Maastricht University

Near infrared fluorescence imaging in surgery

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Valorisation

Every surgical procedure incorporates a potential risk for complications. As described in the introduction of this thesis, part of these complications is caused by misidentification of the anatomy. A technique which improves intra-operative visualization of the anatomy could help avoid such complications, thereby prevent morbidity and mortality and lower health care costs. Near infrared fluorescence (NIRF) imaging concerns an innovative technique that might improve the intraoperative distinction of vital anatomical structures.

The aim of this thesis was to investigate a selection of the currently possible applications of NIRF imaging during surgery in order to prevent iatrogenic injury due to anatomical misrecognition.

Relevance of scientific results in this thesis

The use of the aforementioned technique (NIRF imaging) is aimed at preventing iatrogenic complications during surgery. Avoiding complications has multiple advantages. First, it prevents morbidity and, possibly, even mortality in patients. Second, complications are always accompanied with an increase in health care costs. As mentioned in the discussion of **Chapter 6,** the use of NIRF imaging is quite cheap, since indocyanine green costs only about 80 euros per vial, and for most applications, 1 vial can be used for multiple cases. The fluorescence modality is now incorporated in all new endoscopy systems and therefore does not result in additional costs. By preventing complications with a low-cost intervention, health care costs can be saved. Third, it is assumed that the use of NIRF imaging makes the surgical procedures easier. This means safer and faster, improving speed and outcome and thereby quality of care.

The three parts of this thesis cover four complications that are attempted to be prevented. The first complication is iatrogenic bile duct injury during laparoscopic cholecystectomy. In this case the use of NIRF imaging is applied for visualization of the cystic duct. We started a multicenter randomized controlled trial (**Chapter 2**) to investigate whether the use of NIRF imaging is actually as promising during elective laparoscopic cholecystectomies, as was suggested by earlier research. Next, in a systematic review combined with ex vivo experiments (**Chapter 3)** we found important factors to take into consideration while using the technique to obtain the best possible results. Also, a new fluorescent dye showed very promising images of the cystic duct, facilitating clear visualization of this structure during surgery (**Chapter 4**).

The second investigated complication is anastomotic leakage in colorectal surgery. Sufficient perfusion of the bowel at the location of the anastomosis is essential for

anastomotic healing. By visualizing the bowel perfusion with NIRF imaging, it is expected that anastomotic leakage will occur less often. A systematic review was performed, indeed describing a lower anastomotic leak rate when using NIRF imaging (**Chapter 6**). Based on these results, the use of NIRF imaging to prevent anastomotic leakage is increasingly becoming standard practice. Our experiments show a possible relation between subjective and measured fluorescence intensity of the bowel using NIRF imaging and anastomotic leakage (**Chapter 7**), further supporting its use in practice.

The third complication we focused on is ureter damage in colorectal surgery. The use of NIRF imaging could facilitate visualization of the ureter. When the surgeon knows the exact location of the ureter, ureteral damage seems to be less likely. We showed that the ureter could be visualized using methylene blue as a fluorescent dye (**Chapter 8**), however, without added value compared to the naked eye. Novel dyes were tested in pigs and seemed more promising by providing a clear visualization of the ureters during surgery (**Chapter 9 and 10**).

In part four of the thesis, unwillingly parathyroid removal during thyroid surgery was the subject of investigation. Using NIRF imaging in thyroid surgery to identify the parathyroid glands provided more certainty about the location of the parathyroid glands (**Chapter 11**).

Target population

This thesis contributes to the patients requiring surgery, especially elective laparoscopic cholecystectomy, colorectal surgery or thyroid surgery. Based on the results of this thesis, other researchers and surgeons might be encouraged and inspired to further explore aspects of these applications, thereby improving these further and exploring other applications of the technique, helping patients undergoing other specific types of surgery.

Innovation and future

At the start of this thesis, the use of NIRF imaging was merely used in research settings. The protocol of the RCT described in **Chapter 1** is the first started RCT regarding the intraoperative use of NIRF imaging. This RCT is the first step to assess whether the technique should be used in standard practice and should be incorporated in guidelines. The RCT in itself also improved the cooperation between surgeons, industry and research facilities since all these parties are actively involved in the RCT. However, although the RCT is an important step in the application of NIRF imaging, it might be unfit to illustrate the benefit of reduction of a complication with low frequency. This is the case with both bile duct injury and ureteral injury. The way to go here is prospective registration of all procedures performed in an international multicenter database. Our group is part of the international community of fluorescence imaging that is at present taking such initiatives. This community is also evaluating by several Delphi rounds the present status of application of the NIRF technique

in any field that has been described so far. All these initiatives have in part been stimulated by the contribution of our group, by its research and by its active communication.

The use of methylene blue as a fluorescent dye seemed not of added value in this thesis. The excitation and emission wavelength of MB is different compared to the more successful indocyanine green. To visualize these dyes, a fluorescence imaging system providing the right excitation wavelength and filtering the right emission wavelength are needed. Since the use of MB was somewhat disappointing in our experiments, these wavelengths are not incorporated in standard fluorescence imaging systems. This led to the development of new dyes on the same excitation and emission wavelength as indocyanine green, so that standard fluorescence imaging systems can be used. This shows that the results of research in NIRF imaging influences the actions of the industry and the products that are developed and made commercially available.

During the progression of this thesis the use of NIRF imaging has become standard practice in several hospitals, mainly for the application of assessing perfusion during anastomotic bowel surgery.

One of the problems in assessing perfusion of anastomotic surgery is the decision when the bowel is 'fluorescent enough'. A start to answer this question was made in **Chapter 7** of this thesis, although further research in a large cohort is needed to set a cutoff value of the fluorescence intensity that is ideally intra-operatively measured. Other future point of improvement of this technique include standard quantification of the signal (of which we made a start by writing **Chapter 5**), but also better dyes, better equipment and standard overlay of white and fluorescent light images

The application of NIRF imaging in thyroid surgery requires additional research to further assess the added value of the technique and improve the application. Because of the results produced in this thesis, one of the manufacturers of NIRF imaging systems is now re-evaluating their system to further improve the application of this technique in thyroid surgery. As soon as this system is available new research is required to re-assess the added value of this technique in thyroid surgery.