General introduction, aims and outline of the thesis

GENERAL INTRODUCTION, AIMS AND OUTLINE OF THE THESIS

Endoscopic ultrasound (EUS)-guided tissue sampling was introduced in the nineties and offers a minimal invasive and accurate modality for real-time tissue acquisition [1, 2]. Since Vilmann first described its performance in solid pancreatic lesions, the technique has considerably evolved [3]. Today, its use is continuously growing, with an expanding role of tissue analysis in the era of patient tailored medicine [4]. Although EUS-guided tissue sampling can indeed provide a tissue diagnosis with a high level of diagnostic accuracy, its outcome strongly depends on the skills and experience of the performer, the sampling tools and techniques, and the way the tissue is handled and processed [5]. Consequently, EUS-guided tissue sampling has been subject to numerous innovations.

Adjusting and improving the design of EUS-needles has been and still is a major focus of innovation. Traditionally, tissue sampling was performed using fine needle aspiration (FNA) devices, which mainly harvest loose target cells for cytologic evaluation. Unfortunately, its yield depends on rapid on-site tissue evaluation (ROSE) by a dedicated pathologist, which is not generally available in most EUS-centers [6-9]. Furthermore, cytology is suboptimal for the identification of tumor invasion or the diagnosing and staging of specific diseases that require additional (immunohistochemical and molecular) testing, such as auto-immune pancreatitis, submucosal or stromal lesions, and neuro-endocrine tumors [10-12].

Fine needle biopsy (FNB) devices were introduced to overcome these limitations by offering the possibility to harvest histologically intact tissue fragments rather than loose target cells. Although the first devices, the TruCut™ (Travenol Laboratories, 1980) and Quick-Core® (Cook Medical, 2003) needles achieved acceptable diagnostic accuracy rates, their use was hampered by a rigid design, and somewhat difficult deployment of the cutting and firing system [13-15]. Consequently, the ProCore reversed bevel needle (Cook Medical, Ireland) was introduced in 2012. This needle has a reverse bevel located at the lateral side near the tip, which collects tissue when the needle is moved in a retrograde motion. However, the diagnostic performance of the ProCore needle was not convincingly better than the conventional FNA needles [16-20].

As a response to this, several novel FNB needles were designed and introduced. The first was an adjusted ProCore needle, only available as 20-gauge (diameter), which has a forward facing rather than a reversed bevel, and a more flexible design (Cook Medical, 2015). Secondly, the Fork-tip or SharkCore needle (Medtronic, 2016) was introduced, which has a characteristic prominent long tip-edge and an opposing beveled tip-edge with a total six distal cutting-edge surfaces. Last, the Franseen or Acquire needle (Boston Scientific, 2017) was launched, which has a large crown-tip with three cutting edges and a long insertion length. Due to the relatively recent introduction of the newest ProCore, Acquire and SharkCore needle, evidence on their performance is limited.

Parallel to these needle design innovations, EUS-sampling techniques evolved. One adaptation is the application of negative pressure. With the 'slow pull technique, the stylet is slowly

removed during sampling to create negative pressure at the tip of the needle, which should promote the harvest of tissue. Another way to increase negative pressure is through suction applied by using a vacuum syringe at the proximal end of the sampling device. So far, there is no convincing evidence for the benefit of either technique, or superiority of one over the other [21]. In addition, the 'fanning technique' was introduced, which is named after the fan-like-movement that is made with the needle within the lesion, allowing the lesion to be targeted from different angles, and collecting tissue from different areas of the target lesion. This technique has been proven to increase the diagnostic accuracy of EUS-guided tissue sampling, and is recommended by the European Society for Gastroenterology (ESGE) [22].

Another field of interest is EUS-tissue preservation and processing. Traditionally, specimens were collected with FNA-needles, and handled using the so-called 'smear technique'. Here, the collected material is smeared onto a glass slide and stained for pathological analysis. Unfortunately, smears are sensitive to preparation and contamination artifacts, causing suboptimal diagnostic accuracy rates [23, 24]. Obviously, it would be ideal to assign a dedicated pathologist to handle this on-site, but, as previously mentioned, many centers lack this service due to reimbursement and cost issues [6-9].

A way to bypass the vulnerable smear-preparation is to collect the sample in a liquid-based medium, the so-called liquid-based cytology (LBC) technique, i.e. ThinPrep, SurePath, Cellprep plus, and cell block. LBC makes samples less vulnerable to contamination or artifacts, since debris, blood and exudates can easily be removed from the collected tissue sample [25]. Furthermore, it allows for ancillary tissue tests, such as immunohistochemistry or molecular testing, that could previously only be performed on histological samples. Although these LBC tissue preparation techniques have proven their value in other specialties, such as gynaecology, its diagnostic benefit in gastroenterology remains to be established [24, 26-35].

Although innovations have evolved rapidly, the number of well-conducted studies to assess their value are running behind. Some adaptations may impact others. For example, if the new generation FNB needles turn out to outperform FNA, LBC preparations may become redundant.

AIMS AND OUTLINE OF THE THESIS

This thesis explores if and how technical factors can improve the diagnostic outcome of EUS-guided tissue sampling, by

1. gaining insight in the current practice of the endosonographer community
2. searching for the optimal EUS-sampling device
3. exploring ways to improve EUS-specimen preparation and handling

Part one focuses on the current clinical practice. Although EUS-guided tissue sampling is globally established, little is known about intercontinental practice variations. It is also unknown how

practice guidelines are locally implemented, especially since they lack firm scientific evidence. Therefore, **chapter 2** describes the practice patterns of EUS-guided tissue sampling in today's endosonographic community. An online questionnaire was sent out to 400 endosonographers from the United States (US), Europe, and Asia to identify differences and concordances between practice patterns, and to assess how they match the recommendations expressed in the guidelines of the American and European Society of Gastroenterology (ASGE and ESGE).

Part II aims to identify the optimal EUS-sampling device by focusing on the diagnostic performance of FNA and FNB needles. **Chapter 3** compares the diagnostic performance of a new FNB needle, the 20G ProCore FNB needle, to a conventional FNA needle, the 25G EchoTip Ultra device, in terms of diagnostic accuracy, tissue core yield, sample quality, the number of needle passes, and the number of adverse events in patients with a solid gastrointestinal lesion. A randomized controlled trial, the ASPRO study (Aspiration versus PROcore), was performed in 13 EUS-centers in the US, Asia, Australia, Europe, and the Middle-East.

Ideally, the performance of a diagnostic device is reproducible in expert and non-expert hands. **Chapter 4** compares the diagnostic agreement on the samples obtained in the above-mentioned trial amongst academic and non-academic pathologists. In addition, we assess if, and to what extent, the experience of the pathologist and the characteristics of the specimen influence diagnostic accuracy.

Instead of choosing one EUS-needle over the other, some advocate the use of FNA and FNB consecutively (dual needle sampling). **Chapter 5** therefore explores the yield of combined use of the 20G ProCore FNB and the 25G FNA needle in patients with a suspicious solid gastrointestinal lesion, and assesses the indication, the optimal needle order, and safety of this strategy. **Chapter 6** aims to identify the optimal sampling device, by providing an updated meta-analysis on the diagnostic performance of FNA compared to the new generation of FNB needles, including the ProCore reversed and forward facing bevel, the SharkCore, and the Acquire needle.

The third and final part of this thesis focusses on the optimization of the tissue samples that are collected through EUS-guided tissue sampling. It is known that the traditional, so called, smear-technique, harbors a high artifact rate. Since most EUS-centers do not have the resources for a dedicated, on-site pathologist to handle and prepare the collected tissue (ROSE), **chapter 7** explores if a one-day-hands-on tissue preparation training for endoscopy staff can improve sample quality and thus diagnostic accuracy. **Chapter 8** continues to find a solution to the suboptimal FNA-sample quality in centers lacking ROSE, by assessing the diagnostic benefit of tissue collection using LBC, with the ThinPrep and cell block technique.

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