

suspected recurrent OG cancer in previously asymptomatic patients. **Methods:** A web-based survey of 42 questions was sent to surgeons performing OG cancer resections at high volume centers. The first section evaluated the structure of follow-up and the second, determinants of follow-up. Two rounds of a modified Delphi consensus process and a further consensus workshop were used to determine symptoms warranting further investigations. Symptoms with a 75% consensus agreement as suggestive of recurrent cancer were included in the core symptom set. **Results:** 27 surgeons completed the questionnaires. A total of 70.3% of centers reported standardized surveillance protocols, whereas 3.7% of surgeons did not undertake any surveillance in asymptomatic patients after OG cancer resection. In asymptomatic patients, 40.1% and 25.9% of centers performed routine imaging and endoscopy, respectively. The core set that reached consensus, consisted of eight symptoms that warranted further investigations included; dysphagia to solid food, dysphagia to liquids, vomiting, abdominal pain, chest pain, regurgitation of foods, unexpected weight loss and progressive hoarseness of voice. **Conclusion:** There is global variation in monitoring patients after OG cancer resection. Eight symptoms were identified by the consensus process as important in prompting radiological or endoscopic investigation for suspected recurrent malignancy. Further randomized controlled trials are necessary to link surveillance strategies to survival outcomes and evaluate prognostic value.

KEY WORDS: esophageal cancer, gastric cancer, surveillance, symptom, endoscopic.

INTRODUCTION

Esophago-gastric (OG) cancers are associated with a range of symptoms, including progressive dysphagia and weight loss.¹ These symptoms may also be associated with recurrent disease after initial curative treatment, which typically involves a combination of surgery, and chemotherapy alone or combined chemoradiotherapy.² Symptoms such as dysphagia or weight loss may trigger endoscopic and radiological investigations on a suspected cancer pathway, which is designed to diagnose OG malignancies in a timely manner.³ However, in the United Kingdom, the National Institute of Clinical Excellence (NICE) does not have any standardized recommendations for follow-up after curative treatment for OG cancer in the previously asymptomatic patient.^{4,5} Furthermore, follow-up protocols vary considerably on a global scale.¹¹⁻¹³ For example, in Japan, high intensity follow-up involving both computed tomography (CT) and endoscopy is advocated in many high-volume OG centers, and in some centers in the United States three monthly CT scans and blood tests are recommended for the first 3 years after curative treatment.^{6,13}

Unlike other GI cancers, there is an international lack of consensus concerning standardized surveillance protocols following curative treatment of OG cancer.⁷ Previous observational studies have evaluated different surveillance protocols consisting of clinical examination, imaging and endoscopy; however, they are usually underpowered to show significant differences.⁸ Furthermore, follow-up regimens vary considerably between OG centers. In fact, we have previously captured this variation in clinical practice and physician attitudes towards surveillance within the UK's centers.⁹ As such, patients may have developed advanced disease by the time they report new and unexpected symptoms suggestive of recurrent cancer. For example, symptoms such as dysphagia may suggest post-operative complications such as a benign anastomotic stricture, or recurrent cancer, especially

if experienced later on in the timeline since surgical intervention.¹⁰ It is important to recognize the presentation of specific new onset symptoms in a previously asymptomatic patient require further investigations for recurrence, so that clinicians can offer appropriate treatment options early enough to optimize survival outcomes. In this study, we aim to identify a core set of new-onset symptoms that should trigger radiological or endoscopic investigations following OG cancer resection through an electronic Delphi (modified Delphi) consensus process.

Methods

This study is the culmination of a larger evidence generation process on surveillance after resection of OG cancer.^{9,11} The Delphi methodology was used based on previous similar evidence generation processes within the field.^{12,13} This modified Delphi consensus was carried out in three stages using Qualtrics, an online survey platform (Qualtrics XM, USA). Access to Qualtrics was provided by Imperial College London. For each stage, a link to an online survey was sent via e-mail to selected consultant/attending-level OG surgeons working in high-volume centers in the UK, Europe, North America and Australia. Both centers and respective surgeons were selected based on the volume of OG cancer resections performed on average each year. Initially, a scoping survey was performed that sought to delineate factors such as case volume per year, variation in frequency and modality of follow-up investigations after surgery for OG cancer and clinical factors such as tumor histology and post-operative complications in triggering endoscopic or radiological follow-up investigations.

The second stage of the consensus included two rounds which were pre-determined at study conception. A set of 28 symptoms was sent to all participating surgeons to start to identify the core symptom set triggering endoscopic or radiological

investigations for suspected cancer recurrence. These symptoms were selected based on the Lasting Symptoms After Esophageal Resection (LASER) study where they were the most prevalent seen by long-term survivors following surgery.¹⁴ Surgeons were therefore asked to rate, in their opinion, the level of importance of each symptom at triggering radiological or endoscopic investigation to detect cancer recurrence, using a 5-point Likert scale (1 = not at all important, 5 = extremely important). After the first round, any symptoms with a 75% or higher overall consensus were accepted if deemed as important in triggering endoscopic or radiological investigations. The value of 75% was used as consensus threshold based on a systematic review by Diamond *et al.* on methodology in reporting Delphi studies.¹⁵ All remaining symptoms were carried forward into the second round of the Delphi where this process was repeated to generate the final core symptom set. Feedback was anonymized between rounds, and the data from each round was collated and presented to the invited surgeons. Both rounds of modified Delphi were user tested prior to being sent. Finally, a third virtual consensus workshop was organized to discuss the addition of other symptoms that were not initially covered by the questionnaire but proposed in the open-ended sections of the first two rounds. All data are expressed as percentages where frequency or proportions are reported. The complete questionnaire and the list of participating centers are provided as a supplementary file (Supplementary file 1).

RESULTS

Characteristics of survey responders

Twenty-seven surgeons completed the questionnaire. Of the survey responders, all were consultants or attending surgeons. Six were from the UK; two from Australia; three from North America; and the remaining sixteen from European centers. All responses came from centers that performed at least 20 esophageal resections per year, with over 59.3% of centers carrying out more than 60 resections. Centers generally carried out fewer gastric resections with 88.9% of centers performing fewer than 60 gastric resections. Seven centers performed more than 100 esophageal resections, although none performed over 100 gastric procedures in a year. Furthermore, 74.1% of centers had fewer than five surgeons, while the remainder had 5–10 surgeons undertaking these resections.

Pattern of surveillance protocols

All patients were followed up by a member of the surgical team in the outpatient clinic setting. For both esophageal and gastric cancers, 96.3% of surgical departments arranged routine follow-up, while the

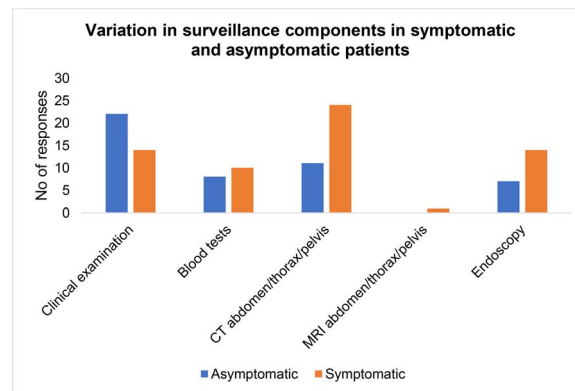


Fig. 1 Variation in surveillance components in symptomatic and asymptomatic patients.

remainder followed their patients based on specific clinician or patient related factors. After esophagectomy or gastrectomy, 70.3% of centers reported standardized surveillance protocols for all patients, while 29.6% tailored it to patient and physician preferences. One center did not undertake surveillance of asymptomatic patients. The average time taken to the first outpatient follow-up appointment after discharge varied from 2 weeks to more than 6 weeks, with 75% of centers, seeing patients within 4 weeks of surgery, and two centers at more than 6 weeks post-surgery.

The components of follow-up varied by center (Fig. 1). In asymptomatic patients, 81.4% performed clinical examination of the chest and abdomen, while 29.6% also carried out blood tests such as basic blood panel and tumor markers. Furthermore, 40.7% arranged routine CT scan of the thorax, abdomen and pelvis. In 25.9% of centers, patients also underwent planned esophagogastroduodenoscopy during follow-up. In contrast, 51.8% only perform clinical examination on symptomatic patients. A total of 37% of surgeons also arranged for blood tests. In symptomatic patients, 88.8% surgeons reported they arrange for CT scan of the thorax, abdomen, and pelvis, while 51.8% would also opt to carry out endoscopy. Lastly, 31% routinely discuss patients in a multi-disciplinary team (MDT) setting if requiring endoscopic or radiological investigation for possible cancer recurrence. In 23.1%, this is done on a case-by-case basis. Of note 7.7% centers never discuss patients in an MDT even if cancer recurrence was suspected on endoscopy or cross-sectional imaging.

Factors prompting further investigations in surveillance

New symptoms were the most important factor initiating investigations during follow-up (Fig. 2). The majority of centers (85.2%) reported this as either a very important or extremely important factor. This was closely followed by pathological tumor stage/grade, which was rated as important

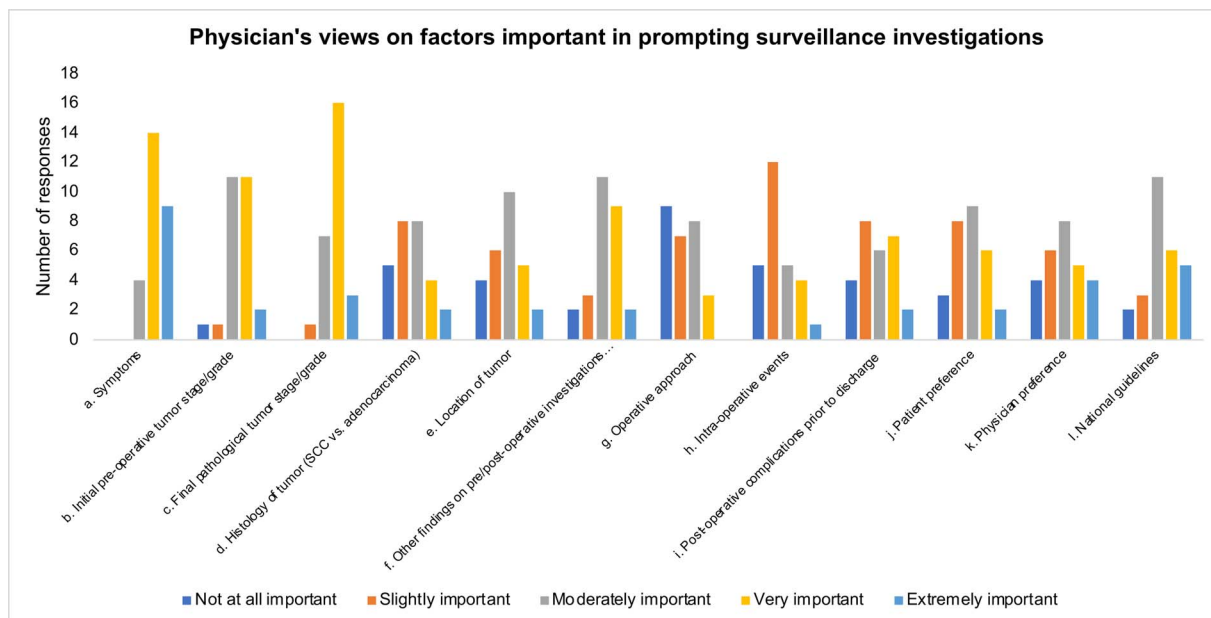


Fig. 2 Factors to prompt surveillance investigation for possible cancer recurrence.

by 70.4% of surgeons. Half of the surgeons also rated initial pre-operative tumor stage/grade as important in influencing post-operative surveillance, while 41% mentioned findings on investigations such as blood tests, imaging and endoscopy as a crucial determinant. This was closely followed by patient preference, physician preference and national guidelines as important factors in initiating further surveillance, with 37%, 33.3% and 40.7% of surgeons rating them as important. Other tumor-level factors such as location and post-operative histology were not considered important (22.2% and 25.9%, respectively). Operative factors such as surgical technique (open/laparoscopic/robotic) or intra-operative events were not considered as important, with 59.2% and 62.9% of responding surgeons rating each as either not at all or only slightly important respectively. Post-operative events prior to discharge and first clinical visit did not rank highly either, with only 33.3% rating it as important.

New-onset symptoms prompting further investigations in surveillance

In round 1 of the Delphi process, only three symptoms reached consensus as important new onset symptoms in a previously asymptomatic patient to initiate further investigations during surveillance. These included dysphagia to solid food; dysphagia to liquids; and vomiting. In contrast, three symptoms were deemed as unimportant, including intermittent voice problems, pain from scars on the chest, and pain from scars on the abdomen. These six symptoms were not carried onto the second round of the Delphi process (Table 1). From the second round, three

further symptoms reached consensus as important in association with recurrence, including abdominal pain (88.4%), chest pain (84.6%), and regurgitation of foods (84.6%) (Table 2). Four symptoms were not deemed as important after round 2, which included sweating after eating (19.2%), dizziness after eating (19.2%), loose bowel motions or diarrhea after eating (15.4%) and low mood (15.4%). In the third online consensus workshop, two symptoms, namely unexpected weight loss and progressive hoarseness of voice, were added after reaching 100% consensus amongst the attendees. The remainder of the symptoms failed to reach consensus after two rounds of the Delphi process (Table 2).

DISCUSSION

This study highlights the large degree of global heterogeneity between centers relating to post-operative surveillance after esophageal or gastric resection for cancer. In addition to this, it reflects the lack of standardized national protocols for surveillance of patients after surgery for esophageal and gastric cancers in high volume international centers. Furthermore, it highlights a discrepancy between surgeons with respect to the most important factors influencing how surveillance is undertaken. As expected, investigations were not routine. The most pertinent factor was whether the patient was symptomatic or not. Of the various possible symptoms given, our respondents indicated that the new onset of eight of these in a patient who has previously undergone OG resection for cancer and has been asymptomatic, were suggestive of possible disease recurrence and should

should be considered in how surveillance is carried out, specifically, what investigations it should comprise of and how frequently they should be performed. Further prospective, large-scale national trials are required to standardize how monitoring for recurrence should be undertaken in symptomatic and asymptomatic patients, and link these to both survival outcomes and patient-related outcomes on quality of life. The eight-symptom tool generated here should further be validated within existing cohorts to test if it is possible to identify patients at risk of recurrence based upon symptoms alone.

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