The role of endoscopic imaging for an improved diagnosis of colorectal neoplasia

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Publication date
2010

Summary and future perspective

Summary

The department of Gastroenterology and Hepatology of the Academic Medical Centre in Amsterdam has had a strong interest in novel endoscopic imaging techniques for many years. This thesis comprises the recent research of our department on endoscopic imaging in the colon. The purposes of our work were to obtain evidence for supporting to or dissuading from using advanced endoscopic imaging techniques in clinical practice and to supply a methodological background for future research in this field.

In chapter 1 of this thesis, written in the beginning of the year 2007, the existing evidence on the use of advanced colonoscopic imaging techniques was reviewed. Scientific evidence had been merely confined to chromoendoscopy (CE) at that time. Since the recognition of the existence of flat and depressed colonic lesions in western countries, many efforts were made to improve the visualization of these subtle lesions that appear to harbour a particularly high risk of malignant progression. Chromoendoscopy seemed to do quite well with respect to improving the detection of these lesions, especially in patients with ulcerative colitis (UC). Narrow-band imaging (NBI) and autofluorescence imaging (AFI) had scarcely been evaluated in a structural way, which prohibited us from doing any recommendation regarding their routine use in clinical practice. When critically appraising the trials that favoured CE however, we found that in these studies the CE procedures were performed by highly experienced endoscopists only and also that the examination time during CE was increased, possibly acting as confounder. Nevertheless, CE seemed to be a good candidate for implementation in surveillance programs for high risk patients (e.g. UC patients), but its labour-intensive and time-consuming nature has prevented its widespread use thus far.

As NBI became commercially available worldwide during the time span of this thesis, more and more research on NBI was published. Despite the analogy between NBI and chromoendoscopy, our systematic review in chapter 2 demonstrated that NBI did not improve the detection of sporadic adenomas and UC-associated neoplasia. With respect to endoscopic differentiation of neoplastic from non-neoplastic lesions, pooled data-analysis of diagnostic accuracy studies demonstrated that NBI had a comparable accuracy as CE. With a sensitivity of 92% and specificity of 86%, NBI appeared to have potential to be used in clinical practice for differentiation of innocent hyperplastic polyps and premalignant adenomas.

When critically reviewing the existing literature on endoscopic imaging techniques and their role for improving the detection of premalignant lesions, we found that highly different study designs and statistical analyses had been used despite similar objectives. Although endoscopic imaging techniques are diagnostic tests which appear to have to be evaluated by using a classical diagnostic accuracy study design, i.e. comparing index test results against reference standards, no feasible reference standard appears to exist for the evaluation of colonoscopic techniques with respect to their ability to detect polyps. We therefore evaluated the most commonly reported study designs in chapter 3, focusing on their validity and efficiency. The parallel randomized design has been used most but, although it is free from bias, its power turned out to be disappointingly low. Endoscopic researchers should carefully consider whether a cross-over study design can be used instead since this design has much greater power, but at the same time will

be more cumbersome for patients and endoscopic researchers. Whatever research design is finally chosen, reporting of possible confounders (i.e. gender, age, race, indication of colonoscopy, experience of endoscopists, degree of bowel preparation, examination time, and type of endoscope used) is important and should be considered an obligation.

Our randomized cross-over study described in chapter 4 was the first to report on the use of endoscopic tri-modal imaging for the diagnosis of colonic polyps. With respect to the detection of sporadic adenomas, the miss-rate of AFI was 20% *vs.* 29% by high-resolution endoscopy (HRE). Although the difference was not statistically significant, one may question whether the small sample size of the study may have accounted for this. In case the difference of 9% in adenoma miss-rate is considered clinically relevant, additional research seems necessary to further evaluate the value of AFI. As secondary outcome, we found that the sensitivity, specificity and accuracy of the Kudo classification by NBI for differentiating neoplastic from non-neoplastic lesions were 90%, 70% and 79% respectively, with a negative predictive value of 90%. These figures appear too low for routine use in clinical practice. Interestingly, an algorithm which combined information from AFI and NBI was able to reach a putative sensitivity, specificity and accuracy of 98%, 74% and 84%, and a negative predictive value of 98%. This algorithm was noticed during the analysis of the results and considered all AFI-purple as well as all AFI-ambiguous lesions with Kudo type III-V on NBI as suspicious for adenoma; whereas AFI-green and AFI-ambiguous lesions with Kudo type I-II on NBI were considered non-suspicious.

The algorithm from chapter 4 was subsequently assessed in the image evaluation study in chapter 5. Images of polyps taken with AFI and NBI were assessed by both experienced and non-experienced endoscopists. This study showed that experienced endoscopists had better interobserver agreement for NBI (κ=0.77) than AFI (κ=0.33), whereas non-experienced endoscopists had better interobserver agreement for AFI (κ=0.58) than NBI (κ=0.33). These findings suggest that AFI-colour is easier to assess by endoscopists without experience in endoscopic imaging than the more sophisticated Kudo classification. A more remarkable finding was that the simultaneous presentation of AFI- and NBI-images increased the interobserver agreement among non-experienced endoscopists, and significantly improved the overall specificity. It appeared that the combination of AFI and NBI synergistically improved their value regarding differentiation. The abovementioned algorithm led to a significantly increased accuracy (85%) when compared to AFI alone (74-77%) or NBI alone (63-70%). This finding was confirmed in the second part of the study among 6 non-experienced endoscopists from 5 non-university hospitals, who only received a training of 17 image examples and then already had a 'moderate' interobserver agreement (κ=0.53). Their sensitivity, specificity and overall accuracy were 96%, 69% and 80% which seem very reasonable for practical use.

In chapter 6 we addressed the use of HRE, AFI and NBI for differentiating polyps in patients with hyperplastic polyposis syndrome (HPS). This study demonstrated that the diagnostic accuracies of AFI and NBI were both unsatisfactory for differentiating sessile serrated adenomas from hyperplastic polyps (accuracies 55%; upper limit of the 95%-confidence interval was 68% at best). To the contrary, differentiating conventional adenomas from serrated polyps was well possible using both pit pattern and vascular pattern intensity with NBI. In the end, proximal colonic location combined with a size ≥3mm proved to be the most accurate variable for dif-

ferentiating sessile serrated adenomas from hyperplastic polyps with a diagnostic accuracy of only 76%. We therefore concluded that endoscopic tri-modal imaging appeared inadequate for differentiation purposes in patients with HPS.

Regarding the detection of polyps in HPS, we performed a randomized cross-over trial comparing polyp miss-rates between NBI and HRE in chapter 7. The miss-rate of NBI was 10% *vs.* 36% of HRE (odds ratio 0.21; 95%-CI: 0.094-0.45). Our study showed that NBI was of particular value for the detection of flat serrated adenomas. During NBI, all serrated polyps appeared light in colour, thereby increasing the contrast between these polyps and their surrounding colonic tissue, which might explain the lower miss-rate of serrated polyps by NBI. Therefore NBI appears to be the technique of first choice for colonoscopic surveillance of HPS patients. With respect to differentiating hyperplastic polyps from sessile serrated adenomas and conventional adenomas, NBI again proved unsatisfactory in this study. The achieved diagnostic accuracy was only 65% which is far from clinically practical.

In chapter 8 we presented our retrospective study assessing the yield and clinical value of random biopsies that were taken during a 10-year period of colonoscopic surveillance in UC patients at our institution. The yield of neoplasia by random biopsies was 16% per-site, 5.7% per-colonoscopy, and 7.5% per-patient. Hence, 84% of all detected neoplastic sites could be visualized by conventional colonoscopy. In addition, only 1 of 167 patients (0.6%) who underwent surveillance colonoscopy in our study had a relevant change in clinical management due to positive random biopsies. As the yield of random biopsies was low and their clinical consequences were very limited, we proposed to omit random biopsies during UC surveillance and use the extra endoscopy time for pancolonic CE.

Chapter 9 described the first randomized cross-over study comparing first generation (prototype) NBI to conventional colonoscopy for the detection of neoplasia in patients with UC. This study showed that NBI led to the detection of twice as many suspicious lesions and hence to more targeted biopsies, which however did not lead to an improved detection rate of neoplasia. Both NBI and conventional colonoscopy failed to detect approximately one third of all patients with neoplasia, reflecting the low sensitivity of these methods. Only the sequential use of both techniques would have detected 11 out of 12 patients with neoplasia.

In chapter 10, the use of endoscopic tri-modal imaging in patients with longstanding UC was described. Patients were randomized in a cross-over design to AFI or HRE showing a neoplasia miss-rate of 50% for HRE *vs.* 0% for AFI (p=0.036). In this study, the yield of random biopsies was low as well (0.1% of biopsies showed neoplasia). The fact that all neoplasia was coloured purple on AFI and that random biopsies did not detect neoplasia in additional patients, underlines the question whether random biopsies should be taken if AFI reveals a normal 'green' appearing colon. As secondary outcome measure, the accuracy of NBI for differentiating between neoplasia and non-neoplastic mucosa was assessed and again proved unsatisfactory with a sensitivity of 75% and specificity of 81%. The abovementioned algorithm combining AFI and NBI had a putative sensitivity of 100% and specificity of 77%. We concluded that endoscopic tri-modal imaging appeared promising for UC surveillance.

In chapter 11 new-generation NBI with a different spectral filter and improved brightness was compared against high-definition endoscopy (HDE) in patients with longstanding UC. Once again NBI proved suboptimal by detecting only 81% of neoplastic lesions *vs.* 69% by HDE (p=0.727). The disappointing results may be explained by the fact that NBI provided a darker overall image as well as by the fact that the high-definition technology may have levelled out any difference in contrast between NBI and HDE. Our secondary objective in this study was to evaluate NBI for real-time differentiation of neoplastic and non-neoplastic mucosa. Both the Kudo classification and the vascular pattern intensity proved unsatisfactory for this purpose as their respective sensitivities were only 76% and 80%, and their respective specificities 66% and 72%. In summary, NBI did not improve the detection of neoplasia and also was not accurate in the differentiation of neoplastic and non-neoplastic colonic mucosa.

As in published studies on patients with UC endoscopic confocal laser endomicroscopy (eCLE) had been shown to be a good candidate for accurate differentiation of neoplastic from non-neoplastic mucosa, we evaluated the feasibility and diagnostic accuracy of probe-based CLE (pCLE) in chapter 12. We found that pCLE was feasible during UC surveillance, even though in our first experience the colonoscopy time was significantly increased. Technical enhancements appear necessary to provide images of better quality and increased experience should reveal whether enhanced technical skills would improve the ease-of-use of pCLE. Furthermore, the achieved diagnostic accuracy (sensitivity 65%; specificity 82%) and reproducibility (κ=0.47; full agreement 83%) were justifiable in view of our learning phase and blinded assessments, but are currently falling short when compared to the accuracy that was achieved with real-time HDE and NBI.

Future perspective

Chromoendoscopy

Although pancolonic CE has shown promising results in several randomized studies regarding an improved detection of adenomas and UC-associated neoplasia, the technique remains cumbersome, operator-dependent, and is regarded by some as messy. Methodological inadequacies in the reported trials and the limited number of trials in general setting have prevented its widespread recommendation in guidelines. Future research should therefore focus on the practicability of CE in daily general practice (evaluating time and costs) and on training of less experienced endoscopists. Head-to-head comparisons of CE versus 'push-on-a-button' endoscopic imaging techniques have yet not been performed and would be an interesting field of future research. Finally, as it remains unknown which dye (methylene blue, indigo carmine, others) is preferred for usage, research aiming at answering this question seems also to be important.

Narrow-band imaging

Thus far, NBI did not lead to an improved detection of adenomas or UC-associated neoplasia compared to white-light endoscopy. High quality colonoscopy with HRE or HDE may be sufficient for these purposes. Future research on this topic should focus on comparing of CE with HDE and/or NBI. However, NBI did improve the detection of serrated polyps in HPS patients

when compared to HDE. Therefore, NBI may better prevent the occurrence of interval cancers during endoscopic surveillance of these patients. Future research should confirm our findings which may lead to new practical recommendations for this patient population.

Regarding the differentiation of neoplastic from non-neoplastic polyps, NBI appears to have a reasonable diagnostic accuracy as demonstrated by our systematic review. We believe that NBI is sufficiently accurate to be used routinely for this purpose among low- or intermediate-risk patients since in this population the negative predictive value of NBI will be high. However, as the negative predictive value among large polyps or within high-risk patients may be lower, future research should focus on assessing the accuracy of NBI among these subgroups. Since NBI is currently widely spreading throughout the world, research should aim to define a learning curve for NBI with respect to differentiation. In addition, we should aim to use only one validated and accurate classification system since many different classification systems (e.g. Kudo classification, vascular pattern intensity) have been used until now.

Autofluorescence imaging

Whereas NBI has failed to demonstrate an improved detection of sporadic adenomas and UC-associated neoplasia, AFI has shown promising results in this thesis. Although the relative gain in sporadic adenoma detection may be low, the results of our studies and those of others prompt further research to this technique for adenoma detection. Especially in patients with UC we found that AFI should be further evaluated. In particular, comparisons between AFI and CE may be very interesting.

Since the combined use of AFI and NBI in endoscopic tri-modal imaging has shown to further improve the diagnostic accuracy with respect to differentiating neoplasia from non-neoplastic lesions, the algorithm combining AFI- and NBI-information needs further validation. The comparison between this algorithm and the promising confocal laser endomicroscopy (which is in fact in-vivo histopathology) could lead to interesting results.

Conclusion

This thesis has shown that advanced endoscopic imaging techniques are more and more used in general colonoscopic practice and are frequently objective of scientific research. By critically appraising the literature we have summarized the current level of evidence for using these techniques and we have provided recommendations regarding which study design is the most efficient and valid for evaluating these techniques. These recommendations may be useful for future endoscopic research.

By our own clinical studies we demonstrated that the use of endoscopic imaging techniques is feasible during colonoscopy among patients who are under surveillance for polyps as well as for UC-associated neoplasia. In particular, the combined use of AFI and NBI in 'endoscopic tri-modal imaging' appears easy-to-learn and has shown promising results regarding an improved detection of UC-associated neoplasia as well as an improved differentiation of neoplastic and non-neoplastic mucosa. Since we were the first to demonstrate these advantages of 'endoscopic tri-modal imaging' in relatively small studies, additional research is necessary to confirm our findings in a broader and general clinical setting.

As NBI is currently becoming commercially available worldwide, we want to make a last special note on this technique. The sole use of NBI appears to fall short with respect to improving the detection of neoplastic polyps and UC-associated neoplasia, but seems valuable for differentiating polyps in daily practice. Colonoscopists should be aware of the learning curve of NBI for this purpose and should take notice of the level of risk that patients harbour of having premalignant lesions when using NBI for differentiation. Among patients with hyperplastic polyposis syndrome however, NBI may be better than standard colonoscopy for detecting polyps but needs further confirmation in larger trials.