcinoma. Although the patterns of lymph node metastatic spread are somewhat well described, the anatomy of pancreatic lymphatic system itself is complex and poorly understood. The aim of the study was to study precisely the lymphatic drainage of the pancreas in order to find an anatomic basis for lymphadenectomies in oncological surgical procedure. Methods: Using computer-assisted anatomic dissection (CAAD), we studied the duodeno-pancreato-splenic area of three human fetuses aged from 18 to 34 weeks of gestation. Results: We observed that pancreatic lymphatic drainage is a diffuse, rich and boundless network. We did not find any structural pattern to the lymphatic pathways either on the retro-portal lamina or the fatty tissue surrounding the caudal pancreas. Conclusion: According to our findings and compared to the anatomical definition of "meso", the term "meso-pancreas" doesn't appear to be a distinct anatomic entity and should be considered only as a surgical concept. Also, the feasibility of lymph node procedure in pancreatic surgery is unsupported by this anatomic description.


## Introduction:

Pancreatic cancer is the fourth leading cause of death by cancer worldwide, making it one of the most lethal malignant pathologies in the world [1]. Moreover, the incidence of pancreatic ductal carcinoma has risen over the last few years and has become a pressing health care concern. The main prognostic factor is lymph node (LN) involvement in the surgical specimen [2-7] after the presence of positive margin resection in the surgical specimen. Within the last decade, numerous studies have been undertaken to understand the pattern of lymph node metastatic spread in pancreatic malignancies [8-10]. LN metastasis is the result of an invasion by tumor cells through the lymphatic vessels of the pancreatic gland. Recently, it has been shown another LN involvement model by direct tumor invasion which seems to be associated with a prognosis similar to the prognosis of patients without LN

metastasis [9,11,12]. However, lymphatic pancreatic anatomy is extremely complex and imperfectly known [13]. In the last decade, there has been a growing interest in two different fields: the utility of the LN sentinel procedure and the study of the "meso-pancreas". However, even if a mesentery has a precise anatomic definition [14], there is still debate regarding its existence[15-17]. For both topics, the interest is linked to the possibility of improving surgical approaches of pancreatic ductal adenocarcinoma (PDAC) and, therefore, the prognosis of patient suffering from PDAC. Computer-Assisted Anatomical Dissection (CAAD) technique is a recent technique [18-20], which has provided useful results in anatomical studies [18,19,21-30].

Thus, using CAAD, we aimed to study precisely the lymphatic drainage of the pancreas in order to find an anatomic map for lymphadenectomies in oncological surgical procedure.

## Methods:

### Ethics and background

The laboratory and this experiment were approval by the French Biomedical Agency (ethics approval number: PFS14-020). The laboratory of Experimental Anatomy of the University of Montpellier-Nîmes is part of the FETTAL project, (Fetal Enhanced Tridimensional and Translational Anatomical Landscape, co-directed by Professors Genevieve and Captier) facilitating the acquisition of fetal specimens. Fetuses were collected with signed consent of the parents and in accordance with the French Biomedical Agency.

The study was conducted in the laboratory of Experimental Anatomy at the University of Montpellier-Nîmes. The Gynecology-Obstetric Department of the Montpellier University Hospital and the Department of Medical Genetics, Reference Center for Developmental Abnormalities and Constitutional Bone Diseases, CHRU, Montpellier, France also participated in this study.

### Fetuses

We studied three human fetuses with estimated ages of 22+2, 23+5 and 33+6 weeks of amenorrhea (WA) (Table 1). Ages were determinated using sizing charts during the autopsies. Fetuses were obtained from therapeutic abortion or late miscarriage, with the donation of the fetus for research purposes approved by the parents, as specified in French law. These procedures were performed at the

Gynecology-Obstetric Department of the Montpellier University Hospital. These fetuses had no abnormalities of the abdominal cavity on antenatal ultrasound or on macroscopic dissection.

***Table 1: Histological data of the three studied foetuses***
*Sections were cut at 5µm, with each level separated by 50µm*
*(CRL: Crown-to-Rump length; FL: femur length; WA: week of amenorrhea; HE: Hematoxylin-Eosin; MH: Hematoxylin of Mayer; TM: Masson trichrome)*

**Macroscopic dissection and histology**

We removed the duodeno-pancreas and the spleen from each foetus as a single block. Samples were cut in 4-mm blocks then fixed at least for 48 hours in formalin (formaldehyde 10%). Then, the blocks were dehydrated and manually embedded in paraffin. We collected between three to five 5µm-thick paraffin sections, with each level separated by 50µm. Blocks were cut until no tissue remained in the block.

Sections were manually stained. After removal of paraffin and rehydration, sections were stained with either Hematoxylin-Eosin (HE), Mayer's Hematoxylin (MH) or Masson's Trichome (MT) (Table 1). The first section from each level, the reference one, was stained with HE or HM. All the other sections from each level were stained with Masson's trichrome, as it is well suited for distinguishing cells from the surrounding connective tissue.

**Microscopical study and three-dimensional modelization**

We utilised a Leitz Laborlux K microscope (Leica Microsystems, Germany) equipped with a Canon EOS 400D digital camera (Canon, Tokyo, Japan). We identified the different anatomical structures on the first section stained with HE. In Masson's trichrome stained sections, we observed the fasciae in blue which made it possible to identify lymphatic vessels and their relationship with the pancreatic gland. Lymphatic vascular elements were identified as a vessel with a single endothelial layer and the irregular distribution of the endothelial nuclei. To differentiate between capillaries and lymphatic vessels, a larger channel following the capillaries, we utilized the size of the lymphatic vasculature involved. We double-checked section if the differentiation was not unclear. Sections stained with Mayer's hematoxylin permitted the precise identification of peri-pancreatic lymph nodes.

All the sections were scanned using a high-performance scanner (Epson Perfection V850 Pro, Japan, 4,800 dpi). The sections were aligned semi-automatically using the Register Virtual Stack Slices plug-in of ImageJ software (National Institutes of Health, USA) and Adobe Photoshop (Adobe

Corporation, USA) [31]. At last, the aligned stack of images was recnstructed in three dimensions with WinSurf (Version 4.3, SURFdriver Software, Kailua, Hawaii, USA). Reconstruction was performed utilizing a WACOM Intuos (Saitama, Japan). This segmentation step was done with the help of the NLM's Visible Human Project® accessible via the IMAIOS platform [32,33].

## Results:

We identified a median number of peri-pancreatic lymph nodes of 65. Lymph nodes were almost equally distributed between the head (including the uncinate process) and the body-tail part as shown on Table 2. The lymphatic drainage was organized around the right and left celiac nervous plexus, inside these plexuses we found a significant concentration of lymphatic vessels. We also observed a lymphatic vascular network originating from the celiac ganglions, with lymph vessels running along nerve fibers towards the distal ends of the hepatic and splenic petyle="font-family:'Times New Roman'"> We also observed a nervous and lymphatic plexus all around the superior mesenteric artery.

***Table 2: Anatomic repartition of peri-pancreatic lymph nodes between right and left pancreas on fetal specimens (NE: not evaluated)***

### Study of the "meso-pancreas"

*Right pancreas*

Microscopic examination of stained sections revealed a quadrangular area extending from the posterior part of the right pancreas to the para-aortic region posteriorly and from the uncinate process to the right side of the superior mesenteric artery. This area was composed of cellular and fatty tissue containing blood and lymphatic vessels, nerves fibers and lymph nodes. These nerves fibers originated from the right celiac ganglion and formed part of right celiac plexus. We did not observe a peritoneal fascia surrounding all these anatomical structures (Fig. 1). The posterior lymphatic drainage appeared to be continuous with the para-aortic region (LN stations 16a and 16b of the Japan Pancreas Society classification) [34].

***Figure 1 - Microscopic characteristics (magnification factor 25) of the right retro-portal area, sections stained with Masson's Trichrome. Fetal sample 01F-001.***

*Large right retro-portal lymph node (1a). Absence of posterior peritoneal fold and partial view of the superior mesenteric nerve plexus on the right side of the figures (1b and 1c). Nervous fiber continuous with a right retro-portal lymph node (1d)*

*(ln: lymph node; nf: nervous fiber; p: uncinate process; v: superior mesenteric vein)*

Neither was visualized any anterior peri pancreatic fascia. From these observations; vascular, lymphatic, and nervous elements surrounding the pancreas were not organized as a meso.

3D reconstruction (Fig. 2) enabled a spatial observation of the anatomical relationships between structures and confirmed that this anatomical area did not contain all the right pancreatic vascularization as would be expected from a meso [14].

***Figure 2 - 3D reconstruction of the right retro-portal lamina (white translucid area) without (2A) or with (2B) anterior** (blue arrow) **and posterior (white arrow) cephalic LN (left antero-lateral view)***

*Left pancreas*

As far as left pancreas is concerned, similar observations were made. No peritoneal layer encompassing the pancreas and all its vascular components could be identified. The lymph nodes of the caudal part of the pancreas were in the splenic hilum. Some intra-pancreatic lymph nodes were also observed in the distal part of the caudal pancreas.

## Discussion

### Lymphatic drainage pathways

We observed, on one hand, that the lymphatic drainage was organized jointly with the nerve fibers emanating from the celiac ganglia: the right and left celiac plexuses with respect to the head of the pancreas. We have visualized a continuity between the lymphatic vascularization from the celiac trunk (on its entire circumference), the common hepatic artery on the right (towards the hepatic pedicle), the splenic artery on the left (towards the body and the tail) and posteriorly with the para-aortic ganglia.

These different drainage paths are consistent with the findings of Hirono who demonstrated the existence of seven drainage channels at the head of the pancreas, including the anterior and posterior pancreatico-duodenal arches, the hepato-duodenal ligament or the para-aortic region [35]. Thus, this lymphatic architecture did not seem to respond to the concept of sentinel node. Moreover, a study concluded that it was impossible to perform the sentinel lymph node procedure in the case of adenocarcinoma of the pancreas [36]. The issue of lymph node picking on some targeted lymph nodes (common hepatic artery lymph node / HALN or para-aortic lymph nodes / PALN) remains open.<

### Lymph node procedure or part of the standard lymphadenectomy?

*Para-aortic lymph nodes (PALN):*

First, the prognostic impact of lymph node involvement in para-aortic ganglia is discussed. According to a recent meta-analysis [36], PALN invasion was correlated with a poorer prognosis. Indeed, the median survival of PALN + patients was evaluated from 5 to almost 16 months according to several studies [37-40]. On the contrary, two studies dating from 2015 [41] and 2017 [42] ran counter to this conclusion. The retrospective study of Sho et al, including 822 patients, found that 12% of patients had positive PALN (PALN +) comparable to other studies [8,37-40] and a median survival of 16.7 months. They asserted that some PALN + patients could have a median survival better than would ordinarily be expected and that the main prognostic element was the number of positive para-aortic LN, rather than the positive character alone [41]. Sperti and al observed that PALN metastasis were not an independent factor of poor prognosis [42]. According to our anatomical observations (continuity of the lymphatic drainage between the para-aortic space and the trunk), the PALN should be considered as regional lymph nodes.

*Hepatic artery lymph nodes (HALN):*

As far as HALN is concerned, the literature is less rich but also divided. The studies by Cordera and al., [43] and LaFemina and al., [44] showed that lymph node involvement in the common hepatic artery was associated with reduced recurrence-free survival and decreased overall survival. On the contrary, Philips and al., [45] concluded that in lymph node positive patients survival was similar regardless of the lymph node status of HALN. Currently, the removal of the hepatic pedicle is an integral part of the lymphadenectomy in case of adenocarcinoma of the head of the pancreas and it seems to us that this anatomical site is not adapted to be the subject of a possible glandular picking determining the continuation of the surgical procedure.

**Limits**

CAAD is precise, inexpensive but extremely time-consuming since slice alignment has been performed manually. Most of the studies have been performed on human fetal specimens in order to gain time, rather than adult tissues. Indeed, studying fetal specimens has some advantages such as treating smaller samples and vascular anatomic structures (blood or lymph vessels) or nerves proportionally larger than in adult specimens. This time-consuming aspect has been the major drawback of this technique making it impossible deal with large samples in anatomical studies.

Another limitation of this analysis is the small number of fetal specimens studied. Despite of the obtention of the legal and ethics agreements, we faced difficulties to obtain fetal specimens. Indeed, to include a specimen we had to be sure that the fetus had no abnormalities of the abdominal cavity on antenatal ultrasound or on macroscopic dissection and that the Genetics Department did not need pancreas sampling during the autopsy. Moreover, it was not possible to repeat the same analysis on all the samples since the second sampling (fets 17F-099) was strictly limited to the pancreatic parenchyma without the loose fatty tissue surrounding the body and tail that does not allow evaluation of the ganglionic structures.

Unfortunately, because our fetal specimens were not fresh enough it has been impossible to compare our findings with immune-dissection using anti-LYVE1 antibodies.

## Conclusion

This anatomical study on human fetus using computer-assisted anatomic dissection provide additional data on pancreatic lymphatic anatomy. According to our findings and compared to the anatomical definition of meso, the term "meso-pancreas" doesn't appear to be a distinct anatomic entity. It should be considered only as a surgical concept. We observed a continuity between the lymphatic vascularization from the celiac trunk to the common hepatic artery (towards the hepato-duodenal ligament), to the splenic artery (towards the body and the tail) and posteriorly with the para-aortic ganglia. These different drainage paths are consistent with previous studies. In our opinion, the feasibility of lymph node procedure in pancreatic surgery is unsupported by this anatomic description.

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

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| ID | Sex | FL (mm) | CRL (mm) | Estimated age using sizing charts (WA + days) | Cause of death | Tissue quality | Stainings |
|---|---|---|---|---|---|---|---|
| 01F-001 | Male | 38 | 270 | 22 + 2 | Unknown | Not fresh | HE + MT |
| 17F-099 | Male | 43 | 310 | 23 + 5 | Myelomeningocele | Fresh | HM + MT |
| 17F-114 | Male | 65 | 700 | 33 + 6 | Achondroplasia | Fresh | HM + MT |

***Table 1: Histological datas of the three studied fetuses***

*(CRL: Crown-to-Rump length; FL: femur length; WA: week of amenorrhea; HE: Hematoxylin-Eosin; HM: Hematoxylin of Mayer; TM: Masson trichrome)*

| Localisation | 01F-001 | | 17F-099 | | 17F-114 | |
|---|---|---|---|---|---|---|
| | Number | Ratio (%) | Number | Ratio (%) | Number | Ratio (%) |
| Right pancreas | 33 | 53.2 | 31 | - | 33 | 47.9 |
| Left pancreas | 29 | 46.8 | NE | NE | 36 | 52.1 |
| | **62** | **100** | **31** | **100** | **69** | **100** |

***Table 2: Anatomic repartition of peri-pancreatic lymph nodes between right and left pancreas on fetal specimens***

***(NE: not evaluated)***

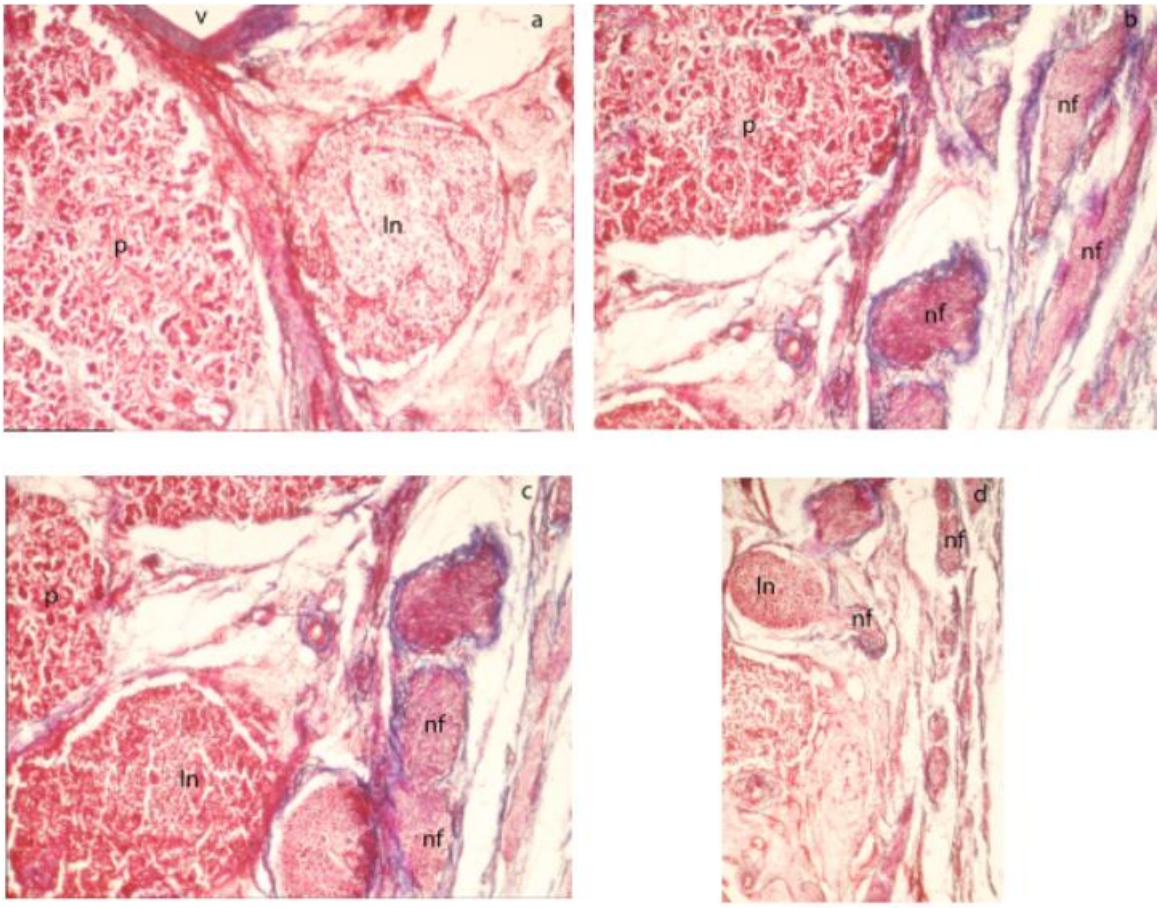


***Figure 1 - Microscopic characteristics (magnification factor 25) of the right retro-portal area, sections stained with Masson's Trichrome. Fetal sample 01F-001.***

*Large right retro-portal lymph node (1a). Absence of posterior peritoneal fold and partial view of the superior mesenteric nerve plexus on the right side of the figures (1b and 1c). Nervous fiber continuous with a right retro-portal lymph node (1d)*

*(ln: lymph node; nf: nervous fiber; p: uncinate process; v: superior mesenteric vein)*

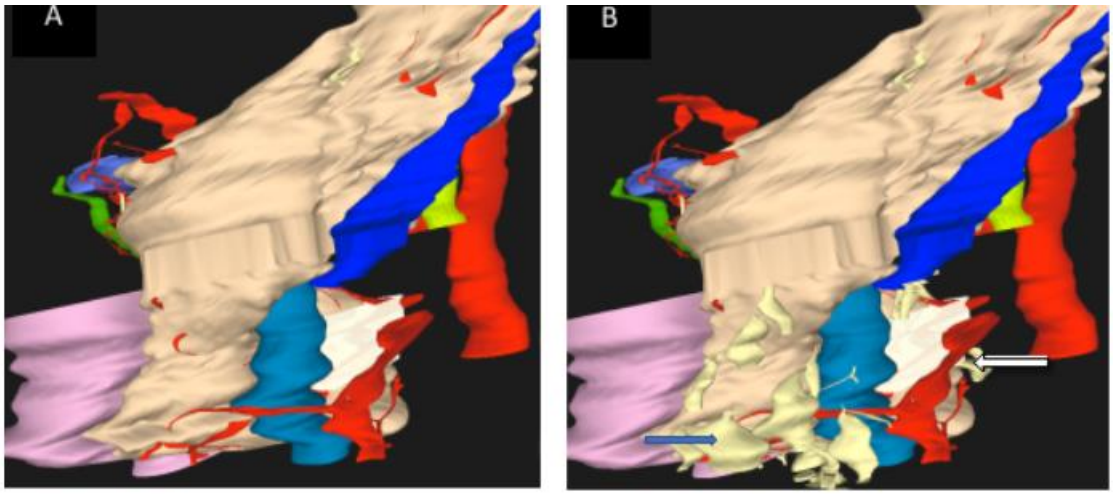

***Figure 2 - 3D reconstruction of the right retro-portal lamina (white translucid area) without (2A) or with (2B) anterior (blue arrow) and posterior (white arrow) cephalic LN (left antero-lateral view)***