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A large pill to swallow? How health-seeking behaviors can impact a screening program

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Globally among malignancies, esophageal cancer ranks seventh in incidence and sixth in mortality, with the highest regional incidence in East Asia due to the large disease burden in China [1]. While the age-standardized incidence and deaths from esophageal cancer have been declining in China, the overall number of new cases and deaths from the disease are increasing [2]. Esophageal cancer is often fatal, but can have excellent survival rates when treated at early stages.

Numerous screening programs with heterogeneous methodology have been implemented to help improve early detection [3]. An ideal screening test should be effective, cost-efficient, well-tolerated, and also accessible to the at-risk population. Both rigorous trial-level data and real-world evidence are needed to ensure that the benefits of a screening program outweigh any potential harms, and to specifically demonstrate an improvement in survival as the primary outcome. As per the American Society for Gastrointestinal Endoscopy's (ASGE) 2019 guideline on screening and surveillance of Barrett's esophagus, "the ideal study to assess the effectiveness of screening and surveillance is an RCT [or randomized clinical trial] of individuals...to undergo screening upper endoscopy (EGD) compared with no screening [4]."

The first large-scale RCT evaluating the efficacy of a population-based endoscopic screening program was performed by Yang Ke and colleagues from 2012 to 2016 in a high-risk region in northern central China [5]. The Endoscopic Screening for Esophageal Cancer in China (ESECC) trial randomized almost 34,000 individuals to screening with upper GI endoscopy and biopsies or a control arm. Of 15,299 screened individuals, 136 screened positive for malignancy. Two-thirds were "early-stage" lesions defined as severe dysplasia and carcinoma-in-situ, and the rest were considered "non-

early stage" carcinoma. The 10-year results from this study are still pending.

The authors, meanwhile, have performed an interim evaluation of screen-positive ESECC patients to determine the achievability of timely follow-up and treatment [6]. This mixed-method study used claims data from China's national rural health insurance system and semi-structured interviews conducted at least 586 days, or 1.5 years, after initial screening. The authors obtained clinical records for 98% of the ESECC screen-positive participants and had a commendable 84% interview response rate.

Despite receiving counseling about a positive screen, almost 40% of participants did not obtain the recommended follow-up. Notably, the vast majority had early-stage lesions that would benefit from early intervention. Subsequent interviews revealed that 55% of these participants correctly sought further evaluation but received management that did not cohere to consensus guidelines. The remaining 44% did not seek further clinical care due to low health awareness or socioeconomic reasons. These results highlight the importance of patient and provider education in ensuring that all parties agree on the clinical recommendations after being screened. For those obtaining treatment, radical surgery with or without chemo-radiation was most common, and only 25% of early-stage lesions were treated endoscopically, leading to suspected overtreatment for many patients. This was likely due to accessibility, as all endoscopic resections were performed at tertiary health-care facilities, and rural areas may not have the institutional availability of endoscopic services.

A successful screening program relies on screen-positive participants obtaining the recommended treatment in a standardized fashion. The findings by Wang et al illustrate the obstacles to effective screening for their target population, and the authors provide a patient-centered evaluation of the barriers to appropriate care. They point towards a need to involve patients at a commu-

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nity level, and specifically discuss engaging village doctors and local health officials who may hold greater sway in the local population. They also demonstrate that having a streamlined referral network increased both their rates of timely treatment and endoscopic resection for early-stage lesions by almost 20% each. These types of interventions may be essential to preserving any potential benefit of a screening test.

The lack of outcome data is a major limitation of this study. By 1.5 years after a positive screen, untreated patients may begin to exhibit symptoms due to progressive disease, and treated patients may have adverse sequelae from surgery or chemoradiation. It would be useful to compare the morbidity and mortality of patients based on whether they followed treatment recommendations. We ultimately await the clinical results of the ESECC trial, but it is possible that the study's conclusions will be limited by low rates of compliance with medical guidelines.

Additional limitations are inherent to the study design, such as the retrospective nature and potential for recall bias. However, by achieving an impressive interview participation rate after screening, the authors were able to provide a comprehensive evaluation of the factors affecting patient follow-up. These insights will be vital in guiding future endoscopic screening programs in similar demographic settings.

Declaration of Competing Interest

We declare no competing interests.

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