Research

Reducing colorectal cancer mortality in South Africa: experiences and progress from the South African National Cancer Prevention Services

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Aim

The incidence rates of colorectal cancer are rapidly increasing in South Africa. Previous studies have shown that the prevalence of inherited colorectal cancer in South Africa is 3-5 times higher than in high-income countries. Targeted screening and surveillance programmes for individuals with known colorectal cancer-causing mutations have resulted in increased life expectancy. The South African National Cancer Prevention Services (SANCaPS), was established to implement national systems for identifying individuals with inherited cancers, improving their clinical management, and reducing the overall disease burden.

Methods

Using colorectal cancer as an example, SANCaPS aimed to extend surveillance and management practices from the Western Cape to a national level. The goals included improving the quality of pathology reporting, establishing counselling systems for at-risk individuals, developing cost-effective mutation detection protocols, identifying and counselling at-risk family members, providing mutation testing, organising endoscopic surveillance programmes for high-risk individuals, setting ethical frameworks for research, and extrapolating learnings from the inherited colorectal cancers surveillance programme to other cancers with known hereditary predispositions.

Results

SANCaPS initiated the standardisation of national pathology reporting for colorectal cancers. Currently, a minimum core pathology dataset collection is being piloted in the National Health Laboratory Service's TrakCare system. Subsequently, SANCaPS aims for broader adoption through stakeholder engagements. This will help to identify patients with mismatch repair-deficient colorectal cancers, facilitate research, and improve reporting.

Conclusions

To improve patient outcomes, this consultative process and framework will be replicated to introduce standardised management workflows for other common cancers, including breast, prostate, uterine, and others.

Introduction

Cancer is among the leading causes of death worldwide. The World Health Organization (WHO) identified that, in 2020, non-communicable diseases (NCDs) accounted for approximately 70% of the 55.4 million deaths around the world, with nearly 10 million of those being caused by cancer.[1] Historically, cancer deaths have been overshadowed by infectious diseases such as HIV/AIDS, and many other conditions associated with poverty. However, as cancer mortalities increase, nations represented by the United Nations (UN) and WHO have emphasised the need to address the rising tide of these insidious pathologies.

As a member of the UN, South Africa (SA) needs to grapple with this circumstance. This paper proposes that by attending to the most easily traceable cancers, systems can be put in place that ultimately will form the backbone from which some cancers can be identified early; an activity that is so important for the containment of malignancy. Screening for cancers, then, should be an imperative that SA cannot deny. The most common cancers are breast, lung, colorectal and prostate cancers. A proportion of cancers are inherited,[2] thus mortality of cancers can be reduced by targeted screening and early interventions.[3]

The incidence rates of colorectal cancer (CRC) are rapidly increasing in SA, with disproportionately high mortality rates.[4] Previous studies have shown that the prevalence of inherited CRC in SA is 3-5 times higher than in high-income countries.[5,6] Targeted screening and surveillance programmes for individuals with known colorectal cancer-causing mutations may result in increased life expectancy.[7,8]

Many high-income countries have population-based national screening programmes for common cancers.[9] These programmes either do not exist, or are very limited in middle and lower-income countries.[9] Population-based screening programmes are unlikely to be introduced in South Africa in the short term, even for the most common cancers, because of the complexity of the pathways of care needed for the execution of most screening programmes.

A different approach to preventing death from cancers is to identify individuals who are at particularly high risk for their development. Management can then target these individuals and their cancers, either by preventing them, or by detecting them at an early stage while they are still curable.

Hereditary cancers represent a definable and significant risk, irrespective of class and ethnicity. Any programme attending to the subset of hereditary cancers, through necessity, will ultimately have to engage with poor isolated communities and will engender services that are equitable in provision. In addition, inherited cancers tend to occur more in younger individuals than the sporadic variety and are likely to have a greater effect on minors.[10,11]

The South African National Cancer Prevention Services (SANCaPS) was established to set up national systems to identify individuals with inherited cancers, improve their clinical management, and reduce the disease burden. Based on evidence, SANCaPS, nationally, has:

1. Established systems for the detection of inherited cancers.
2. Streamlined identification of genetic disease-causing mutations in already affected patients.
3. Established systems for identifying at-risk family members.
4. Coordinated cost-effective preventative medicine for at-risk family members.

Methods

The National Cancer Registry of South Africa (NCR) is mandated to collect the incidence of histopathologically diagnosed cancers nationally. Public and private healthcare laboratories report all histology, cytology, and bone marrow examinations of newly diagnosed cancer patients to the NCR.[12] The Registry currently provides excellent epidemiological data on cancer incidence but is not used as a primary care preventative tool. The NCR has consistently published data on the incidence of cancers in South Africa, deriving their data from histopathology records.

Currently, histopathology reports are narrative. Searching these reports electronically is complex. Many countries have adopted minimum dataset pathology reporting as a mandatory standard. We have developed a minimum dataset colorectal cancer report format, based on the colorectal cancer template of the International Collaboration on Cancer Reporting (ICCR), which uses dropdown menus and essential fields.[13] (See Supplemental Table 1).

Results

Histopathological reports within the National Health Laboratory Service (NHLS) are uploaded daily into the Central Data Warehouse. We plan to sort these reports electronically as they arrive and to identify those individuals

who are likely to have inherited predispositions to their tumours. It is estimated that between 10 and 15 colorectal cancers per week will be flagged nationally for further investigation. This will include the preparation of a family pedigree and the determination of the at-risk family members. Mutation identification will be performed cost-effectively. At-risk family members will be invited to undergo testing for the disease-causing mutation identified in the proband and will then be offered surveillance.

This format is currently undergoing testing within the NHLS. The SANCaPS group has chosen to include immunohistochemical testing for mismatch repair gene products on all colorectal cancer specimens in patients under 60 years of age. Once testing has been completed, the minimum dataset reporting is planned to be integrated into the NHLS TrakCare system. With time, we anticipate that this will be integrated into the private sector as well.

Discussion

As much preliminary work has already been done on colorectal cancers, albeit in the Western Cape and Northern Cape provinces, it would be a logical place to start with an expansion programme for the rest of the country. This development has been regional and largely a contribution of the University of Cape Town. A programme to expand the provision of services capable of detecting families with inherited risk for colorectal cancer will necessitate the replication of the capabilities developed within the University of Cape Town. A national network of integrated clinical teams will best suit the management of the individual in a broader context of their family. Once systems are established, other heritable cancers, such as ovarian and uterine, breast, multiple endocrine neoplasia, etc. should be included.

Although colorectal cancer incidence is lower in South Africa (8/100 000)[4] than in many high-income countries (45-50/100 000),[14] the relative mortality rate is high (7.9/100 000 in South Africa vs 8.4/100 000 in North America, respectively[15]). Advancing age is the most important risk factor for cancer overall.[16] The population pyramid for a developing country such as South Africa differs greatly from that of developed countries as the population is much younger.[17,18] The published proportion of colorectal cancers associated with germline mutations appears to be about 6%,[19-21] but these data come from developed countries. There is evidence that in developing countries, the disease burden from inherited colorectal cancers is far higher.[22,23] Work on breast cancer in Nigeria,[24] Uganda and Cameroon,[25] and South Africa,[26] suggests a similar phenomenon. In South Africa, the breast cancer incidence is much lower than in developed countries at 1 in 27 vs about 1 in 8. In many high-income countries better access to screening has been shown to be linked to overdiagnosis, but by how much is difficult to say.[27,28]

The Familial Colorectal Cancer Unit at Groote Schuur Hospital and University of Cape Town was established nearly 30 years ago. Protocols for managing inherited colorectal cancers have been developed for use mainly in the Northern Cape and Western Cape. Currently, the largest families on pedigree have in excess of 1 000 members, and the unit manages 1 157 families (Lynch and Lynch-like families = 1 040, familial adenomatous polyposis families = 105, Peutz-Jeghers Syndrome families = 8, and juvenile polyposis families = 4). Seventy-five disease-causing mutations have been identified in 162 of these families (40 FAP, 82 Lynch hMLH1, 34 Lynch MSH2 and six other mutations) (unpublished data). Surveillance colonoscopy adds significantly to the life expectancy of individuals with a locally common hMLH1 mutation for colon cancer.[29] In addition, it is cost-effective to use molecular genetics to determine who requires surveillance.[30] An outreach surveillance programme has been developed to manage individuals who live in remote areas, and the quality of service is similar to that of the established endoscopy unit.[31]

Currently, we have yet to identify efficient software that provides the composite functions for the management of these at-risk family members. The Familial Colorectal Cancer Unit at Groote Schuur Hospital and the University of Cape Town uses several computer programs that offer different aspects of the management required. Colleagues around the world have similar software problems. We are in the process of surveying established units that manage inherited cancers. We anticipate that we will need to use the software we currently use for the near future, but we plan to work with a number of international units to develop more appropriate management tools.

Once colorectal management is in place and functioning, ovarian and uterine cancers will be subject to a similar process. Between 40 and 60% of women with mismatch repair gene mutations develop uterine cancers at a young age, frequently before they manifest colonic neoplasms. Breast cancer will then need to be integrated on a national basis.

Recommendations

Cancer mortality can be reduced by designing and implementing strategies to identify family members at high risk of developing cancers. SANCaPS aims to identify cancers that have germline mutations from pathology reports collected by the National Cancer Registry and implement management for those high-risk individuals.

Conclusion

In a resource constrained environment, population screening is unaffordable. However, the identification of young individuals at extremely high risk for the development of cancers of the colon, breast, uterus and ovary and the institution of management protocols will reduce cancer related mortality.

Supplemental Table 1. Minimum database for colorectal cancer reporting. Compiled by A van Wyk & H Vreede on behalf of the SANCaPS group. Based on the ICCR Colorectal Cancer Dataset (1st ed.). Apr 2020.

REPORTING SHEET FOR COLORECTAL CARCINOMA (includes neuroendocrine carcinoma and MiNEN but excludes well-differentiated neuroendocrine tumours)	
CLINICAL:	
Clinical history:	
Neoadjuvant therapy: *Administered / Not administered / Not specified* Operative procedure: *Abdominoperineal resection / Anterior resection, high / Anterior resection, low / Anterior resection, not further specified / Hemicolectomy, left / Hemicolectomy, right / Hemicolectomy, right extended / Hartmann's procedure / Proctocolectomy / Sigmoid colectomy / Transverse colectomy / Total colectomy /* *Not specified / Other*	
If other: specify	
MACROSCOPIC:	
Tumour site: *C18.0 Caecum / C18.2 Colon, ascending / C18.3 Colon, hepatic flexure / C18.4 Colon, transverse / C18.5 Colon, splenic flexure / C18.6 Colon, descending / C18.7 Sigmoid colon / C18.9 Colon, not otherwise specified / C19.9 Colon, rectosigmoid / C20. 9 Rectum / Not identified / Other*	
If other: specify	
Maximum tumour dimension: mm	
Additional tumour dimensions *(optional):* x mm	
Perforation: *Not identified / Present, not involving tumour / Present, through tumour (tumour perforation)* ***Note:*** *This element refers to perforation that is evident on macroscopy*	
Other macroscopic:	
Key to blocks:	
For rectal cancers only: Relation to anterior peritoneal reflection: *Astride / Entirely above / Entirely below / Not applicable* Plane of mesorectal excision: *Intramesorectal (near complete) / Muscularis propria (incomplete) / Mesorectal fascia (complete) / Not applicable*	
MICROSCOPIC:	
Histological tumour type: *Adenocarcinoma not otherwise specified (NOS) 8140/3 / Serrated adenocarcinoma 8213/3 / Adenoma-like adenocarcinoma 8262/3 / Micropapillary adenocarcinoma (>=5% micropapillary morphology) 8265/3 / Mucinous adenocarcinoma (>50% mucinous differentiation) 8480/3 / Signet-ring cell adenocarcinoma (>50% signet-ring cells) 8490/3 / Medullary carcinoma 8510/3 / Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) 8154/3 / Neuroendocrine carcinoma, large cell type 8013/) / Neuroendocrine carcinoma, small cell type 8041/3 / No evidence of residual tumour / Other*	
If into other structures: specify	
Lymphovascular and perineural invasion:	
Small vessel: *Not identified / Present* Large vessel (venous), intramural: *Not identified / Present* Large vessel (venous), extramural: *Not identified / Present* Perineural invasion: *Not identified / Present*	
Lymph node status:	
Number of lymph nodes examined: Number of involved lymph nodes: Tumour deposits: *Not identified / Present, specify number below* Tumour deposits, number	
Tumour budding: *Bd1 – low budding (0–4 buds) / Bd2 – intermediate budding (5–9 buds) / Bd3 – high budding (>=10 buds) / Cannot be assessed / Not applicable*	

Response to neoadjuvant therapy: *Complete response – no viable cancer cells (score 0) / Near complete response – single cells or rare groups of cancer cells (score 1) / Partial response – residual cancer with evident tumour regression (score 2) / Poor or no response – extensive residual cancer with no evident tumour regression (score 3) / Cannot be assessed / Not applicable – no known neoadjuvant therapy*

If cannot be assessed: reason:

Margin status:

Longitudinal margin status: *Cannot be assessed / Proximal margin involved / Distal margin involved / Proximal and distal margins involved / Longitudinal margin involved, unspecified / Not involved*

If not involved: distance to margin: mm

Circumferential margin status: *Cannot be assessed / Involved: specify 0 mm or to nearest 0.1 mm below / Not involved: estimate distance to nearest 1 mm or >=10 mm below*
Note: The circumferential margin is considered to be involved if tumour is 1 mm or less from the margin

If not involved (>1 mm): distance to margin: mm *(specify distance to nearest 1 mm or ≥10 mm)*
If involved (≤1mm): distance to margin: mm *(specify 0 mm or distance to nearest 0,1 mm)*
If involved (≤1mm), involved by: *Direct extension of primary tumour to margin / Focus of lymphovascular invasion present at margin / Positive lymph node at circumferential margin / Tumour deposit present at margin /*
Other: specify below

If other: specify:	

Coexistent pathology:

Polyp(s): *Not identified / Present, specify type and number below*
If present: type and number:

Co-existent pathology: *Not identified / Present, describe below*
If present, specify:

Ancillary studies:

Mismatch repair (MMR) IHC (mandatory for patients < 60 years): *Not done / Performed on previous specimen / Performed on this specimen / Result to follow*
MLH1: *Cannot be determined / Normal retained nuclear expression / Abnormal loss of nuclear expression / Not done / Result to follow*

If cannot be determined: reason:

PMS2: *Cannot be determined / Normal retained nuclear expression / Abnormal loss of nuclear expression / Not done / Result to follow*

If cannot be determined: reason:

MSH2: *Cannot be determined / Normal retained nuclear expression / Abnormal loss of nuclear expression / Not done / Result to follow*

If cannot be determined: reason:

MSH6: *Cannot be determined / Normal retained nuclear expression / Abnormal loss of nuclear expression / Not done / Result to follow*

If cannot be determined: reason:

BRAF V600E testing: *Cannot be determined: provide reason below / Not done / Negative for cytoplasmic staining by immunohistochemistry / Positive cytoplasmic staining by immunohistochemistry / Negative for BRAF V600E mutation by PCR testing / Positive for BRAF V600E mutation by PCR testing*
Note: BRAFV600E testing is generally indicated with MLH1 and PMS2 loss to distinguish between cases with sporadic MMR deficiency and possible Lynch syndrome

If cannot be determined: reason:

Comment for MMR IHC:

Loss of nuclear expression of MSH6 only: High probability of Lynch syndrome. Referral to a genetic counsellor ± further genetic testing to confirm or exclude Lynch syndrome is advised.
Loss of nuclear expression of MSH2 and MSH6: High probability of Lynch syndrome. Referral to a genetic counsellor ± further genetic testing to confirm or exclude Lynch syndrome is advised.
Loss of nuclear expression of PMS2 only: High probability of Lynch syndrome. Referral to a genetic counsellor ± further genetic testing to confirm or exclude Lynch syndrome is advised.
Loss of nuclear expression of MLH1 & PMS2, BRAFV600E negative: absence of BRAFV600E mutation suggests the possibility of Lynch

syndrome. Referral to a genetic counsellor ± further genetic testing is advised to exclude or confirm Lynch syndrome.
Loss of nuclear expression of MLH1 and PMS2, BRAFV600E positive: the presence of a BRAF V600E mutation and/or MLH1 methylation suggests that the tumour is sporadic and germline evaluation is probably not indicated.
Normal retained nuclear staining for PMS2 and MSH6 makes Lynch syndrome unlikely.
Normal retained nuclear staining for MLH1, PMS2, MSH2 and MSH6 makes Lynch syndrome unlikely.
MSI status by PCR: Microsatellite instability high (MSI-H) / Microsatellite instability low (MSI-L) / Microsatellite stable (MSS) / Not tested / Test failed

Other ancillary tests:

Histologically confirmed distant metastasis:

Distant metastasis: *Not identified / Present, specify site below*

If present: specify site:

COMMENT:

PATHOLOGICAL STAGING (AJCC/UICC TNM 8th edition):

TNM descriptor 1: *m – multiple primary tumours / r – recurrent / y – post therapy / Not applicable*
TNM descriptor 2: *m – multiple primary tumours / r – recurrent / y – post therapy*
Primary tumour: (Will be automatically completed from information already provided above)
Regional lymph nodes: *N0: No regional lymph node metastasis / N1a: Metastasis in 1 regional lymph node / N1b: Metastasis in 2 to 3 regional lymph nodes / N1c: Tumour deposit(s), i.e. satellites, in the subserosa or in non-peritonealized pericolic or perirectal soft tissue without regional lymph node metastases / N2a: Metastasis in 4 to 6 regional lymph nodes / N2b: Metastasis in 7 or more regional lymph nodes / NX: Regional lymph nodes cannot be assessed*
Distant metastasis: *M1a: Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s)) without peritoneal metastasis / M1b: Metastasis in more than one organ / M1c: Metastasis to the peritoneum with or without organ involvement / Not applicable*

DIAGNOSIS:

Tumour site: (Will be automatically completed from information already provided above)
Procedure: (Will be automatically completed from information already provided above)
Histological type: (Will be automatically completed from information already provided above)
Histological grade: (Will be automatically completed from information already provided above)
Surgical margins: *R0: No residual tumour (margins clear) / R1: Microscopic residual tumour / R2: Macroscopic residual tumour at the primary cancer site or regional node sites / RX: Presence of residual tumour cannot be assessed*
MMR status by IHC: *MMR deficient / MMR proficient / Not tested*
MSI status by PCR: (Will be automatically completed from information already provided above)

REPORTED BY:

REGISTRAR:

PATHOLOGIST:

Abbreviations

Abbreviation	Description
AIDS	acquired immunodeficiency syndrome
CRC	colorectal cancer
FAP	familial adenomatous polyposis
HIV	human immunodeficiency virus
ICCR	International Collaboration on Cancer Reporting
MiNEN	mixed neuroendocrine neoplasms
NCDs	non-communicable diseases
NCR	National Cancer Registry of South Africa
NHLS	National Health Laboratory Service
SA	South Africa
SANCaPS	South African National Cancer Prevention Services
UN	United Nations
WHO	World Health Organization

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