How to handle esophageal metaplasia in 2014 : a practical guide

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Abstract

Metaplasia of the esophagus is a precursor of esophageal adenocarcinoma, a cancer with a poor prognosis and an increasing incidence. Guidelines for surveillance are proposed by all professional societies with small differences in timing. However, there is still no consensus on the definition of Barrett's esopaghus (only intestinal metaplasia or all subtypes). The goal of surveillance of esophageal metaplasia has evolved from early detection of cancer to early detection of pre-cancerous metaplasia to allow endoscopic therapy. The endoscopic therapy has the intention to stage, to cure, to prevent progression and to prevent metachronous lesions to develop. Firm indications for endoscopic therapy are high rade dysplasia and mEAC. The actual treatment is EMR/ESD for all visual abnormalities and areas of cancer on biopsies, followed by RFA for the remaining metaplasia. For low grade dysplasia (LGD), surveillance versus RFA is still under discussion. The main reason for this is the wide interobserver variability with large differences in evolution between confirmed and unconfirmed LGD. The endoscopic treatment allows complete remission of dysplasia in most cases and of metaplasia in the majority of cases, with low complication rates and acceptable morbidity (treatable stenosis). However, a median of 3 treatments is usually required to achieve remission, and recurrence is as high as 15% in the following 5 years. Strategies to reduce recurrence like chemotherapy or anti-reflux surgery need to be explored better and can actually not decrease or replace surveillance. (Acta gastroenterol. belg., **2015**, 78, **30-37**).

Key words : Barrett, esophageal metaplasia, review, practical guide, barrett, esophageal metaplasia.

Abbreviations : CE, chromoendoscopy ; CLE, confocal laser endomicroscopy ; EAC, esophageal adenocarcinoma ; EMR, endoscopic mucosal resection ; ESD, endoscopic submucosal dissection ; GEJ, gastro-esophageal junction ; HGD, high grade dysplasia ; IEN, Intraepithelial neoplasia ; IM, intestinal metaplasia ; LGD, low grade dysplasia ; mEAC, mucosal esophageal adenocarcinoma ; smEAC, Submucosal esophageal adenocarcinoma ; PPI, proton pump inhibitor ; RFA, radio frequency ablation ; VC, virtual chromoendoscopy.

Metaplasia of the esophagus as the result of gastro-esophageal reflux is a frequent pathology and there is no doubt anymore that evolution to high grade dysplasia (HGD) and subsequently to esophageal adenocarcinoma (EAC) is present in a subset of patients. Although still much less frequent then colorectal cancer, EAC is the fastest rising malignancy in the Western countries over the past decades and is more lethal than colorectal cancer (1).

Surveillance endoscopy, although costly, leads to detection of EAC in early stages with better survival than EAC found outside surveillance programs (2).

The development of efficient non-surgical treatments of mucosal esophageal cancer (mEAC) reshaped the management of metaplasia of the esophagus. It is accepted that endoscopic treatment is standard of care in patients with HGD and mEAC. Esophagectomy is now rarely an option in mucosal disease and is mainly reserved for more advanced cancer.

However, still some debate exists about the definition of Barrett, the handling of short Barrett and indication of treatment for low grade dysplasia (LGD). This has resulted in different guidelines concerning the management of Barrett between gastroenterological societies.

Metaplasia of the esophagus : Barrett or not ?

Metaplasia signifies replacement of the lining of an organ with type of lining found in another organ. In the esophagus it means replacement of the normal squamous epithelium of the esophageal mucosa by gastric, cardiac or intestinal type mucosa which is easily recognized on endoscopy.

The clinical relevance of esophageal metaplasia is the increased risk of developing adenocarcinoma. Malignant degeneration is thought to start as non-dysplastic epithelium and then to evolve to cancer trough the different stages of dysplasia or intraepithelial neoplasia (IEN) (= synonym of dysplasia).

Whether "Barrett's esophagus" can be used as synonym for metaplasia or whether its use should be restricted to the presence of intestinal metaplasia (IM) stays a matter of discussion. The different opinions on the subject are mainly due to discussions about the cancer risk of non-IM metaplasia and evaluation and cancer risk of short Barrett (metaplasia < 3 cm from the gastro-esophageal junction (GEJ)) which will be discussed below.

1. *Are all forms of metaplasia precancerous ?*

There is no discussion about dysplasia being a precancerous stage of EAC. The discussion however focuses on the different types of metaplasia (cardiac, gastric or intestinal) without dysplasia. The definition of "Barrett's

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esophagus" which meant initially the same as metaplasia of the esophagus, was changed to "metaplasia with presence of intestinal metaplasia (IM) ", due to articles that suggested that only this type of mucosa had increased risk for developing EAC. Nowadays however, many studies support an increased risk also in "non-goblet" metaplasia, on an epidemiological as well as on a molecular basis (3,4). Some find lower risk in "non-goblet" metaplasia (0,06 versus 0,31%) but others find a similar risk in both types of metaplasia (3,5). Furthermore, biopsies of metaplasia can never rule out with certainty that intestinal metaplasia is absent since both gastric and intestinal metaplasia can exist next to each other.

Although the Montréal consensus group stated in 2006 that "Barrett esophagus" should be used for all types of metaplasia with the qualifier whether IM is present or not, this was not implemented worldwide (6). Especially the American Society of Gastroenterology (ASGE) continues to use Barrett only for IM metaplasia (2). The argument to continue to use the restricted definition of "Barrett" is to identify a premalignant condition, which, in the argumentation of the ASGE, is still only proven for IM.

2. *Short Barrett's esophagus and the GEJ.*

In short Barrett there is the problem of the nearness of the GEJ, making it very hard to distinguish cardia-type epithelium from esophagus in the lower region of the esophagus. An international working group in Prague in 2006 proposed a standardized endoscopic description for the evaluation of metaplasia. The GEJ was defined as the proximal margin of the gastric fold during minimal insufflation of esophagus and stomach. Although inter-observer agreement for this grading system was generally high, it was poor when metaplasia extended < 1 cm above the GEJ (7). The proponents for the restricted use of Barrett (IM only) argue that biopsies in short Barrett's could have been taken at the level of the cardia where IM is judged not to be pre-neoplastic. Furthermore, they argue that cancer risk is directly proportional to the length of the Barrett which makes cancer risk negligible in this entity.

Authors do not always specify in their articles the definition of Barrett used.

Metaplasia of the esophagus can be of different types : cardiac, gastric and intestinal. All have malignant potential but the relative risk is unclear. In literature nowadays, the definition of Barrett's esophagus can mean the selected group of intestinal metaplasia (especially in the US) or can be a synonym of metaplasia.

It is important to mention where biopsies were taken (< or > 3 cm from the GEJ) because of the uncertain importance of short metaplasia (< 3 cm) concerning cancer risk and the inability to identify the GEJ.

Surveillance endoscopy

Evolution to cancer has been estimated to be 0,5%/year, taking into account all stages of dysplasia and eliminating cancers found in the first year of surveillance (2). However, the real risk is unknown and estimates vary widely in literature.

Once metaplasia has been diagnosed, an endoscopic surveillance program is started to discover in time HGD or mucosal cancer and apply appropriate treatment depending on histological criteria.

Histological evaluation of metaplasia is based on 5 grades of IEN or dysplasia : negative for IEN/dysplasia, indefinite for IEN/dysplasia, low grade IEN or LGD, high grade IEN or HGD and adenocarcinoma (8). However, for correct evaluation of dysplasia it is essential to control active inflammation with acid suppressive treatment to permit distinguishing reparative changes from true dysplasia.

Because of the patchy distribution of dysplasia and the fact that endoscopic abnormalities are not mandatory for the presence of HGD and cancer, 4 quadrant biopsies at 1 to 2 cm interval together with mapping are proposed (9,10). Subtle mucosal abnormalities must be actively searched for and extensively biopsied, using a high definition endoscope.

Surveillance intervals are determined by the grade of dysplasia. They are arbitrary and have never been subjected to randomized trials. Furthermore, guidelines differ depending on the professional societies.

Summarized (10,11,12,13).

No dysplasia

- Surveillance every 2-5 years

Differences between societies concern details like :

- Confirm after 6 months (ASGE ; IM necessary for diagnosis of Barrett)
- No surveillance if metaplasia < 3 cm, no IM and confirmed on repeat endoscopy (British society)
- Different intervals for different Barrett length (French society SFED)

LGD

- Confirm by expert pathologist
- Confirm after 8-12 weeks of intensive acid suppression therapy
- Surveillance every 6 months during 1 year and then yearly
- Decrease surveillance to every 2-3 years if dysplasia is absent after > 2 endoscopies without dysplasia

Although all stages of metaplasia of the esophagus are considered precancerous, cancer risk increases with the

presence of dysplasia. The problem in LGD is the high Inter-observer variability with, as a consequence, studies finding very high risk for evolution to cancer and others finding a very low risk. These conflicting results can be overcome if 2 or more pathologists reevaluate the biopsies. In the majority of cases (75%-85%), LGD will be downgraded to "no dysplasia" (14). If LGD is confirmed, cancer risk will be substantially higher (15).

HGD

- Confirm by expert pathologist
- Confirm within 2 to 3 months
- If confirmed : endoscopic eradication therapy with the aim of eradicating all dysplasia

Although most societies will agree on endoscopic therapy as a first line option for HGD because of the high yearly risk of developing cancer (6-10%), in older patients with a short life expectation, surveillance can be a good option (10,16).

Early adenocarcinoma (mEAC) (10)

- EMR is essential for proper diagnosis and staging
- Only T1m tumors are suitable for endoscopic treatment
- After EMR removal of all visible lesions, the remaining metaplasia should be eradicated, the preferred treatment being radio frequency ablation.

For <u>correct evaluation</u> of dysplasia it is essential to control active inflammation with acid suppressive treatment to permit distinguishing reparative changes from dysplasia.

For <u>surveillance</u>, critical visual evaluation with biopsies of suspected areas, followed by 4 quadrant biopsies at 1 to 2 cm interval and mapping of the area are proposed

The cancer risk in LGD is substantially higher when confirmed by expert pathologists

The selection of patients to enter a surveillance program changed with the shift from surgical treatment to efficient endoscopic treatment for HGD and mEAC. Criteria such as operability and age are not relevant anymore. A better criterion seems to be the likelihood of survival over the next 5 years.

New imaging techniques : to use or not to use ?

High resolution endoscopes (higher amount of pixels) and high definition television screens (higher amount of scanning lines) have invaded the endoscopy market and allow, with careful inspection, good evaluation of the mucosa. The limiting factor here is the equipment and skills of the endoscopist.

For correct screening, biopsies must be taken from every endoscopic abnormality and at every 1 to 2 cm, which can be laborious, especially in long Barrett's. New enhanced imaging techniques were developed aiming at better visualization to allow targeted biopsies. The most studied techniques are chromoendoscopy (CE), virtual chromoendoscopy (VC), and confocal laser endomicroscopy (CLE). CE is an old technique that uses dyes (indigo carmine, methylene blue, crystal violet, and acetic acid) to improve visualization of the esophageal mucosa. VC (NBI, FICE), installed on most modern endoscopes, uses light filters to highlight vessel and mucosal patterns. Both techniques are easy to apply but there is a learning curve for interpretation. CLE magnifies the gross image of the esophageal mucosa by a thousand-fold to allow visualization of the mucosa at the microscopic, cellular level. This technique is difficult, laborious and time consuming and actually only used in specialized centers.

The added value is under discussion with some authors "pro" and some claiming that, until now, there is no clear proof of added value (11,17,18). The answer lies probably in between. In experienced hands, CE and VC can increase detection and decrease the number of biopsies, especially in long Barrett's.

White light high resolution endoscopy used with a high definition video monitor gives a good evaluation of the mucosa and is sufficient for surveillance endoscopy. However, careful inspection is mandatory (look longer and better).

Endoscopic treatment modalities for dysplasia

Different treatments are available. The choice of treatment will depend on the area involved, the endoscopic appearance, the histological results, the availability of the devices and the skills of the operator.

Radiofrequency ablation (RFA) (19)

Different ablation techniques have been developed to obtain total eradication of intraepithelial neoplasia, aiming at the restoration of the native squamous epithelium. Of all different techniques, for the moment only RFA survived due to the advantage of simplicity and safety with fewer side effects and less post treatment stenosis. This has been attributed to the fact that the depth of ablation is limited to 1000 microns which is sufficient to treat non-nodular Barrett and generally does not go deep enough to damage the deep muscle layer. This also determines the indication for treatment which is flat dysplasia without mEAC.

Although RFA is effective, several treatments are usually required to obtain complete remission. Different formats of the system are available to obtain this. There is a circumferential system for long circular Barrett's and there are focal devices of different sizes that can be attached to the tip of the scope for shorter or smaller segments like tongues, islands or short circumferential segments. Material required is the ablation catheter depending on the area to ablate, a sizing balloon when using the circumferential system and a generator, usually made available by the industry.

Endoscopic mucosal resection (EMR)

Two techniques are available to perform EMR : band ligation and cap-snare technique with injection. These techniques have similar success but the band ligation is easier to use. The equipment and ligation technique is the same as for esophageal varices and the pressure of the ligation permits the muscularis propriae to fall out of the created pseudopolyp. The difficult part is to do the resections side by side without leaving residual islands between individual resections.

Before starting EMR, the area to be resected is marked with a cautery device, ensuring wide margins. There is no limit in the number of resection that can be performed during one session but circumferential resection increases significantly the risk of post treatment stenosis, requiring one or more dilations (20). Usually, no more than 60% of the circumference is resected in one session. With RFA available it is better to keep flat areas of metaplasia without visual abnormalities and without cancer on biopsies for later treatment with RFA.

The risk of complications with piecemeal EMR is low and generally manageable endoscopically. Acute bleeding is the most frequent. Delayed bleeding (3%) usually stops spontaneously. Perforation (0-1%) is very rare and can be managed by clip closure or temporary stent placement. Stenosis is frequent, especially after large resections (20-40%) and can be managed by balloon or Savary dilatations. More than one dilation is usually necessary. Preventive pharmacological treatment for stenosis with corticosteroids, locally injected as well as systemically administrated, is being investigated and seems promising but is not yet standard (21,22,23). Preventive stent placement 10 days after EMR in the prevention of strictures had an unacceptable complication rate in a small study, only published as an abstract (24).

EMR is a piecemeal resection, which means that pathology will be unable to tell anything about resection margins. After EMR, it can be useful to take biopsies at the margins of the resection.

The fact that EMR permits correct staging and treatment determines its indications which are suspicious lesions on endoscopy and areas of cancer on biopsies. It is thus important to use mapping when doing surveillance endoscopy.

Endoscopic submucosal dissection (ESD)

ESD was initiated in Japan for resection of early gastric cancer in one piece and subsequently applied to the rest of the gastrointestinal tract. It is a technique that has a long learning curve, is time consuming, needs endoscopic skills and is only performed by few endoscopists in Europe. After injecting a viscous liquid into the submucosa (as for the lifting in polypectomy), a resection in one piece of the mucosa and part of the submucosa is performed, using special knives.

The advantage is the "en bloc resection" with clear margins. Although rarely compared with EMR, procedure time, cost and rate of stenosis is higher than in EMR with comparable eradication rates (25). Furthermore, R0 resection (= complete resection with free margins) is not achieved often enough to prefer this technique over EMR in most situations (26).

The endoscopic treatment of LGD

Discussion is still ongoing whether LGD should be treated or just followed-up. The general acceptance of treatment is hampered by several issues like the cost-efficiency, taking into account the high cost of endoscopic therapy and the low risk of developing cancer. Furthermore, huge inter-observer differences exist in the interpretation of LGD. When routine biopsies are reevaluated by 2 independent pathologists, up to 85% LGD is down staged to "no dysplasia" or "indefinite for dysplasia" with large difference in evolution. The risk of evolution to HGD changes from 0,98 and 1,80% per year in "no" or "indefinite" dysplasia to 13,4% per year in confirmed LGD (27). This high risk was also seen in the first study of RFA on dysplasia with 14% evolution from LGD to HGD in the sham group (28). The recently published SURF study support these results. This study compared RFA and endoscopic surveillance in confirmed LGD. The study was terminated early due to superiority of RFA. Evolution from LGD to HGD in the control group after a median follow up of 36 months was 26,5% and even 8,8% to EAC. These results are very high with 40% evolution in the first year. The fact that only expert reference centers were included may have influenced the results (15).

With such data, it can be clinically recommended to treat consistent and persistent LGD in patients with high life expectancy or patients at risk. If one chooses to treat LGD, RFA is the preferred treatment with complete eradication of dysplasia in ± 90% of patients and intestinal metaplasia in 88%. Furthermore, it is an easy technique with a low risk and low adverse event profile. Recurrence rate seems low around 1,5% but long term follow up studies are lacking so that surveillance needs to be continued and no recommendations can be given concerning surveillance intervals (15,29).

Taking into account the difficulties of interpreting LGD and thus the subsequent risk of EAC, many bio-

markers have been evaluated to help distinguishing low and high risk patients, until now with little utility.

Low grade dysplasia will be downstaged in up to 85% of cases when reevaluated by 2 independent pathologists.

The preferred treatment for confirmed LGD is RFA.

The endoscopic treatment of HGD /mEAC

Although only a small percentage of the patients with metaplasia will evolve to HGD (0,12 to 0,31% per year), the rate of progression from HGD to cancer is from 6 up to 19% a year (3,10,16,30). In situations where the risk of lymph node metastasis is negligible, endoscopic therapy should be applied to prevent evolution. It is now clear that the risk of lymph node invasion is 0% in patients with HGD and < 2% (0,7-1,93%) in mEAC (31,32).

The best way to stage correctly HGD/mEAS is EMR because in > 25% of cases there will be upgrading or downstaging compared to the biopsies taken previously (26,33,34). Furthermore, the pathologist receives a large sample of the mucosa and part of the submucosa which will give information on submucosal, lymph vessel and neural invasion, allowing staging and eradication at the same time.

EUS lacks accuracy for staging mucosal or submucosal disease as well as for detecting lymph nodes (35). EUS can be used to puncture suspected lymph nodes but sensitivity is low and care must be taken not to puncture trough the dysplastic epithelium. Radiological tests (CT or PET) perform worse than EUS for regional lymph node staging and are of no use in this context (36).

In most cases, endoscopic evaluation, helped by using the lifting sign and the feeling on probing the lesion, is trustworthy in evaluating resectability. The Paris classification, developed by Japanees endoscopists for superficial lesions, can be used to describe the lesions and evaluate resectability (37). Excavating lesions are not suitable for EMR.

Actually, RFA and EMR/ESD are the preferred treatments, alone or combined, with the aim of complete eradication of HGD/mEAC but also of coexisting metaplasia. EMR/ESD is used to treat all visible lesions and areas where adenocarcinoma is diagnosed histologically. RFA is applied to eradicate the remaining metaplasia since 30% of metachrome tumors can be expected to recur in the remaining metaplasia.

The safety and efficacy of endoscopic therapy has been supported by multiple meta-analyses (38). Complete remission of dysplasia is between 85 and 100% and complications are mild and usually treated endoscopically. The calculated 5 year survival for mEAC after endoscopic therapy ranges between 93 and 98% without procedure related deaths (34,39).

However, recurrence rates are very divergent and can be as high as 22% after 2 years. Surveillance endoscopy must thus be continued (40,41). Retreatment seems to be safe and efficient (42).

EMR, with or without RFA, is an efficient and safe treatment for HGD and mEAC

EMR is indicated in all superficial visible lesions and in all flat lesions with HGD or cancer (staging and treatment).
After EMR removal, the remaining metaplasia should be eradicated, preferably by RFA.

Staging for HGD/mEAC

- **Visual**
- **Lifting sign**
- **EMR**

The utility of EUS is controversial

Is there still a place for surgery in mEAC ?

Given the mortality that ranges from 2% in expert centers to 20% elsewhere, versus 0,04% for endoscopy and, the morbidity that ranges from 18-48% after esophagectomy, surgery cannot be justified anymore for mEAS (43,44).

However, in some individual cases esophagectomy could be discussed, e.g. in patients in whom no endoscopic follow up can be assured.

Submucosal cancer (smEAC)

The submucosa in divided in 3 equal layers sm1, sm2 and sm3. In submucosal (sm) cancer lymph nodes are present in at least 8,3% in superficial mucosal disease (sm1) and in ≥ 15% in sm2 and sm3. These patients should be referred to surgery (32).

Discussion exists about invasion depth of < 500 μm, especially in small tumors (< 2 cm) polypoid or flat, with good to moderate grade of differentiation and without invasion in lymph vessels or veins (45,46). Indications must be discussed case by case, taking into account the risk of surgery and the general condition and the personal medical history of the patient.

If endoscopic treatment has been performed in these discussable cases, endoscopic and EUS surveillance every 3 months for 2 years and every 6 months for at least 5 years have been proposed (38).

Submucosal invasion is a contraindication for endoscopic therapy

In high risk patient, case by case discussion is necessary when limited (< 500 μm) invasion in the submucosa is present

The treatment of patients with portal hypertension and esophageal varices

When HGD or mEAC is found in patients with coagulation problems and portal hypertension but without visible varices, EUS Doppler should be used to search for submucosal varices. If varices are present (visible on endoscopy or EUS Doppler) varices should be eradicated with the techniques available (rubber banding, injection therapy). After minimum one month, once eradication has been confirmed, EMR or RFA can be applied.

When concern of bleeding is too high or eradication has failed, rubber banding without snaring can be applied with biopsies taken from the top of the pseudopolyp (47,48).

Chemoprevention or anti-reflux surgery

The underlying cause of metaplasia is gastro-intestinal reflux disease which creates the idea that preventing reflux could alter evolution. However the key drivers of the development of dysplasia and EAC are unknown and until now, neither proton pump inhibitors (PPI) treatment nor anti-reflux surgery has been able to show convincing data in preventing EAC.

Nevertheless are PPI the most used agents for chemoprevention although the prevalence of EAC is increasing significantly despite increased use of PPI. Multiple studies addressing the question are published but most are epidemiological non-controlled studies or small surgical series. However, most studies agree on the fact that the progression to cancer is slowed down when PPI are used, taking into account that 40% of patients will have incomplete acid suppression with a PPI treatment (49).

Results with NSAID, aspirine and statins are more promising, showing a reduced risk for developing adenocarcinoma of 41% for regular NSAID use and 43% for statins and even a 74% decrease when used together. Nevertheless, because of conflicting results, possible side effects and cost benefit (a large number of patients should be treated to prevent one EAC), routine use is not yet advocated in patients with no other indication for these medications (e.g. cardiovascular disease) (50). Consequently, in search for an inexpensive and safe agent, a randomized trial with esomeprazole, with or without low dose aspirin (ASPECT) was started. End results are to be expected in 2020 (51).

Concerning anti-reflux surgery, there seems to be a trend to less cancer compared to PPI therapy. However, results are conflicting and anti-reflux surgery is actually not advised in the prevention of EAC (52,53).

What about chemoprevention after endoscopic treatment ? This issue has been addressed by a small study and shows a negative relationship between ongoing acid exposure and the likelihood of remission after ablation (54). Until more evidence is available it seems best to keep patient on high dose PPI after endoscopic treatment.

Whatever treatment is pursued, surveillance remains important, because the risk of cancer, although smaller, still remains present.

Conclusion

Metaplasia of the esophagus is a precursor of esophageal adenocarcinoma, a cancer with a poor prognosis and an increasing incidence. Guidelines for surveillance are proposed by all professional societies with small differences in timing. However, there is still no consensus on the definition of Barrett's esopaghus. Some societies continue to use Barrett in the restricted form (intestinal metaplasia) while others accept any metaplasia, independent of the subtype (cardiac, intestinal or gastric).

The goal of surveillance of esophageal metaplasia has evolved from early detection of cancer to early detection of pre-cancerous metaplasia to allow endoscopic therapy. The endoscopic therapy has the intention to stage, to cure, to prevent progression and to prevent metachronous lesions to develop. Firm indications for endoscopic therapy are HGD and mEAC. The actual treatment is EMR/ESD for all visual abnormalities and areas of cancer on biopsies, followed by RFA for the remaining metaplasia. For LGD, surveillance versus RFA is still under discussion. The main reason for this is the wide interobserver variability with large differences in evolution between confirmed and unconfirmed LGD.

The endoscopic treatment allows complete remission of dysplasia in most cases (90-100%) and of metaplasia in the majority of cases, with low complication rates and acceptable morbidity (treatable stenosis). However, a median of 3 treatments is usually required to achieve remission, and recurrence is as high as 15% in the following 5 years which means that a tight endoscopic surveillance is mandatory. Strategies to reduce recurrence like chemotherapy or anti-reflux surgery need to be explored better and can actually not decrease or replace surveillance.

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