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Malignancy Workup in Cryptogenic Stroke

A Survey of Canadian Stroke and Thrombosis Experts

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Abstract

Background and Objectives

The diagnostic workup for patients with cryptogenic stroke includes investigating for occult cancer, which is known to increase the risk of stroke. Current guidelines do not provide specific recommendations regarding the optimal approach for occult cancer screening after cryptogenic stroke. We surveyed Canadian stroke and thrombosis physicians to determine current workup preferences for detecting occult cancer after cryptogenic stroke.

Methods

We designed and distributed an anonymous online survey targeting physicians who manage patients with cryptogenic stroke through professional memberships of the Canadian Stroke Consortium and Thrombosis Canada. Using 4 clinical scenarios representative of patients with cryptogenic stroke with different ages (younger or older than 50 years) and from both sexes, we asked respondents which tests they routinely recommend when investigating for occult cancer among a list of laboratory investigations, imaging, and procedures. Results were analyzed using descriptive statistics.

Results

We received 138 responses to 5 survey questions. The most commonly recommended investigations were complete blood count (79%), creatinine (63%), and coagulation tests (56%), and the most frequently recommended imaging test was CT of the abdomen and pelvis (39%). A minority of respondents indicated they would order guideline-directed age-appropriate cancer screening. Approximately half of surveyed specialists deferred the workup of cancer to a primary care physician, and 12% did not suggest any cancer workup at all.

Discussion

This survey of stroke and thrombosis experts found heterogeneity in testing for cancer screening in patients with cryptogenic stroke, with the majority either not screening at all or deferring tests to primary care providers. Our survey highlights the need for better evidence and evidence-based recommendations to guide the approach to cancer screening in this population.

MORE ONLINE

Supplementary Material

Introduction

Cryptogenic stroke is a subtype of ischemic stroke in which the etiology remains unknown or uncertain after standard and advanced and specialized diagnostic testing.[1] In these situations, the American Heart Association/American Stroke Association (AHA/ASA) and Canadian Stroke Best Practice recommend investigating for rarer causes of stroke, which include occult cancer.[2,3] Despite these recommendations, no clear guidance exists on the optimal approach to screening for occult cancer in patients presenting with cryptogenic stroke.

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Cancer has been linked to an increased risk of stroke through multiple potential mechanisms including hypercoagulability, direct tumor effects, and cancer treatment effects.[4] Approximately 6% of patients with cryptogenic stroke are diagnosed with cancer within 1 year.[5] Patients with cancer-associated stroke have worse functional outcomes, higher mortality, and higher rates of stroke recurrence than patients with stroke in the absence of cancer.[6,7] Early detection of cancer is therefore important to optimize outcomes, by timely cancer treatment and appropriate selection of antithrombotic therapy for secondary prevention in this specific population.

Aim

Our objective was to report the current physician preference in ordering investigations for the evaluation of occult cancer in patients with cryptogenic stroke across Canada.

Methods

In collaboration with a survey methodologist and physicians specialized in stroke, thrombosis, and oncology, we designed an online anonymous survey study targeting Canadian stroke neurologists and thrombosis specialists (hematologists and internists).[8] The survey was conducted electronically on the *Limesurvey*[9] platform. Participants were recruited through email through their association with the Canadian Stroke Consortium and Thrombosis Canada.[10,11] One initial invitation and 2 reminders were sent over a period of 1 month. By beginning the survey, physicians were deemed to have given consent for their participation. We presented 4 clinical cases representing 4 demographic groups (female patients <50 years, female patients >50 years, male patients <50 years, and male patients >50 years) and asked respondents to indicate which screening tests they would recommend when investigating for occult cancer in each of these patients with cryptogenic stroke (the survey is available in eAppendix 1). Additional data are listed in eTable 1. The cutoff of 50 years was chosen given that routine cancer screening is generally recommended starting at age 50 years for individuals at standard risk of common types of cancers (e.g., breast cancer and colon cancer) with the exception of those patients with a family history or cancer and cervical cancer screening in women.[12-14] Male and female patients were also separated into 2 categories to allow respondents to select sex-specific investigations and because cancer screening guidelines differ between sexes.[12-14] We also inquired about the use or knowledge of specific guidelines to help inform decision making. The survey was piloted among local stroke experts who did not participate in the final survey. Data were analyzed using descriptive statistics and Z-scores as appropriate.

Standard Protocol Approvals, Registrations, and Patient Consents

Institutional review board approval was obtained from the Ottawa Health Science Network Research Ethics Board (OHSN-REB Protocol 20220704-01H).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

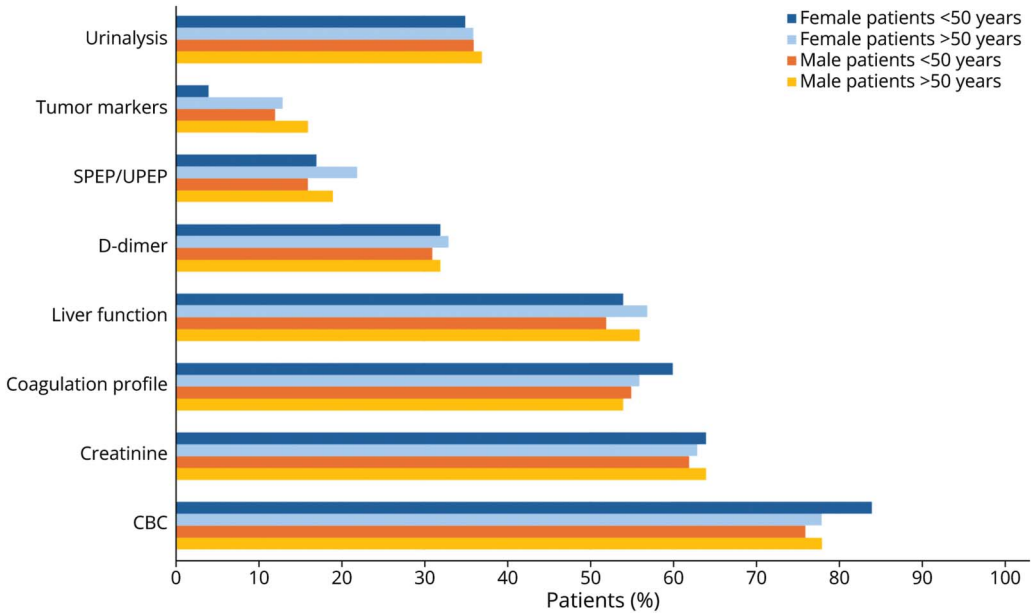
Our survey was sent to 1,169 physician members of Thrombosis Canada or the Canadian Stroke Consortium, but because of privacy restrictions, we did not have access to the number of potentially eligible respondents within these organizations (i.e., those clinicians who routinely manage patients with cryptogenic stroke). We collected 138 responses, of which 98 were complete for all 5 questions. The most frequently ordered investigations were complete blood count (CBC), creatinine, and coagulation tests (79%, 63%, and 56%, respectively), with breakdown by sex presented in Figures 1–3. Overall, 12% of physicians did not recommend any cancer investigations, including any guideline age-appropriate screening. The proportion of physicians recommending at least 1 cancer screening test was the same across age groups (88% for both <50 years and >50 years groups), and there were no differences across sexes (89.5% female patients vs 86% male patients; $z = -1.51$, $p = 0.13$). The most frequently recommended imaging test was CT of the abdomen and pelvis (36% for female patients <50 years, 43% for female patients >50 years, 38% for male patients <50 years, and 40% for male patients >50 years). With respect to guideline-directed age-appropriate cancer screening,[12-14] only 16% of respondents recommended fecal immunochemical test (FIT), fecal occult blood test (FOBT), or sigmoidoscopy in male patients older than 50 years. Moreover, only 19% of physicians recommended PAP test for female patients younger than 50 years and 15% for female patients older than 50 years ($z = -0.83$, $p = 0.41$), with 35% recommending mammogram. Approximately half (49%) of respondents indicated they would defer cancer screening decisions to primary care physicians.

Among surveyed physicians, 23% were not aware of any existing guidelines to help direct their decision and another 22% were aware of guidelines but stated they do not apply them to this patient population. When guidelines were used, 53% of all physicians reported using the Canadian Stroke Best Practice recommendations,[2] 14% specified using the Canadian Task Force on Preventative Health Care,[12,13] and fewer used AHA/ASA[3] or European Stroke Organisation (ESO).[15]

Discussion

This survey of Canadian stroke and thrombosis specialists showed heterogeneity in screening preferences for occult cancer after cryptogenic stroke, with generally low rates of screening even when age appropriate and guideline based, ranging from 16% (colorectal cancer in men older than 50 years) and 35% (mammograms in women older than 50 years). Half of respondents deferred screening to general

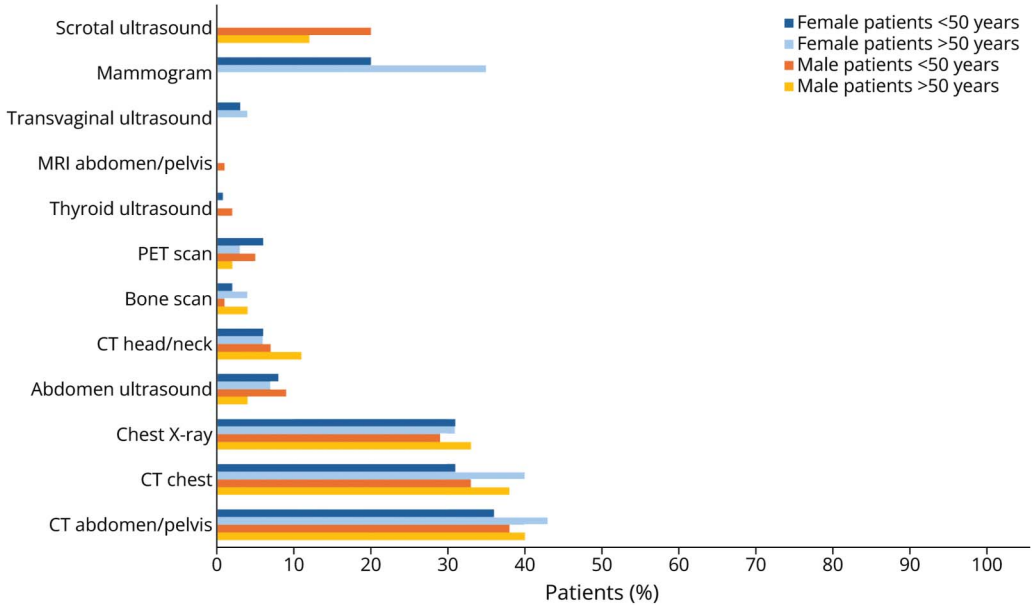
Figure 1 Distribution of Recommended Laboratory Investigations for All Patient Groups



Navy blue bars indicate responses for female patients younger than 50 years, light blue bars for female patients older than 50 years, orange bars for male patients younger than 50 years, and yellow bars for male patients older than 50 years.

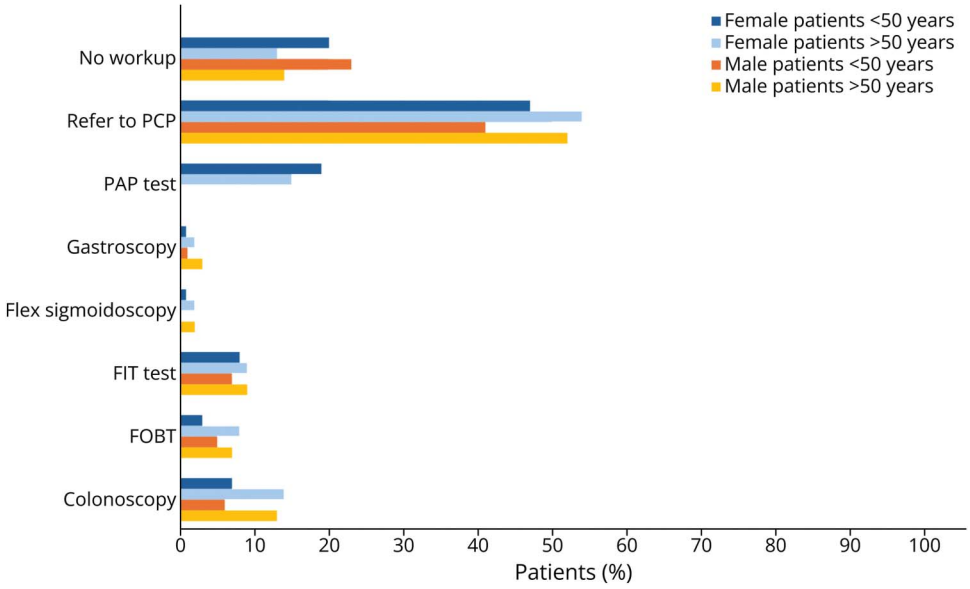
practitioners. Although most physicians ordered at least 1 test to screen for cancer, they were often nonspecific (CBC and serum creatinine), which are typically ordered as part of the first-line stroke investigations. Less than one third of specialist physicians ordered cancer-specific screening tests such as mammography, Pap smear, or colonoscopy/FIT testing. Moreover, these decisions were often made without reference guidelines. Where respondents indicated they did use guidelines, they only listed those that do not include directions for methods of cancer screening in cryptogenic stroke (Canadian Stroke Best Practice recommendations, AHA/ASA, and ESO).

Figure 2 Distribution of Recommended Imaging Investigations for All Patient Groups



Navy blue bars indicate responses for female patients younger than 50 years, light blue bars for female patients older than 50 years, orange bars for male patients younger than 50 years, and yellow bars for male patients older than 50 years.

Figure 3 Distribution of Recommended Procedural Investigations for All Patient Groups



Navy blue bars indicate responses for female patients younger than 50 years, light blue bars for female patients older than 50 years, orange bars for male patients younger than 50 years, and yellow bars for male patients older than 50 years.

Our survey addresses the question of real-world preferences for cancer screening in patients with cryptogenic stroke. Our results are strengthened by having included specialist physicians from 2 national organizations who would have experience in the workup of occult thrombotic events, although we did not collect specific details around responder specialty. Additional limitations to our study include the potential for selection bias because our survey was only sent to 2 associations representing stroke and thrombosis. We cannot exclude the possibility that there are specialty stroke clinics run by family physicians, internists, or other vascular specialists who are not part of these associations, although this is uncommon in Canada. We also note potential participation bias and jurisdictional bias (it is possible that the single-payer public health care system in Canada predisposes to more conservative approaches to testing and screening). Moreover, the relatively small number of participants limited our ability to perform more in-depth statistical analysis of response patterns. Nevertheless, the aim of the study was to obtain an overall impression of cancer screening preferences across the country; given the degree of heterogeneity across the responses collected, it is unlikely that a larger pool of respondents would have showed a clearer pattern of screening preferences that was missed with this study. Although CBC was included in our survey as a potential screening test for hematologic malignancies, clinicians may have selected it as part of routine investigations because half stated they deferred malignancy workup to general practitioners. Some may, on the other hand, not have recommended CBC, electrolytes, and creatinine because they assumed those had already been done as part of the stroke investigations and, as per the prompt, were focusing on targeted malignancy workup. In addition, we did not offer respondents the opportunity to consider different clinical scenarios for patients with normal vs elevated d-dimer levels or lacunar vs embolic pattern of stroke on imaging; the latter being more strongly associated with coexisting cancer.[16] Finally, our clinical scenarios were designed to capture a more global view of screening preference for true cryptogenic stroke (with no risk factors) and therefore did not include important cancer and stroke co-risk factors, such as smoking. Further studies into cryptogenic stroke workup should provide more granular scenarios to explore the effects of preexisting risk factors.

The results of this survey are concerning for several reasons. Despite the known association between cancer and cryptogenic stroke, a minority of respondents would recommend age and sex-appropriate guideline-directed screening investigations even in populations for which screening is recommended by the Canadian Task Force on Preventive Health Care,[12] such as colorectal cancer screening in male patients aged 50 years and older or cervical cancer in female patients of all ages and breast cancer in female patients aged 50 years and older. Respondents recommended colon and breast cancer screening for an even lower percentage of male and female patients younger than 50 years, who overall are at lower risk of malignancy as compared with their older counterparts, but have seen their incidence of cancer rise since the 1980s.[17] If these results adequately reflect real-world clinical practice, then there is a significant possibility that cancers may be missed in patients with cryptogenic stroke, affecting both the risk of stroke recurrence and affecting cancer prognosis. This concern is even more acute in the context of embolic stroke of undetermined source (ESUS), a subcategory of the cryptogenic stroke population in whom cancer may be found 10%–20% of the time.[18]

Although the reasons for low levels of screening were not addressed in this study, possibilities include a relative absence of evidence supporting or directing specific screening strategies in the cryptogenic stroke population. Physicians may prefer to avoid nonevidence-based cancer screening algorithm out of concerns of harm from false-positive testing or some may feel that it does not fall within their scope of practice. This is concerning because, as nonexperts, general practitioners may not be aware of the risk of cancer in this setting. Moreover, some studies suggest that nontargeted screening diagnoses cancer relatively rarely. For example, the National Opinion Research Center group in Chicago reported that only 14% of annual cancer diagnoses were made by screening tests, while the rest were found by targeted testing when patients presented with symptoms or signs.[19] However, it is uncertain to what degree these data are applicable when there is a recognized association between cancer and cryptogenic stroke.

In conclusion, our results support the importance of gathering better data to inform clinical practice in cryptogenic stroke. Specifically, results from clinical trials such as INCOGNITO (NCT05733416) and INVISIBLE-1 (NCT06100718) assessing the added diagnostic value of cancer screening in patients with cryptogenic stroke could inform clinical practice in important ways.[20]

TAKE-HOME POINTS

- There is heterogeneity in screening practices. There is significant heterogeneity in the screening approaches for occult cancer among Canadian stroke and thrombosis physicians managing patients with cryptogenic stroke. This highlights a lack of consensus on optimal screening strategies in clinical practice.
- There is limited use of guideline-directed screening. Only a minority of specialists recommended age-appropriate cancer screening tests such as mammograms, colonoscopy/FIT, or Pap smears, even in patient populations for whom these are generally advised.
- Specialists defer to primary care. Approximately half of the surveyed specialists deferred cancer screening decisions to primary care providers, potentially creating gaps in timely cancer detection and management in patients with cryptogenic stroke.
- There is a need for further research. Trials such as INCOGNITO and INVISIBLE-1, which are investigating the role of cancer screening in cryptogenic stroke, could provide crucial evidence to inform future clinical practice and guidelines.

Author Contributions

L. Poirier: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D.M. Siegal: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. D. Bossé: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J. Brehaut: study concept or design. B. Dewar: drafting/revision of the manuscript for content, including medical writing for content R. Lun: drafting/revision of the manuscript for content, including medical writing for content. M.C.F. Shamy: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. D. Dowlatshahi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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