Minimally-invasive imaging of the small intestine

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Chapter 11

General discussion and future perspectives

Introduction

This thesis focuses on two minimally-invasive modalities used to investigate the small intestine: magnetic resonance (MR) enteroclysis and video capsule endoscopy (VCE). The studies on MR enteroclysis report on patients suspected of having a small-bowel neoplasm, and on a subset of patients with coeliac disease (CD), suspected of having refractory CD (RCD), a condition associated with small-bowel malignancies. The part on VCE describes the results of studies on two very specific indications: suspected RCD, and midgastrointestinal bleeding (MGIB) in patients using anti-thrombotic therapy. Additionally, this thesis highlights several aspect of quality in VCE, including safety and complication management, and assessment of bowel preparation. The last part describes the findings in patients who underwent both MR enteroclysis as VCE.

Two indications for small-bowel imaging, either with MR enteroclysis or with VCE, were not studied in detail in this thesis: Crohn's disease and MGIB in the general population. This is not because these are considered to be unimportant, on contrary: these are the most prevalent indications for small-bowel imaging worldwide. Because of that, many investigators have already studied these topics, and even though there is still much to learn, some general conclusions can be drawn regarding these two conditions. Regarding Crohn's disease, MR imaging provides excellent information on the presence and activity of this condition in the terminal ileum. VCE may be superior to MR in diagnosing superficial disease, but the risk of capsule retention is a large drawback. Regarding MGIB, it is important to realize that in a Western population, small angioectasia are the most prevalent cause. These minute, flat lesions are better detected by means of VCE than with any radiologic modality. Therefore, VCE is the first modality of choice, in patients MGIB without signs of small-bowel obstruction.

Small-bowel disorders are rare. For instance, the annual age-adjusted incidence of small-bowel adenocarcinoma is 17 per million, compared to 463 per million for colorectal adenocarcinoma.[1, 2] Of all patients with gastrointestinal bleeding, only 5% suffer from a focus located in the small bowel distal to the duodenum.[3] This relative rarity of small-bowel disorders often results in studies with relatively small numbers of patients being included. Additionally, the relatively low numbers of patients often results in pooling of patients with different small-bowel problems into larger, but consequently more heterogeneous groups. For instance, the study on the diagnostic accuracy of MR enteroclysis in the diagnosis of small-intestinal neoplasms included an 18-year old patient with Peutz-Jeghers syndrome undergoing elective small-bowel imaging, as well as an 80-year old patient with longstanding iron deficiency caused by small-bowel adenocarcinoma. A similar situation occurred in the studies on suspected RCD, where the number of patients was too small to allow for comparison of all subgroups, so pooling was necessary in order to draw more general conclusions. In the future, multicentre prospective studies are needed not only to confirm the results obtained in the retrospective studies, but also to further specify and compare the diagnostic accuracy of these tests in more specified and larger groups of patients.

Many studies on diagnostic accuracy of small-bowel examinations, including the study described in chapter 7 of this thesis, suffer from a lack of reference standard. This is understandable in light of the invasive nature of, for instance, double-balloon endoscopy (DBE) or surgery, which are therefore usually reserved for patients with positive findings in the imaging tests. Because of this, it is often not clear whether positive findings – often referred to by the term 'yield' – represent true-positive or false-positive findings. In the studies on diagnostic accuracy of MR enteroclysis and VCE in this thesis (chapters 3, 4, 6, and 10), care was taken to define positive findings as findings confirmed by histopathologic examination. Patients in whom small-bowel imaging did not reveal abnormalities very often did not undergo such an invasive reference test. In these circumstances, the absence of disease during long-term follow-up was considered the standard of reference.

Hopefully, this has helped establishing what '*it*' was, when '*it*' was found.

Part One: MR enteroclysis

The chapters in the first part of this thesis focused on MR enteroclysis.

In **chapter 2**, an overview is given of the radiological methods used to depict the small bowel. In general, it can be concluded that there is a transition from the classical small-bowel studies like small-bowel follow-through and conventional enteroclysis toward cross-sectional imaging like computed tomography (CT) enterography/enteroclysis and MR enterography/enteroclysis. It is important to realize that it takes quite a lot of time before the so-called state-of-the-art methods find their way into clinical practice, and that the results of novel modalities are often obtained in expert centres with highly experienced small-intestinal radiologists.

The study on MR enteroclysis in the diagnosis of small-bowel neoplasms (**chapter 3**) showed sensitivity and specificity in the diagnosis of small-bowel neoplasms was 0.91–0.94 and 0.95–0.97, respectively; the κ value was 0.95. These results indicate that MR enteroclysis is a reliable modality in patients suspected of having a small-bowel neoplasm. Additionally, the high level of agreement between the highly experienced and the moderately experienced radiologist suggests that reliable interpretation of MR enteroclysis studies is not accomplished by experts only. We found factors associated with malignancy were the presence of longer solitary nonpedunculated lesions, mesenteric fat infiltration, and enlarged mesenteric lymph nodes. These results were in line with other studies on MR enteroclysis in patients suspected of having small-bowel neoplasms.[4, 5] Recently, it was shown that similar diagnostic accuracy was obtained with MR enterography with intravenous administration of gadolinium chelate.[6] There are no comparative studies on MR *vs* CT in case of suspected small-bowel neoplasms. A study on the use of contrast- and water-enhanced multidetector CT enteroclysis showed overall accuracy of 84.7% for depiction of small-bowel neoplasms.[7] A more recent study found the overall sensitivity and specificity of CT enteroclysis in identifying patients with small-bowel carcinoid tumours were 100% and 96.2%, respectively.[8]

In patients with CD, small-bowel imaging is only required when RCD is suspected, because this is associated with high morbidity and mortality.[9, 10] We showed in **chapter 4**

that the presence of less than 10 folds per 5 cm jejunum, mesenteric fat infiltration and bowel wall thickening were associated with the aggressive RCD type II. Using these factors, a scoring system was composed. The sensitivity and specificity of this scoring system in diagnosing RCD type II was 0.87 and 0.96 respectively. The 5-year survival rate was 95% in patients with a negative MR score and 56% in patients with a positive MR score ($p < 0.0001$). Additionally, MR enteroclysis helped to identify the presence of seven of eight malignancies and to diagnose absence of malignancy in 58 of 60 studies. To date, no other studies on MR imaging in patients suspected of having RCD have been published.

It is likely that the future of radiological small-bowel imaging lies in cross-sectional imaging, since it provides direct information of intraluminal, luminal and extraluminal abnormalities, without its efficacy being hindered by overlapping bowel loops.[11] Whether CT or MR is the best imaging modality in case of suspected small-bowel neoplasms is unknown. CT is often more readily available than MR is, which is especially important in cases of acute small-bowel obstruction. The use of ionizing radiation is however a drawback of CT, first of all since it does not allow repeated dynamic imaging, and assessment of small bowel peristaltic activity is therefore not possible. This can result in intermittent spasm or peristaltic contraction during the CT examination being misdiagnosed as a small bowel neoplasm.[11] Secondly, the use of ionizing radiation impairs its use in children and in patients who require repeated or follow-up examinations. In general, in patients with small-bowel polyposis syndromes it is advised to perform radiological surveillance of the small intestine every 2 or 3 years, so in these patients MR seems the preferred modality. Future research comparing small-bowel CT and MR in patients suspected of having a small-bowel neoplasm should therefore focus on patients with suspected malignant neoplasms. Ideally, such studies should not only focus on diagnostic accuracy, but also compare cost-effectiveness of both modalities.

In general, enterography results in less distension of the jejunum than enteroclysis does.[11, 12] Especially in cases where optimal distension of the jejunum is required, the more invasive enteroclysis method maybe preferred. In patients with small-bowel polyposis syndromes or in patients suspected of having a malignant small-bowel neoplasm, the need for optimal distension of the jejunum warrants placement of a nasojejunal catheter. In patients in whom imaging of the ileum is the main goal, such as in patients with Crohn's disease, the less invasive enterography method maybe preferred.[13-15] Studies comparing enterography and enteroclysis in patients with suspected neoplasms ideally include comparisons of cost-effectiveness and patient tolerability, especially when patients requiring follow-up examinations are studied. Placement of the enteroclysis catheter is usually performed using fluoroscopy.[16] Future lines of investigation could compare this method with methods that do not involve ionizing radiation, such as endoscopic catheter placement, or placement using electromagnetic or other guiding systems.[17-19] Additionally, in patients with Peutz-Jeghers syndrome, it may be of interest to investigate the usefulness of MR-surveillance for pancreatic cancer, which is much more prevalent in patients with Peutz-Jeghers syndrome when compared to the general population.[20] In patients

suspected of having RCD an optimally distended jejunum is important for measuring the number of jejunal folds and bowel wall thickness, which are both important factors in the diagnosis of RCD type II. It is therefore not likely that enterography techniques can be used to establish the presence of these parameters.

Although the use of intravenous contrast is useful in assessing disease activity in Crohn's disease, its use in MR enteroclysis performed for suspected small-bowel neoplasms has not been established.[21] Our MR protocol did not include routine administration of intravenous contrast agents, such as gadolinium chelate. The diagnostic accuracy of this non-enhanced MR protocol was similar to that of a protocol that included contrast enhancement.[5] Interestingly, in MR enterography the use of gadolinium has been shown to increase the sensitivity for the detection of small-bowel tumours from 0.69 to 0.96.[6] Whether or not contrast enhancement may help in differentiation of tumour types remains open to debate.[12] Dynamic contrast-enhanced MR imaging parameters have been found to differ between patients with untreated CD when compared to patients using a gluten-free diet.[22] The clinical value of these observations is however not clear. Future studies on MR imaging in patients suspected of having a small-bowel neoplasm or RCD should also focus on the use of contrast enhancement protocols.

There are many technical developments in the field of MR imaging that eventually may find their way in to small-bowel imaging, including high-field MR imaging, diffusion weighted imaging and molecular imaging. These techniques can play an important role in tumour characterization, monitoring disease activity, monitoring therapeutic response etcetera. Peristalsis, respiratory motion, presence of bowel gas, affect all these techniques negatively. Therefore, these techniques remain challenging for small-bowel imaging.

Another interesting concept is combining MR imaging with fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging. Simultaneous acquired information on morphology and metabolism may be of interest in the diagnosis and staging of small-bowel malignancies, including gastrointestinal stromal cell tumours, small-intestinal metastasis and lymphoma.[23] To date, there is only limited data on the use of FDG-PET for small-bowel disorders, and even less on FDG-PET combined with cross-sectional imaging.[24] Peristalsis may interfere with projecting FDG-PET images on the MR enteroclysis images.

Part Two: Video capsule endoscopy

Chapter 5 provides an overview of the latest developments in VCE and flexible endoscopy of the small bowel. Additionally, the use of radiologic imaging in the prevention, diagnosis and management of complications of VCE and enteroscopy are discussed.

In **chapter 6** a study on the use of VCE in the investigation of patients with suspected RCD is presented. Proximal focal erythema and absence of progression of the capsule to the distal small intestine were independently associated with the presence of RCD II. Of the 28 patients with none of these two features, none died during follow-up, compared to 2 (13.3%) of the 15 patients with one of both features, and 4 (80.0%) of the 5 patients

with both features. Around the time this study was published, two other studies on the use of VCE in patients with nonresponsive CD were issued.

Atlas and co-workers compared VCE examinations performed in 84 controls, 30 patients with treated, uncomplicated CD and 42 patients with nonresponsive CD.[25] Villous atrophy was detected by VCE in 13 of 42 patients (31%) with nonresponsive CD, compared to none among 84 CD-free controls and 14 of 30 patients (47%) with uncomplicated CD. Single or multiple erosions/ulcerations of the gut were observed in 19% of nonresponsive CD patients, 18% of CD-free controls, and 31% of patients with uncomplicated CD (p = 0.35). Only two severe complications (ulcerative jejunitis and adenocarcinoma) were detected by VCE in patients with so-called nonresponsive CD. Additionally, nonresponsive disease was not further classified, so it is not known whether these patients had true RCD. The fact that only 7% of patients in the nonresponsive group had total villous atrophy suggests a low percentage of true RCD, which makes comparison with our data difficult.

Barrett and co-workers reported on a retrospective study that included VCE examinations from 11 patients with RCD type I, 18 patients with RCD type II, 9 patients with untreated CD and 45 controls without CD.[26] This group in general uses the same criteria for RCD as we do. They found villous atrophy and numerous or distally located ulcers were more frequent in patients with CD than in controls. Extensive mucosal damage on VCE was associated with RCD type II. Additionally, three cases of overt lymphoma were detected by VCE during the follow-up. Although the definition of VCE parameters differed from those we used, the abnormalities seen in patients with RCD type II were similar to those identified in our series.

Many studies on VCE focus on its use in patients MGIB. None of these studies specifically addressed MGIB in the presence of anti-thrombotic therapy. Since the use of these drugs – which can either cause small-bowel injury or aggravate blood loss from pre-existing lesions – is increasing, we conducted a study on VCE in patients with MGIB while using anti-thrombotic drugs (**chapter 7**). We identified a probable cause for gastrointestinal bleeding in 28 (50%) of the 56 studies. As other studies on MGIB had shown in more general populations, angioectasia were the most prevalent bleeding source in patients using anti-thrombotic therapy as well. Multivariate logistic regression analysis showed that reinstitution of anti-thrombotic therapy before VCE was carried out was the only independent predictor of positive VCE findings (OR 8.61; 95% CI, 1.20–60.42; p = 0.032). This finding was completely new, and offers interesting perspectives for future research, which could include studies on performing emergency capsule endoscopy in this patient category, before withdrawal of antithrombotic drugs is performed, or even the use of antithrombotic agents to provoke bleeding during VCE.

The study described in **chapter 8** is one of the largest single-centre studies on the risk of capsule retention. Capsule retention occurred in eight patients (incidence: 0.88%; 95% CI, 0.41%–1.80%), and caused acute small-bowel obstruction in six patients. Besides presenting data on the risk of retention, we also described the first series of

patients in whom the retained capsules were removed during DBE, which was successful in all patients. Five patients underwent elective surgery to treat the underlying cause of capsule retention. One patient required emergency surgery because of multiple small-bowel perforations. This study helped in establishing DBE as the first method of retrieval, instead of emergency surgery.[27-30] The risk of capsule retention remains an important issue in VCE, especially since it limits its use in patients with established Crohn's disease.[31]

The last study included in part two of this thesis describes a novel grading system to assess the quality of bowel preparation in VCE (**chapter 9**). We designed a computed assessment of small-bowel mucosal visibility based on the ratio of colour intensities of the red and green channel of the tissue colour bar. This score showed to be more reproducible than existing subjective scales. This computed scale could be integrated in VCE reading software. The scoring system can be used to compare different bowel preparation regimens. Additionally, the score could be used to score the quality of mucosal visualization in individual VCE examinations, which informs the physician on the reliability of an examination, especially when no abnormalities were detected. Currently, studies are performed to externally validate this scoring system, and to relate the scoring system to diagnostic yield. Additionally, a study is carried out to design a similar scoring system for capsule endoscopy of the colon.

The future of capsule endoscopy is bright: technical developments regarding image quality, battery-lifetime and more energy-efficient ways of data-transmission will results in more complete studies of the small bowel, and eventually of the complete digestive system.[32] The variable frame rate and double-camera system of a current type of colon capsule will probably be introduced in small-bowel capsules as well. Studies are needed to investigate whether such improvements also result in increased sensitivity and specificity of VCE. For this, it is essential that the VCE community quickly adapts to accepted standards of investigating and reporting data on diagnostic accuracy, such as those proposed in the STARD initiative.[33, 34]

The holy grail in this field is a completely steerable wireless device, that is able to obtain biopsy specimens, or even able to perform haemostatic interventions. Several prototypes of steerable capsules exist, but to date, no system is at a stage from which introduction into clinical practice can be expected to occur soon.[32]

Part Three: MR enteroclysis and video capsule endoscopy

Little is known on the comparative diagnostic accuracies of both state-of-the-art radiology and VCE for the investigation of conditions other than Crohn's disease. We performed a retrospective study on 77 patients who underwent both VCE as MR enteroclysis (**chapter 10**). This was a heterogeneous study population: findings included malignant neoplasms (n = 13), benign neoplasms (n = 10), RCD (n = 4), Crohn's disease (n = 2) and miscellaneous conditions (n = 10). Specificity of MR enteroclysis was higher than that of VCE (0.97 *vs* 0.84, p = 0.047), whereas sensitivity was similar (0.79 *vs* 0.74, p = 0.591). A more important finding was that in 2/32 (6.3%) patients with both negative VCE and

negative MR enteroclysis a positive diagnosis was established, compared to 5/11(45.5%) patients in whom VCE was positive and MR enteroclysis was negative (likelihood ratio 8.1; $p = 0.004$), 9/11 (81.8%) patients in whom MR enteroclysis was positive and VCE was negative (likelihood ratio 23.5; $p < 0.0001$), and all 23 patients in whom both VCE and MR enteroclysis showed abnormalities (likelihood ratio 60.8; $p < 0.0001$). These results suggest that VCE and MR enteroclysis are complementary modalities. VCE and MR enteroclysis can both be used to confirm negative or positive single-study findings. Additionally, both modalities can be used to further investigate patients with a high clinical suspicion of having small-intestinal disorders, despite negative single-study findings.

It is clear that in patients with MGIB VCE is superior to any radiological imaging modality, especially since in the Western world, minute and flat angioectasia are the predominant cause for MGIB.[35] Therefore, patients with suspected MGIB and no signs of intestinal stenosis should undergo VCE first.[36]

When there are accompanying symptoms suggestive of obstructive small-bowel disease, VCE is however contraindicated. In such cases, MR enteroclysis could be considered, and VCE could be reserved for patients in whom MR enteroclysis is normal. In case of suspected small-bowel neoplasms, there is increasing evidence that VCE is inferior to MR enteroclysis. A study from the Mayo clinics compared CT enterography with VCE for the diagnosis of small-bowel neoplasms. CT enterography detected tumours in 16/17 patients (sensitivity 94%) and VCE in 6/17 patients (sensitivity 35%). The matched paired difference in the sensitivity of the two techniques was statistically significant ($p = 0.004$).[37] Therefore, MR enteroclysis could be used as the first modality, and VCE could be performed only if MR enteroclysis is normal. In both situations, abnormalities depicted with MR enteroclysis could be further investigated with device-assisted enteroscopy, in order to obtain a certain histologic diagnosis.

In the future, prospective studies on restricted categories of patients would hopefully shed more light on the way VCE and MR enteroclysis can be used efficiently. Such studies could include studies on polyp surveillance in patients with for instance familial adenomatous polyposis or Peutz-Jeghers syndrome, patients suspected of having a malignant small-bowel neoplasm or patients suspected of having RCD.

Conclusion

There is no such thing as 'the best' small-bowel imaging modality. The rarity of small-bowel diseases – especially those involving a risk of malignancy – often do not allow for an approach completely guided by the principles of evidence based medicine: a tailor-made approach is often necessary. Therefore, close collaboration between all disciplines involved in the care of patients with small-bowel disease is mandatory. In order to make optimal use of the modalities available, gastroenterologists and radiologists need to be aware of the advantages and drawbacks of both radiologic as endoscopic imaging techniques. These principles should also guide research in this area: we should not aim to determine

superiority of one modality over another, but rather invest in research that learns which diagnostic algorithm to use in which situation, in order to have the most reliable, quick, safe, and cost-effective diagnostic path for our patients.

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