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EDITORIAL

Early detection of pancreatic adenocarcinoma

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In an article in this edition of the journal Mthunzi et al. report on the geographic distribution of pancreaticobiliary malignancy in central South Africa.[1] The incidence of pancreatic adenocarcinoma (PDAC) that was calculated in clusters according to geographical region seemed to be higher than the incidence in the general South African population. This comparison needs to be interpreted with caution as the diagnoses in the study were made on clinical and radiological grounds, as opposed to the National Cancer Registry (NCR), where the diagnosis is based on histological confirmation.[2] With only a small proportion of patients with PDAC in South Africa being operated or biopsied, there is significant underestimation of the true incidence, which could have resulted in overestimation of the incidence of PDAC in the cohorts included in the study. In 2020 a total of 502 patients with PDACs were reported into the South African NCR, where it ranked as the 22nd and 21st most common tumour forms in males and females, respectively. The study in this issue identified only two PDAC patients with a family history and concluded the need for further research into identifying the obstacles around accurate identification and possibly under-reporting of genetic and familial contributors.[1]

The authors are to be commended for contributing to the epidemiology of PDAC in the South African context, as it is a leading cause of cancer death worldwide and the third leading cause of cancer death. The disease is estimated to become the second most common cause of cancer-related death in several countries by 2030.[3,4] The death rate of 11.0 deaths per 100 000 person-years is marginally lower than age-adjusted annual incidence rates of 12.9 cases per 100 000 person-years.[5] Five-year survival rates in high-income countries (HICs) for metastatic disease, regional disease and localised disease are 2.9%, 12.4% and 37.4%, respectively.[6] Unfortunately, most patients with PDAC are diagnosed with advanced-stage disease, and only 15%–20% of patients with localised disease will qualify for surgical resection.[3] This is because PDAC is notoriously difficult to diagnose in its early stages due to the tumour's subtle initial symptoms. Most patients that present with typical symptoms such as abdominal pain, unintended weight loss, and jaundice have advanced-stage disease.

As in many other cancer types, early detection of PDAC is the cornerstone of improving outcomes by diagnosing patients with early disease when curative-intended surgery is possible. Achieving this through secondary prevention entails the identification of high-risk populations, successful screening of the population for the presence of the identified risk factors and surveillance of the at-risk population with methods with high sensitivity and specificity for detection of the disease or better, pre-malignant precursor lesions.

Several risk factors for developing PDAC have been identified, most importantly genetic syndromes and familial predisposition. More than 80% of pancreatic cancers have non-hereditary KRAS somatic mutations.[7] Of the remaining, between 10% and 15% of PDACs are associated with known inherited mutations and/or familial trends. Of the syndromic risk factors, Peutz-Jeghers syndrome and hereditary pancreatitis, both associated with STK11, PRSS1, SPINK1, CTRC, CFTR, and CDKN2A mutations, have the highest risks for PDAC with relative risks of 132 and 69, respectively.[8,9]

Non-genetic risk factors such as tobacco smoking, alcohol overconsumption, chronic type 2 diabetes mellitus, obesity and the presence of chronic pancreatitis (CP) were also identified. A meta-analysis showed that the risk of PDAC in patients diagnosed with CP increased 16-fold within two years of CP diagnosis, and although the risk seemed to decrease over time, patients were still eight times more likely to develop PDAC later.[10]

Three precursor lesions of PDAC have been identified. These are pancreatic intraepithelial neoplasms (PanINs), mucinous cystic neoplasms (MCNs), and intra-ductal papillary mucinous neoplasms (IPMNs). The latter two of these are prime targets for surveillance.

Surveillance of high-risk populations for PDAC is imaging-based, specifically magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). The value of transabdominal ultrasound in the surveillance setting is compromised by suboptimal imaging of the whole pancreas, and computed tomography is not suitable due to the radiation risk. Typically, imaging surveillance for PDAC is performed using MRI and EUS alternatively.[11] The modalities have similar performance in differentiating cystic from solid lesions and for evaluating features in cystic lesions, such as septations, mural nodules, communication with the main pancreatic duct (MPD), and MPD dilatation. MRI is non-invasive and more widely available than EUS. The two imaging techniques are regarded as complementary rather than competitive. MRI has been reported as more sensitive for detecting small cystic lesions than EUS, and EUS has shown higher sensitivity for detecting sub-centimetre lesions.[12,13] EUS can also be used to guide fine needle aspiration or biopsy for a tissue diagnosis when needed.[14]

There are a number of international guidelines on surveillance for PDAC. They define the patient populations that should undergo surveillance, the frequency of imaging, and when surveillance should start and stop.[15,16] General guidelines recommend that for conditions with a lifetime risk of PDAC >10% surveillance should be performed even in the absence of a family history of PDAC. In patients with conditions with a lifetime risk of PDAC <10%, surveillance should only be performed with a family history of PDAC. With a lifetime risk of >10%, surveillance should start at an age of two standard deviations, and for patients with a risk <10%, at an age of one standard deviation before the mean age of PDAC diagnosis in the specific population. For patients with diagnosed precursor lesions, such as IPMN and MCN, a number of societies have published guidelines for surveillance.[17,18] Most guidelines recommend 12-month screening intervals in the absence of concerning abnormalities. In the presence of high-risk lesions, the intervals are shortened to 3–6 months. Surveillance should be discontinued in patients with comorbidities that are more likely to be the eventual cause of death than PDAC or if comorbidities would preclude pancreatic resection in the event of a PDAC being diagnosed.

Ensuring access of at-risk populations to a surveillance program is a prerequisite for an optimal screening and surveillance program. The currently used imaging-based surveillance methods for PDAC are expensive and, in the case of EUS, also invasive. This restricts optimal application of current guidelines to HICs and in LMICs to selected patients with private health insurance that can bear the costs. For the time being, surveillance for PDAC is therefore going to remain an endeavour limited to HICs and will, despite the clearly published guidelines, be of limited relevance in LMICs, including South Africa. The situation will only change with the identification of reliable biomarkers that can be detected in blood, saliva, or urine. Unfortunately, CA19-9, the most extensively investigated and used biomarker in PDAC, lacks both the sensitivity and specificity required for a screening test. Many novel blood biomarkers are being assessed, including circulating DNA testing for circulating miRNAs and exosomal markers, metabolomics and multi-marker panels for early PDAC, but as yet have not translated into clinical applications.[19,20]

In the South African context, a wide role-out of PDAC screening and surveillance programs will be challenging, if not impossible, due to financial constraints and healthcare infrastructure disparities, in particular in the public sector. Precluded by the availability and cost of currently used imaging-based surveillance methods, surveillance will only become a reality with the development of accessible and cost-effective biomarkers. Non-imaging-based techniques, for example, metabolomics and multi-marker panels, which offer more promising avenues for early detection of PDAC, need to be explored in our patient populations.

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