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Today's Mistakes and Tomorrow's Wisdom… In Barrett's Surveillance

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Keywords

Barrett's esophagus · Dysplasia · Surveillance · Risk-stratification · Cost-effectiveness

Abstract

Background: Barrett's esophagus (BE) is the only known precursor lesion of esophageal adenocarcinoma, a malignancy with increasing incidence and poor survival rates. To reduce mortality, regular endoscopic surveillance of BE patients is recommended to detect neoplasia in an (endoscopically) curable stage. In this review, we aim to provide an overview of current BE surveillance strategies, its pitfalls, and potential future directions to optimize BE surveillance. ***Summary:*** Several societal guidelines provide surveillance strategies. However, when practicing those endoscopies multiple drawbacks are encountered. Important challenges are time-consuming biopsy protocols with low adherence rates, biopsy sampling error, interobserver variability in endoscopic detection of lesions, and interobserver variability in diagnosis of dysplasia. Furthermore, the overall efficacy and cost-effectiveness of surveillance are questioned. Using novel techniques, such as artificial intelligence and personalized surveillance intervals, can help to overcome these obstacles. ***Key Messages:*** Currently, there is room for improvement in BE surveillance. Better risk-stratification is expected to reduce both patient and healthcare burdens. Personalized and dynamic surveillance intervals accompanied by novel techniques in detection and histopathological assessment of dysplasia may be tools for a change in the right direction.

Introduction

Over the past decades, there has been a rapid increase in the incidence of esophageal adenocarcinoma (EAC) [1]. This is worrisome, since invasive EAC is the 5th deadliest malignancy worldwide, with a 5-year survival rate of less than 20% [2]. Barrett's esophagus (BE) is the only known precursor lesion of EAC and, therefore, important in the prevention of invasive EAC. In order to reduce mortality, regular endoscopic surveillance of BE is recommended to detect high-grade dysplasia (HGD) or EAC in a (endoscopically) curable stage. However, multiple drawbacks are encountered related to the surveillance of BE patients. This review provides an overview of current surveillance strategies, including challenges faced when practicing. Furthermore, we will address several suggestions for improvement. The current pitfalls and potential future directions of BE surveillance addressed in this review are shown in Figure 1.

Why Surveillance?

In BE, squamous epithelium that normally lines the lower esophagus is replaced by columnar epithelium, as a result of chronic gastroesophageal reflux disease [3]. BE predisposes to neoplasia through different stages of dysplasia [4]. Although the relative risk of developing HGD or EAC is increased more than 30 times in nondysplastic BE (NDBE) patients than in the general population, the absolute risk is low. Estimates of the annual neoplastic progression risk range from 0.4% to 0.7% [5, 6]. The re-

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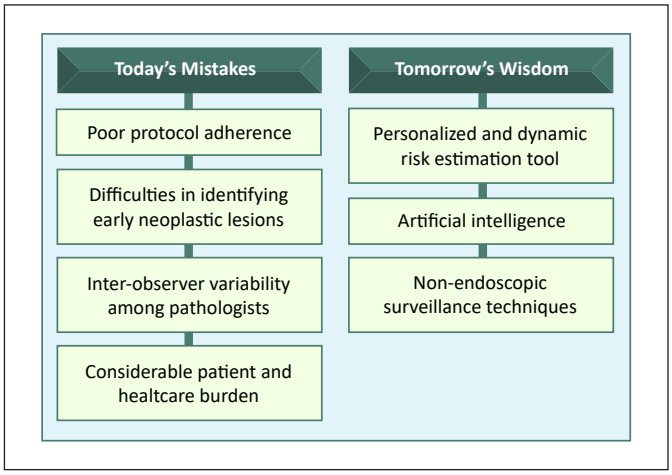

Fig. 1. Barrett's esophagus surveillance: its current pitfalls and potential future directions.

sults for patients with low-grade dysplasia (LGD) are highly variable; a recent meta-analysis including 2684 BE patients from 24 studies showed a pooled incidence rate of 1.7% [7]. Risk factors known to be associated with an increased neoplastic progression risk are age, male gender, and long-segment Barrett's mucosa [8–10]. The aim of surveillance is to improve outcome by detecting neoplastic progression early enough to cure endoscopically. Studies suggest that adequate endoscopic surveillance correlates with detection of EAC at an earlier stage and with improved survival rates [11, 12].

Current Guidelines

Surveillance strategies for BE have been addressed in societal guidelines [13]. For the detection of dysplastic Barrett's mucosa, endoscopic assessment of the esophagus with white light endoscopy is advised. An endoscopic grading system, the Prague classification, has been developed for reporting the extent of the BE segment [14]. Biopsies taken from the esophageal mucosa are required to detect neoplasia. To minimize the chance of missing HGD or EAC, guidelines recommend to take four-quadrant biopsies at each 2-cm interval of the Barrett's segment according to the Seattle protocol [15]. Using this strategy, it is estimated that up to 90% of HGD and EAC cases are detected [16].

Currently, surveillance intervals are based on the grade of dysplasia and BE length, with intervals varying between 6 months and 5 years. It is advised that patients with limited life expectancy due to advanced age or comorbidity are discharged from surveillance. Patients with BE <1 cm are excluded from surveillance due to their low progression risk [17].

Today's Mistakes

Guidelines provide an evidence-based resource for the management of BE patients, but in practice several challenges are faced. First, adherence to guideline recommendations appears to be low. For example, the Seattle protocol has been associated with increased detection of neoplastic lesions [18], but adherence to such an extensive protocol is highly variable. A study with 2,245 surveillance patients showed an average protocol adherence of 51.2%, and longer BE segments were associated with an even lower protocol adherence [16]. To further illustrate this, in a Dutch retrospective study with 150 patients, adherence to the Seattle protocol was as low as 30% in patients with segments >10 cm [19]. This suggests that protocol adherence appears to be worst in BE patients at higher risk of EAC development. A recent meta-analysis showed that short BE length, salaried employment, surveillance in university hospitals, and dedicated BE programs are reported to be associated with better protocol adherence [20].

Second, BE surveillance is also beset by difficulties in the detection of dysplasia. Even when the Seattle protocol is properly executed, only 4%–6% of the BE area can be sampled [21]. As dysplasia is often patchy, its diagnosis is subject to sampling error [22]. Targeted biopsies could solve this problem but are hard to perform since LGD presents itself with very subtle mucosal changes [23]. Given the low neoplastic progression rate among BE patients, most gastroenterologists are unfamiliar with these subtle mucosal changes. Consequently, experienced endoscopists at BE expert centers detect neoplastic lesions at a higher rate than endoscopists at general hospitals [24]. In almost 50% of patients with an initially invisible lesion, a visible lesion was detected after being referred to a BE expert center [25]. Training in recognition of neoplastic lesions in BE imaging is therefore recommended for all endoscopists. It also supports the value of expert centers for the surveillance and treatment of BE patients, especially for those with a higher risk of neoplastic progression.

However, even targeted biopsies taken at expert centers do not automatically lead to correct pathology findings. There is considerable interobserver variability in the interpretation of ND and LGD between pathologists [26], due to the complexity of separating true LGD from benign inflammatory changes. Therefore, BE patients diagnosed with LGD should undergo an expert pathology review, after which 73%–85% are downgraded to NDBE [23]. After expert pathology review the risk of neoplastic progression was 9.1% per year in the confirmed LGD group and only 0.6% per year in patients who were downstaged to NDBE [27]. Interobserver variability among pathologists emphasizes the fact that less subjective markers

than the grade of dysplasia are needed to determine the neoplastic progression risk in individual BE patients.

Those challenges encountered in BE surveillance reflect on its effectiveness. Several studies suggest that adequate endoscopic surveillance correlates with the detection of cancer at an earlier stage [11, 12], but large prospective studies showing improved survival rates are lacking. Consequently, the true effect of long-term surveillance remains under debate, and, therefore, potential harms must be considered carefully. Several potential harms are associated with surveillance, including patient's concerns about the development of EAC, risks associated with the endoscopy, and morbidity associated with therapies used to treat lesions identified by surveillance. Furthermore, there is always a risk of missed lesions despite surveillance. Currently, due to the lack of reliable methods for individual risk-stratification, the majority of BE patients are monitored and carry the burden of long-term surveillance.

Apart from patient burden, the healthcare burden is important as well. Previous studies have shown highly variable results with respect to the cost-effectiveness of surveillance [28–32]. A recent study showed that for patients with long-segment NDBE endoscopic surveillance is cost-effective when intervals of 5 years are used [33]. For patients with LGD, the 6–12 months surveillance intervals that are currently recommended should be extended to at least 3 years to be cost-effective. However, the consequence of prolonged surveillance intervals for all BE patients may lead to detection of neoplasia in more advanced stages. Therefore, improved risk-stratification to identify high-risk patients will be an important next step to improve the cost-effectiveness of BE surveillance.

Tomorrow's Wisdom

As stated previously, current endoscopic surveillance strategies encounter various pitfalls. Several novel techniques have shown the potential to overcome these obstacles.

The intensity of endoscopic surveillance is currently based on only two parameters, i.e., grade of dysplasia and length of Barrett's segment. Besides, only the result of the last endoscopy is included in the risk estimation of neoplastic progression. Recently, a new strategy to stratify neoplastic progression risk per individual BE patient was modeled based on multiple parameters, including grade of dysplasia, immunohistochemical biomarkers (p53 and SOX2), sex, BE length, age, and the presence of esophagitis [34]. Because of the variation in some of these parameters between successive endoscopies, the results of all previous endoscopies were included. Consequently, this dynamic risk prediction model can be updated per individual patient at every surveillance endoscopy. In a microsimulation model of this new strategy, 65% of patients were safely discharged from surveillance after two endoscopies, while retaining effectiveness in timely detection of neoplastic progression [35].

Another promising new strategy is artificial intelligence (AI) technology. AI has been introduced as a tool to improve the detection, characterization, and delineation of neoplastic lesions in BE mucosa [36–38]. Different AI techniques lead to the detection of dysplastic BE with an accuracy of 89%–95% in white light endoscopy [36, 37] and 84% in NBI endoscopy [38]. AI has the potential to provide real-time assistance during endoscopic surveillance, by identifying premalignant and malignant lesions that would otherwise remain undetected. Furthermore, the use of AI may improve the yield of biopsies, by indicating optimal biopsy sites during endoscopic procedures.

Last, as alternative to endoscopic surveillance, nonendoscopic techniques have been developed to sample the esophageal mucosa [39]. For BE detection, the sensitivity and specificity of these novel techniques vary between 60%–94% and 80%–100%, respectively [39, 40]. For detection of dysplasia in BE the use of a sponge technique in combination with specific biomarkers seems promising [39, 40]. Overall, these less-invasive technologies show great promise for BE screening; however, their feasibility within BE surveillance strategies has yet to be proven in large prospective studies.

Conclusion

Endoscopic surveillance is recommended for patients with BE in order to detect neoplasia in an (endoscopically) curable stage. However, the implementation of current surveillance strategies is not without limitations, mainly due to difficulties in distinguishing dysplastic from nondysplastic BE. Time-consuming biopsy protocols have been introduced to reduce sampling error but are difficult to adhere to. Better protocol adherence and higher detection rates of neoplastic lesions in dedicated BE programs highlight the additional value of BE expert centers. It also underscores the need for training in the recognition of neoplastic lesions for endoscopists involved in BE surveillance. AI is a promising new technique that has the potential to provide assistance during endoscopic surveillance, by identifying dysplastic lesions that would otherwise remain undetected.

Furthermore, the true effect and cost-effectiveness of long-term surveillance remain under debate due to a considerable patient and healthcare burden in combination with a low absolute risk of neoplastic progression. Within the current surveillance strategy, the risk assessment

based on grade of dysplasia is subject to considerable inter- and intraobserver variability. Therefore, other tools and markers, including dynamic and personalized surveillance strategies, are likely to improve risk-stratification and reduce this burden. Also, new nonendoscopic techniques for sampling the esophageal mucosa could potentially decrease the burden and costs of BE surveillance.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.C.W.S. was invited for this review and made the conception and design with P.A.Z. and C.A.M.R. P.A.Z. acted as first author of this work, screened articles for inclusion in this review, interpreted data, and drafted the manuscript. C.A.M.R. drafted and co-authored the manuscript. All authors critically read, edited, and approved the final manuscript.

References

1 Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013;19(34):5598–606.
2 Fan J, Liu Z, Mao X, Tong X, Zhang T, Suo C, et al. Global trends in the incidence and mortality of esophageal cancer from 1990 to 2017. Cancer Med. 2020;9(18):6875–87.
3 Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med. 2014;371(9):836–45.
4 Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology. 1989;96(5 Pt 1):1249–56.
5 Yousef F, Cardwell C, Cantwell MM, Galway K, Johnston BT, Murray L. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol. 2008;168(3):237–49.
6 Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010;8(3):235–44; quiz e32.
7 Singh S, Manickam P, Amin AV, Samala N, Schouten LJ, Iyer PG, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79(6):897–909.e4; quiz 983.e1–3.
8 de Jonge PJ, van Blankenstein M, Grady WM, Kuipers EJ. Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63(1):191–202.
9 Thota PN, Lee HJ, Goldblum JR, Liu X, Sanaka MR, Gohel T, et al. Risk stratification of patients with Barrett's esophagus and low-grade dysplasia or indefinite for dysplasia. Clin Gastroenterol Hepatol. 2015;13(3):459–65.e1.
10 Pohl H, Pech O, Arash H, Stolte M, Manner H, May A, et al. Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. Gut. 2016;65(2):196–201.
11 Kastelein F, van Olphen SH, Steyerberg EW, Spaander MC, Bruno MJ, ProBar-Study G. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut. 2016;65(4):548–54.
12 Verbeek RE, Leenders M, Ten Kate FJ, van Hillegersberg R, Vleggaar FP, van Baal JW, et al. Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study. Am J Gastroenterol. 2014;109(8):1215–22.
13 Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–51; quiz 51.
14 Sharma P, Dent J, Armstrong D, Bergman JJ, Gossner L, Hoshihara Y, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology. 2006;131(5):1392–9.
15 Levine DS, Blount PL, Rudolph RE, Reid BJ. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol. 2000;95(5):1152–7.
16 Abrams JA, Kapel RC, Lindberg GM, Saboorian MH, Genta RM, Neugut AI, et al. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. Clin Gastroenterol Hepatol. 2009;7(7):736–42; quiz 710.
17 Thota PN, Vennalaganti P, Vennelaganti S, Young P, Gaddam S, Gupta N, et al. Low risk of high-grade dysplasia or esophageal adenocarcinoma among patients with Barrett's esophagus less than 1 cm (irregular Z line) within 5 years of index endoscopy. Gastroenterology. 2017;152(5):987–92.
18 Fitzgerald RC, Saeed IT, Khoo D, Farthing MJ, Burnham WR. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. Dig Dis Sci. 2001;46(9):1892–8.
19 Curvers WL, Peters FP, Elzer B, Schaap AJ, Baak LC, van Oijen A, et al. Quality of Barrett's surveillance in The Netherlands: a standardized review of endoscopy and pathology reports. Eur J Gastroenterol Hepatol. 2008;20(7):601–7.
20 Roumans CAM, van der Bogt RD, Steyerberg EW, Rizopoulos D, Lansdorp-Vogelaar I, Sharma P, et al. Adherence to recommendations of Barrett's esophagus surveillance guidelines: a systematic review and meta-analysis. Endoscopy. 2020;52(1):17–28.
21 Harrison R, Perry I, Haddadin W, McDonald S, Bryan R, Abrams K, et al. Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. Am J Gastroenterol. 2007;102(6):1154–61.
22 Tschanz ER. Do 40% of patients resected for Barrett esophagus with high-grade dysplasia have unsuspected adenocarcinoma? Arch Pathol Lab Med. 2005;129(2):177–80.
23 Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010;105(7):1523–30.
24 Cameron GR, Jayasekera CS, Williams R, Macrae FA, Desmond PV, Taylor AC. Detection and staging of esophageal cancers within Barrett's esophagus is improved by assessment in specialized Barrett's units. Gastrointest Endosc. 2014;80(6):971–83.e1.
25 Scholvinck DW, van der Meulen K, Bergman J, Weusten B. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy. 2017;49(2):113–20.
26 Kerkhof M, van Dekken H, Steyerberg EW, Meijer GA, Mulder AH, de Bruine A, et al. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. Histopathology. 2007;50(7):920–7.
27 Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015;64(5):700–6.
28 Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. Ann Intern Med. 2003;138(3):176–86.

29 Sonnenberg A, Soni A, Sampliner RE. Medical decision analysis of endoscopic surveillance of Barrett's oesophagus to prevent oesophageal adenocarcinoma. Aliment Pharmacol Ther. 2002;16(1):41–50.
30 Gordon LG, Mayne GC, Hirst NG, Bright T, Whiteman DC; Australian Cancer Study Clinical Follow-Up Study, et al. Cost-effectiveness of endoscopic surveillance of non-dysplastic Barrett's esophagus. Gastrointest Endosc. 2014;79(2):242–56.e6.
31 Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol. 1999;94(8):2043–53.
32 Das A, Wells C, Kim HJ, Fleischer DE, Crowell MD, Sharma VK. An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. Endoscopy. 2009;41(5):400–8.
33 Kastelein F, van Olphen S, Steyerberg EW, Sikkema M, Spaander MC, Looman CW, et al. Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis. Gut. 2015;64(6):864–71.
34 Roumans CAM, Tomer A, Lansdorp-Vogelaar I, Biermann K, Bruno MJ, Steyerberg EW, et al. Personalised dynamic surveillance strategies in Barrett's oesophagus: a multicentre prospective cohort study. UEG J. 2019;7(10):1411–25.
35 Roumans CA, Naber S, Omidvari AM, Kroep S, Wijnhoven BP, van der Gaast A, et al. The potential of personalized surveillance intervals for Barrett's esophagus patients: a microsimulation study. Gastroenterology. 2020;158(6):S-88.
36 de Groof AJ, Struyvenberg MR, van der Putten J, van der Sommen F, Fockens KN, Curvers WL, et al. Deep-learning system detects neoplasia in patients with Barrett's esophagus with higher accuracy than endoscopists in a multistep training and validation study with benchmarking. Gastroenterology. 2020;158(4):915–29.e4.
37 Hashimoto R, Requa J, Dao T, Ninh A, Tran E, Mai D, et al. Artificial intelligence using convolutional neural networks for real-time detection of early esophageal neoplasia in Barrett's esophagus (with video). Gastrointest Endosc. 2020;91(6):1264–71 e1.
38 Struyvenberg MR, de Groof AJ, van der Putten J, van der Sommen F, Baldaque-Silva F, Omae M, et al. A computer-assisted algorithm for narrow-band imaging-based tissue characterization in Barrett's esophagus. Gastrointest Endosc. 2021;93(1):89–98.
39 Spechler SJ, Katzka DA, Fitzgerald RC. New screening techniques in Barrett's esophagus: great ideas or great practice? Gastroenterology. 2018;154(6):1594–601.
40 Iqbal U, Siddique O, Ovalle A, Anwar H, Moss SF. Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: a systematic review. Eur J Gastroenterol Hepatol. 2018;30(11):1261–9.