What makes an expert Barrett's pathologist?

Concordance and pathologist expertise within a digital review panel

van der Wel, M.J.

CHAPTER 9

CLINICAL IMPLEMENTATION OF A DIGITAL NATIONAL EXPERT PATHOLOGY REVIEW PANEL FOR DYSPLASTIC BARRETT'S ESOPHAGUS

L. C. Duits, M. J. van der Wel, E. Klaver, C. A. Seldenrijk, G. J. A. Offerhaus, M. Visser, F. J. W. ten Kate, K. Biermann, L. A. A. Brosens, M. Doukas, C. Huysentruyt, A. Karrenbeld, G. Kats-Ugurlu, J. S. van der Laan, G. van Lijnschoten, F. C. P. Moll, A. H. A. G. Ooms, R. E. Pouw, J. G. P. Tijssen, S. L. Meijer, J. J. G. H. M. Bergman

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ABSTRACT

Background & Aims

Expert pathology review is recommended in case of dysplasia in Barrett's esophagus (BE). To facilitate these review requests in the Netherlands a digital national pathology review panel was previously developed. Using data from the first 80 consecutive panel review requests, we aimed to develop a clinical implementation algorithm to effectively and parsimoniously utilize participating pathologists.

Methods

Eight expert pathologists independently reviewed 80 consecutive consultations for a community-based diagnosis of low-grade dysplasia (LGD) or indefinite for dysplasia (IND). After the independent review a group consensus diagnosis was obtained for all cases. We calculated the mean agreement and disagreement with the consensus diagnosis for a scenario with review by one, two or three pathologists.

Results

In 90.6% of cases in which a single expert pathologist confirmed the dysplasia diagnosis, this diagnosis was concordant with the final consensus diagnosis. When the referral diagnosis was down-staged to NDBE by a single expert pathologist this individual diagnosis was concordant with the consensus diagnosis in 76.2% of cases. This increased to 94.6% when a second pathologist confirmed NDBE, and in only 2.6% of these cases the consensus diagnosis was LGD/HGD.

Conclusion

For the majority of dysplasia review requests in the Netherlands, review by a single expert panel pathologist will suffice. Only in a minority of patients review by three expert pathologists is required to inform management decisions. This clinical implementation algorithm will enable effective utilization of and will limit workload for participating pathologists.

Limitations

These findings are only valid for a homogenous panel of pathologists (as has been demonstrated in our previous work for our national pathology review panel) and a Dutch community-based selection of cases.

INTRODUCTION

Barrett's esophagus (BE) is defined by replacement of the squamous epithelium lining the distal esophagus by columnar epithelium containing goblet cells. [1] BE is the precursor lesion to esophageal adenocarcinoma (EAC) which is thought to develop through subsequent stages of non-dysplastic BE (NDBE), low-grade dysplasia (LGD) and high-grade dysplasia (HGD). [1,2] EAC, when detected at a symptomatic stage, has a dismal prognosis and known BE patients are therefore offered regular endoscopic surveillance in order to detect neoplasia at a curable stage. [2,3] When HGD or EAC is detected patients are offered endoscopic or surgical treatment, mainly dependent on depth of invasion and patient fitness. [2–4]

LGD is an important risk factor for neoplastic progression, yet this is a difficult histological diagnosis with a significant interobserver variation amongst community practice pathologists. [5–10] Recent studies have, however, demonstrated that the risk of neoplastic progression increases significantly when LGD is confirmed by an expert pathology panel. [11–14] Additionally, confirmed LGD carries a high risk of more advanced prevalent neoplasia elsewhere in the BE segment. [12] All current international BE guidelines recommend expert histology review of all LGD cases and to consider strict endoscopic surveillance or prophylactic treatment when the diagnosis is confirmed. [2,3,15] Expert Barrett's pathology assessment is, however, not well defined, divergent in quality and access to this service is not widely available. Furthermore, transfer of microscopy slides across institutions is time consuming and carries the risk of slides getting damaged or lost in the process. In the Netherlands we have therefore developed a national, web-based, digital histology review platform. [16–20] As described previously, the original pathology review panel consisted of five expert BE pathologists (FJWtK, CAS, SLM, MV, and GJAO), considered as such by their (international) peers. These five 'core' pathologists have an extensive track record in the field of BE related pathology, with >10 years of experience (range 10-30 years). Each has a weekly case load of 5-10 BE cases, which is enriched for dysplastic cases due to the referral setting of their institutions. All five pathologists have participated in the previous Barrett's advisory committee for many years, each has co-authored >10 peer reviewed publications in this field and have participated in multiple international training programs for endoscopists and pathologists (www.best-academia.eu).

Previous studies by our group have described the stepwise development of the Dutch national digital pathology review panel for BE in detail. In short, we first showed that digital microscopy, versus traditional microscopy using glass slides, yielded comparable histological assessments of BE biopsies. [16] Second, we collected a digitized set of sixty whole endoscopy slides of Barrett's cases enriched for dysplasia and developed quality criteria to evaluate pathologists' histological assessment. Based on the performance by our five core pathologists we calculated bench mark quality scores for potential future expert panel pathologists. [17] Third, we assessed and confirmed the added value of p53 immunohistochemistry for the homogeneity of the group of (aspirant) expert panel pathologists. [18] Fourth, we evaluated the performance of 10 aspirant panel pathologists in relation to the preset bench mark criteria and demonstrated that three pathologists qualified for the panel, resulting in a new 'core' of eight expert panel pathologists. [19] Most recently, we have evaluated the performance of the eight core expert pathologists and seven aspirant pathologists in a real-time setting using 80 referral cases submitted to the digital review panel. A consensus meeting was held after 40 and 80 cases. At the end of that study an additional six pathologists met the benchmark quality criteria, resulting in a homogenous group of 14 pathologists available for the expert review panel. [20]

This study aimed to develop an algorithm based on the assessments of the previously defined eight core pathologists and the corresponding consensus diagnoses in order to effectively and parsimoniously utilize the pathologists participating in the panel. We hereby aim to minimize the number of required reviews per case which will enable us to limit and evenly distribute the workload across participating pathologists.

METHODS

Setting

The Dutch Barrett's Pathology Review panel has been developed according to the stepwise evaluation as described in the introduction section. Requests for consultation were submitted by gastroenterologists or pathologists via a dedicated website (www.barrett.nl), upon which histology slides were requested by the back office of the review panel. All slides were digitalized, using a scanner with a x20 microscope objective (Slide, Olympus, Tokyo, Japan). Digitized slides were checked for focus and acuity

by the study coordinator, re-scanned if necessary and stored on a secure server. Subsequently pathologists were invited by e-mail to review the slides. All pathologists independently assessed the digital cases using the virtual slide system Digital Slidebox 4.5 (Slide path, Leica Microsystems, Dublin, Ireland), allowing them to select areas of interest and adjust the focal depth of view, similar to conventional microscopic assessment.

Short summary of the underlying assessment study [20]

This study includes the first 80 consecutive BE surveillance cases with an original diagnosis of IND or LGD that were submitted to the Dutch Barrett's Pathology Review panel. The assessments of the eight core expert pathologists who met the benchmark quality criteria previously were analyzed in this study.

Cases were scored according to the modified Vienna criteria for gastrointestinal neoplasms. Diagnostic categories were: NDBE, LGD, HGD or more, or indefinite for dysplasia (IND). Since a panel review diagnosis of LGD and HGD have identical clinical consequences (i.e. referral to an expert BE center for endoscopic work-up) we combined these categories as a single outcome.

The original five core expert BE pathologists had individually assessed all cases at an earlier stage. A consensus diagnosis was considered as such for cases in which their individual scores showed a 4/5 or 5/5 agreement. For all discrepant cases a consensus diagnosis was reached in group discussions for these five pathologists.

Outcomes and data analysis

The outcomes of this study were mean percentage of LGD/HGD review diagnoses corresponding with a final consensus diagnosis of NDBE (false positives) and mean percentage of NDBE review diagnoses corresponding with a consensus diagnosis of LGD/HGD (false negatives). These outcomes were assessed for a scenario with a single expert pathologist' review as well as for expert review by two and three pathologists.

We cross tabulated the assessment of each individual pathologist, each potential pair and each potential triplet of pathologists with the consensus diagnosis. For each scenario (single, double and triple expert pathology review) we then calculated the

mean percentages of agreement and disagreement with the consensus diagnosis in the cross tabulation.

RESULTS

We included 80 consecutive expert panel review requests with a community diagnosis of LGD or IND. Median age of patients at time of endoscopy was 67 years (IQR 61-72) and 68% was male. Cases contained a median of 8 biopsies (IQR 4-12) obtained from a median of 2 BE segment levels (IQR 1-4). The original community diagnosis was LGD in 61% of the cases and IND in 39%. The baseline characteristics for this study are summarized in **Table 1**.

Table 1: Demographic and baseline characteristics

Characteristic	All patients (n=80)
Age, *y*, mean ±SD*	65.9 ±8.0
Male, n (%)	59 (74)
Length of Barrett's segment, *cm*, median (IQR†)	4.5 (2-8)
Circumferential Barrett's extent, *cm*, median (IQR)	2 (0-5)
No. of levels biopsied, median (IQR)	2 (1-3)
Initial community diagnosis, n (%)	
Indefinite for dysplasia	32 (40)
Low-grade dysplasia	48 (60

*SD, standard deviation; †IQR, interquartile range.

Expert review by a single pathologist

For a scenario where a single expert pathologist performs the initial review, mean percentages of agreement with the consensus diagnosis are depicted in **Table 2**. In 76.2% (range 68.8-93.8) of cases in which a single expert pathologist down-staged the diagnosis to NDBE, this down-staged individual diagnosis was concordant with the groups' consensus diagnosis. Incorrect down-staging (individual pathologist diagnosis NDBE, consensus diagnosis LGD/HGD) was observed in 13.1% (range 0-16.7%). When a single pathologist diagnosed the case as LGD/HGD, this was found to be in agreement

with the final consensus diagnosis in 90.6% (range 78.6-97.8) of cases. Over-diagnosis was found to be relatively rare: in only 3.7% (range 0-8.9) of the experts' LGD/HGD diagnoses, the consensus diagnosis was NDBE.

Table 2: Percentages of concordance and discordance between review diagnosis and consensus diagnosis for 80 dysplastic Barrett's esophagus cases submitted for expert histology review. Depicted as the mean percentage for eight individual pathologists.

Diagnosis of a single pathologist	Mean scores for eight pathologists	Consensus diagnosis		
		NDBE	IND	LGD/HGD
NDBE	Mean % (SD*)	76.2 (8.6)	10.7 (5.9)	13.1 (5.5)
	Range	68.8-93.8	0-18.8	0-16.7
IND	Mean % (SD)	15.5 (10.9)	48.8 (16.8)	35.7 (8.5)
	Range	0-27.3	33.3-75.0	25.0-46.7
LGD/HGD	Mean % (SD)	3.7 (3.2)	5.7 (4.1)	90.6 (6.7)
	Range	0-8.9	2.1-12.5	78.6-97.8

*SD, standard deviation

Expert review by two pathologists

Mean percentages of agreement with the consensus diagnosis for different combinations of expert review outcome in a scenario with two pathologists are depicted in **Table 3**. When both the first and second expert pathologist diagnosed NDBE, this diagnosis was found to be concordant with the consensus diagnosis in 94.6% (range 77.8-100); in 2.6% (range 0-11.1) of cases the consensus diagnosis was LGD/HGD. When the two expert pathologists agreed on the diagnosis LGD/HGD, the consensus diagnosis was concordant in a mean 96.8% (range 88.6-100) of cases.

The percentages of agreement between the review diagnosis and the consensus diagnosis in case of disagreement between the two expert pathologists can be appreciated in **Table 3**.

Table 3: Percentages of concordance and discordance between review diagnosis and consensus diagnosis for 80 BE cases submitted for expert histology review. Depicted as the mean percentage for each potential pair of pathologists (56 pairs) in case of agreement between these two pathologists (top panel) and in case of disagreement between these two pathologists (bottom panel).

Agreement between pairs of pathologists	Mean scores for 56 pairs of pathologists	Consensus diagnosis		
		NDBE	IND	LGD/HGD
NDBE	Mean % (SD*)	94.6 (7.0)	2.8 (4.8)	2.6 (3.8)
	Range	77.8-100	0-16.7	0-11.1
IND	Mean % (SD)	8.9 (12.0)	74.4 (20.1)	16.7 (13.5)
	Range	0-33.3	33.3-100	0-40
LGD/HGD	Mean % (SD)	1.2 (1.4)	1.9 (2.3)	96.8 (3.2)
	Range	0-4.8	0-9.1	88.6-100
Disagreement between pairs of pathologists	**Mean scores for 56 pairs of pathologists**			
NDBE – IND	Mean % (SD)	39.9 (33.9)	38.4 (33.2)	12.8 (22.4)
	Range	0-100	0-100	0-100
NDBE – LGD/HGD	Mean % (SD)	27.5 (28.6)	14.7 (17.9)	54.2 (34.5)
	Range	0-100	0-50	0-100
IND – LGD/HGD	Mean % (SD)	4.3 (9.6)	26.6 (25.5)	69.2 (25.8)
	Range	0-50	0-100	0-100

*SD, standard deviation

Expert review by three pathologists

The results of a scenario with expert review by three pathologists are depicted in **Table 4**. When all three pathologists agreed on the NDBE, IND or LGD diagnosis, the consensus diagnosis was concordant in 99.2% (90.1-100), 89.1% (33.3-100) and 99.0% (92.5-100) respectively. When two pathologists diagnosed NDBE and one pathologist diagnosed IND, the consensus diagnosis was LGD/HGD in only 1.8% (0-100) of cases. For a majority diagnosis of LGD/HGD with a single IND diagnosis, the consensus diagnosis was LGD/HGD in 79.8% (0-100) of cases and NDBE in 20.2% (0-100) of cases.

Table 4: Percentages of concordance and discordance between review diagnosis and consensus diagnosis for 80 BE cases submitted for expert histology review. Depicted as the mean percentage for each potential triplet of pathologists (336 triplets) in case of agreement between these three pathologists (top panel), in case of a majority diagnosis (middle panel) and in case of disagreement between these three pathologists (bottom panel).

Agreement between triplets of pathologists	Mean scores for 336 triplets of pathologists	Consensus diagnosis		
		NDBE	IND	LGD/HGD
NDBE	Mean % (SD*)	99.2 (2.5)	0.5 (2.0)	0.3 (1.7)
	Range	90.1-100	0-9.1	0-9.1
IND	Mean % (SD)	6.5 (14.6)	89.1 (19.1)	4.3 (12.2)
	Range	0-50	33.3-100	0-50
LGD/HGD	Mean % (SD)	0.5 (1.1)	0.5 (1.2)	99.0 (1.8)
	Range	0-3.2	0-5.0	92.5-100
Majority diagnosis of triplets of pathologists (minority diagnosis)	**Mean scores for 336 triplets of pathologists**			
NDBE (IND)	Mean % (SD)	49.6 (46.9)	12.3 (27.7)	1.8 (11.9)
	Range	0-100	0-100	0-100
NDBE (LGD/HGD)	Mean % (SD)	38.7 (44.7)	4.7 (16.8)	17.9 (34.1)
	Range	0-100	0-100	0-100
IND (NDBE)	Mean % (SD)	13.4 (27.6)	41.0 (45.0)	4.6 (17.9)
	Range	0-100	0-100	0-100
IND (LGD/HGD)	Mean % (SD)	0.3 (2.9)	38.2 (43.3)	40.1 (43.8)
	Range	33.3-100	0-100	0-100
LGD/HGD (NDBE)	Mean % (SD)	8.7 (20.1)	8.9 (22.5)	58.6 (43.0)
	Range	0-100	0-100	0-100
LGD/HGD (IND)	Mean % (SD)	20.2 (9.8)	13.4 (24.7)	79.8 (31.3)
	Range	0-100	0-100	0-100
Disagreement between triplets of pathologists	**Mean scores for 336 triplets of pathologists**			
NDBE – IND – LGD/HGD	Mean % (SD)	10.3 (26.8)	22.0 (38.4)	19.5 (36.6)
	Range	0-100	0-100	0-100

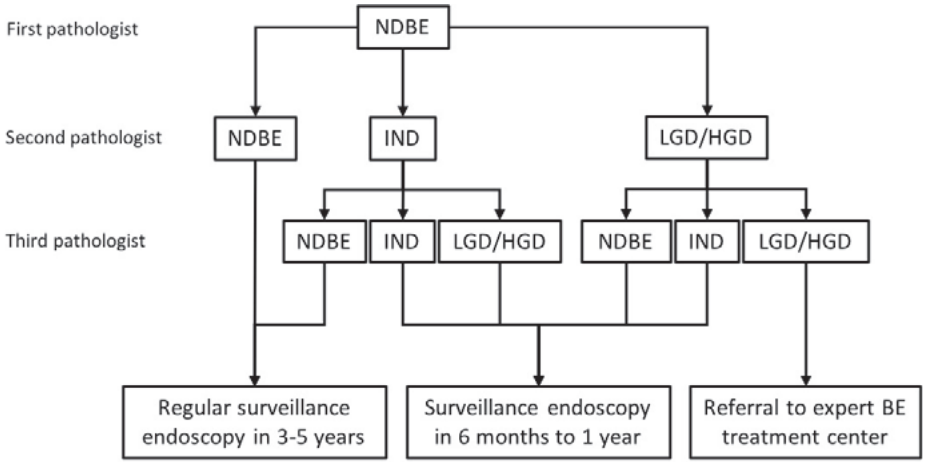
*SD, standard deviation

Clinical implementation algorithm

The clinical implementation algorithm for the digital expert review panel, based on the results described above, is depicted in **Figure 1 and 2**. According to this algorithm, a diagnosis of LGD by the first reviewing expert pathologist results in referral to an expert BE treatment center.

When NDBE is diagnosed by the first reviewing expert pathologist, a second panel pathologist is invited. Confirmation of NDBE by this second expert pathologist results in the recommendation to perform surveillance endoscopy in 3-5 years depending on the length of the BE segment. A discordant review by the second pathologist will result in invitation of a third pathologist. When two pathologists diagnose NDBE and one pathologist diagnoses IND, surveillance is recommended in 3-5 years depending on the length of the BE segment. In case of a majority diagnosis of LGD, the patient will be recommended to be referred to an expert BE center. In all other scenarios surveillance is recommended in 6 to 12 months (**Figure 1**).

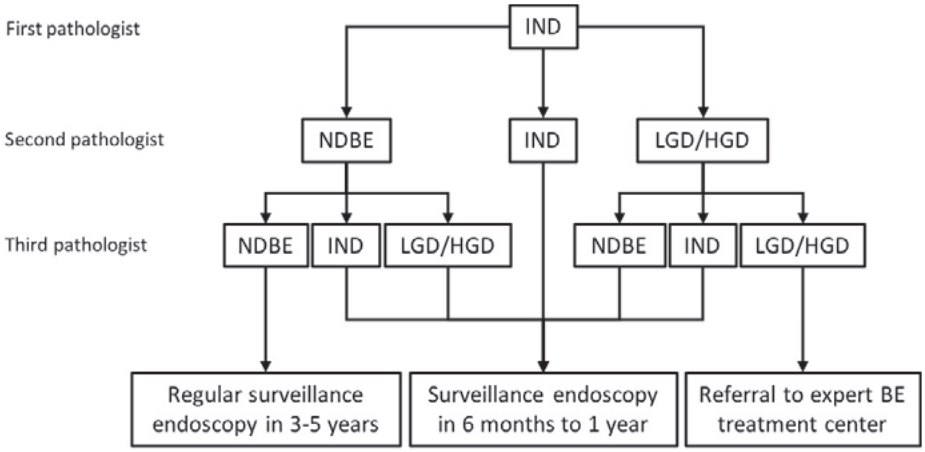
Figure 1: Flowchart of the expert review panel algorithm in case of a diagnosis of NDBE by any single pathologist randomly chosen from an expert panel of eight pathologists.



NDBE, non-dysplastic BE; IND; indefinite for dysplasia; LGD, low-grade dysplasia; HGD, high-grade dysplasia

A diagnosis of IND by the first panel pathologist results in invitation of a second pathologist. When the second pathologist also diagnosis IND the patient will be recommended to undergo surveillance in 6 to 12 months. A discordant diagnosis by the second pathologist will result in invitation of a third panel pathologist. In case of a majority diagnosis of LGD, the patient will be recommended to be referred to an expert BE center. In case of a majority diagnosis of NDBE the patient will be recommended to undergo surveillance in 3-5 years depending on the length of the BE segment. In all other scenarios surveillance is recommended in 6 to 12 months (**Figure 2**).

Figure 2: Flowchart of the expert review panel algorithm in case of a diagnosis of IND by any single pathologist randomly chosen from an expert panel of eight pathologists.



NDBE, non-dysplastic BE; IND; indefinite for dysplasia; LGD, low-grade dysplasia; HGD, high-grade dysplasia

DISCUSSION

In this post-hoc analysis of a real time evaluation of the Dutch Barrett's Pathology Review panel, we have developed a clinical implementation algorithm that enables effective and parsimonious utilization of the participating expert pathologists. Under this algorithm, in the majority (60%) of review requests, expert review by a single panel pathologist suffices to determine subsequent management advice. Expert review by three panel pathologists is only required in a minority (25%) of review requests.

In the preceding study the first 80 prospective LGD reviews submitted to the Dutch Barrett's Pathology Review panel were evaluated by 15 pathologists. [20] Prior to that study, eight of these pathologists had demonstrated homogeneity according to predefined bench mark quality criteria and were regarded as the 'core' panel pathologists. [19] Six additional pathologists met the benchmark quality criteria after completion of the 80 LGD reviews for the current study. [20] For the current study we have, therefore, only taken into account the review results of the eight 'core' panel pathologists. The algorithm presented in the current manuscript is, however, applicable to the complete selection of panel pathologists (n=14) who have demonstrated to be homogenous according to the benchmark criteria. We will continuously monitor and preserve this homogeneity with regular consensus meetings to discuss discrepant cases.

Previous studies have demonstrated that confirmation of LGD by multiple expert pathologists increases the risk of neoplastic progression. [6,13] One might therefore argue that double expert confirmation of LGD should be required to justify referral to a Barrett's expert center. In the algorithm presented in this study, most cases in which LGD is confirmed will only be reviewed by a single expert pathologist. We have chosen this strategy since referral to a Barrett's expert center will result in an additional diagnostic endoscopy to exclude visible abnormalities as well as to confirm persistence of the LGD diagnosis. According to current guidelines, patients should only be considered for prophylactic ablation therapy when LGD is confirmed and persistent. [2,3]

The percentage of LGD review requests in which the diagnosis was confirmed by the expert pathology panel is relatively high, compared to what was described in previous studies by our group. [11,12] This might in part be explained by selection bias in the current study, since the majority of review requests submitted upon initiation of the digital review panel originated from centers that have dedicated Barrett's surveillance programs in place. In these community centers the pathologist might have a slightly higher case load as well as exposure to dysplastic cases compared to other community pathologists, which might have increased the accuracy of the LGD referral diagnosis.

A limitation of this study is the relatively small sample size. Especially for the different scenarios with disagreement between expert pathologists, the number of cases is

limited. Validation of the reported clinical implementation algorithm is therefore required, using prospectively collected consecutive review requests.

In conclusion, this study described a parsimonious strategy for clinical implementation of the digital Dutch Barrett's Pathology Review panel, without compromising reliability of review results. In the majority of review requests, review by a single expert pathologist would suffice and only a minority of requests would require review by three expert pathologists. This clinical implementation algorithm will limit and evenly distribute the workload between participating expert pathologists. Additionally, we can limit the mean duration of the total review procedure since the majority of review requests would only require review by a single expert pathologist.

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