Review

Challenges of Urologic Oncology in Low-to-Middle Income Countries

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Posted Date: 10 July 2024

doi: 10.20944/preprints202407.0771.v1

Keywords: LMIC; Incidence; Mortality; Trends

 doi:10.20944/preprints202407.0771.v1

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Challenges of Urologic Oncology in Low-to-Middle Income Countries

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Abstract: We performed a literature review to identify articles regarding the state of urological cancers in low-to-middle income countries (LMIC). The challenges that LMIC face are multifactorial and can include, poor health education, inadequate screening, as well as limited access to treatment options and trained urologists. Many of the gold standard treatments in high income countries (HIC) are scarce in LMIC due to their poor socioeconomic status leading to advanced stage of disease at diagnosis and ultimately a higher mortality rate. These standards of care are vital components of oncological disease management, however, the current and sparse literature available from LMIC indicate that there are many obstacles delaying early diagnosis and management options in LMIC. In the era of evolving medical diagnosis and treatments, sufficient data must be gathered and understood in order to provide appropriate diagnostic and treatment options to curtail rising mortality rates, and therefore help to alleviate the burden in LMIC.

Keywords: LMIC; Incidence; Mortality; Trends

1. Introduction

Of the 20 million new cases of cancer worldwide in 2022, 29.4% were prostate, 5.6% bladder, 4.4% kidney, 1.7% testis, and 0.79% penile cancer [1,2]. The associated death rates were: 7.3%, 1.8%, 1.5%, 0.21%, and 0.28%, respectively [1,2]. Increases in urologic cancers are observed in most countries, however, the greatest overall rise in incidence and mortality is observed in low-to-middle income countries (LMIC). The expected rise in cancers can be attributed to low physical activity, high consumption of fatty and processed foods, and increased screening rates. [4–6]

Currently, there are 24 low-income and 105 middle-income countries [7]**.** Despite the incidence of urologic cancers increasing universally, the mortality rate is higher in LMIC [3,7]. The causes are likely multifactorial, including patient, provider, and environmental factors [8–10]. Moreover, challenges also stem from knowledge and training deficits, diagnostic support, limited access to operative modalities as well access to disposable tools [8].

The objective of this review is to assess the factors influencing the diagnosis and treatment of urologic cancers in LMIC, while demonstrating the necessity of investing in prevention and management strategies for those diseases in those regions.

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2. Materials and Methods

Literature search

In November 2023, a literature review using MEDLINE, PUBMED, and Google Scholar identified peer-reviewed publications assessing urologic oncology issues in LMIC was performed. Based on our inclusion and exclusion criteria, we identified 50 articles.

3. Results

The Current State of Prostate Cancer in LMIC

Over the last 20 years, there has been an increase in prostate cancer (PCa) cases in LMIC [9,11]. Universally, the incidence of PCa initially increased then gradually decreased, following the implementation patterns of prostate-specific antigen (PSA) screening [4–6,12,13]. The use of PSA screening, including in LMIC, has been influenced by recommendations from internationally endorsed PCa screening guidelines, such as the United States Preventive Services Task Force (USPSTF). For instance, in Lebanon, PSA screening initially increased between 1994 to 2012 [14]. However, following the USPSTF recommendation against use of PSA screening in 2012, only 29% Lebanese providers were recommending screening in men aged ≥50 years [14,15]. This implies that changes in cancer screening guidelines in developed countries (i.e. United States) can have significant repercussions in LMIC. This can have unintended consequences on patient-populations the guidelines were not developed to intentionally impact.

Indeed, variations in cancer screening also vary domestically and internationally amongst LMIC due to socioeconomic factors such as income. For example, Brazil is plagued with socioeconomic inequality, which may produce varying degrees of access to healthcare. This notion is supported by observations of higher PSA screening, resulting in greater PCa detection, in more affluent regions [16]. This is corroborated by Lim et. al., which observed higher incidences of PCa in higher income Asian countries compared to LMIC Asian countries.

Within the past five years, mortality rates increased in LMIC [9,17]. The highest mortality rates were observed in regions such as Polynesia, Western Africa, Southern Africa, Middle Africa, and the Caribbean: Age-Standard Ratio (ASR) per 100,000: 18.8, 20.2, 22.0, 24.8, and 27.9, respectively [1]. Similar to incidence patterns, inter-regional variations both domestically and internationally in mortality rates were observed based on socioeconomic factors. More specifically, regions with higher socioeconomic status had more favorable cancer-specific mortality rates compared to lower socioeconomic areas [6,16,18]. Based on current evidence, it is reasonable to assume factors contributing to limited PCa screening and access to care could be driving the observed cancer-specific mortality rates in LMIC, in contrast to HIC.

Treatment Options

According to the national and international PCa treatment guidelines, management recommendations are stratified based on the risk of disease progression [19,20]. Yet, in LMIC, treatment options may not be feasible due to scarce healthcare and/or patient resources [18,21,22]. As a result, adaptations to the treatment modalities are necessary. For instance, in LMIC, it has been reported that external beam radiation therapy (EBRT) hypofractionation could increase treatment capabilities from 249 to 485 courses [21]. Moreover, in terms of surgical intervention for PCa, due to limited access to advanced surgical technology (i.e. robotic surgery), it is typically performed using open-surgical techniques in LMIC [9]. It should be noted, the open-surgical management is associated with a higher morbidity compared to robot-assisted techniques, despite the oncological outcomes being relatively equivalent [23,24].

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The Current State of Bladder Cancer in LMIC

Incidence & Mortality

Bladder cancer (BCa) is the tenth most common cancer, globally. The incidence and mortality rate is higher amongst males compared to their female counterparts [1,2]. BCa, similar to PCa, has higher incidence rates in developed countries (ASR in males 20 per 100,000 per year and ASR in females 4.5 per 100,000 per year) compared to developing countries (ASR 6 per 100,000 males and 2 per 100,000 female) [25,26]. Moreover, in an observational study, it was reported the incidence of BCa is higher in developed nations (ASR: 12.76 per 100,000) compared to developing nations (ASR: 3.20 per 100,000) [27]. These differences in incidence between HIC and LMIC could stem from exposure to external risk factors. Further research is required to understand these phenomena.

Although the incidence of BC is higher in developed countries, mortality rates are greater in LMIC. More specifically, the ASR per 100,000 for mortality in LMIC was 3.73 versus 2.39 in HIC [27]. The highest mortality rates were observed in Turkey and Egypt at 6.6 and 6.5 per 100,000, respectively [28]. The relatively elevated mortality rates in LMIC may be due the fact that patients present more frequently with an advanced stage at diagnosis [29,30]. Currently, there is a lack of data investigating the incidence of advanced risk-profile at diagnosis in LMIC.

Treatment Options

In HIC various treatment options (i.e. surgery, radiation therapy, chemotherapy, and/or immunotherapy) have aided in the decline of BCa mortality [60]. Though HIC present many modalities for BCa management, barriers to treatment options are challenges in LMIC [31]. These barriers include healthcare cost, or the acquisition of healthcare resources required for treatment (i.e. intravesical therapy agents). For instance, a report from Lebanon showed, from a private payer perspective, the annual cost per patient for treatment increased from $3,114 in 2008 to $4,135 in 2017 [32]. This reflects a 32% increase in healthcare cost [32]. As a result, with the current trajectory, the cost of treatment will severely impact those reliant on the healthcare system in Lebanon that is able to cover only 20% of treatment costs, with the remaining amount burdening the patient [32]. Additionally, as aforementioned, data suggests that 50-90% of oncology patients in LMIC have limited access to treatment due to shortage of equipment and trained personnel [33,34].

The Current State of Kidney Cancer in LMIC

Incidence & Mortality

Similarly, the incidence of kidney cancers (KCa) is higher in developed countries, where the ASR per 100, 000 was 9.71 in HIC compared to 2.27 in LMIC [35]. It can be stipulated that the higher incidence of KCa in developed nations could stem from differences in lifestyle, environmental, and/or social risk factors that contribute to the development of KCa [36]. Conversely, patients in developing countries typically present with a more advanced disease at diagnosis, contributing to a higher mortality [37]. In developed countries, the likelihood of a patient being diagnosed with advanced KCa is lower due to intentional or incidental work-up for KCa, which is not always possible in LMIC due to limited access to care [37].

Regarding KCa mortality, ASR per 100,000 were 0.97 in LMIC versus 2.3 in HIC (where ASR is the weighted mean of age-specific mortality per 100,000 people) [2]. The MIR was the lowest in North America (0.25) and highest in Africa (0.63). Overall, HIC had lower MIR compared to LMIC, 0.37 and 0.50, respectively [2]. MIR is a population-based indicator for a specific cancer in a population, where the mortality rate is divided by the incidence [38]. Sung *et al* also observed that MIR was lower in countries whose total expenditure on health gross domestic product percentage was higher (R^2=0.107 and p= 0.013) [2]. The availability of technology for screening, diagnostics, and treatments in these countries may also contribute to the decreased mortality rate compared to LMIC whose mortality rate is higher compared to HIC [39]. A meta-analysis by Brand *et al* investigating the barriers to cancer care, determined delays in presentation were due to limited access to care [39]. This delay was evident

 doi:10.20944/preprints202407.0771.v1

between low-income countries with a 6.5-month delay compared to upper-middle income countries with a 1-month delay [39]. A recent study by Qu *et al* categorized delays to care as poor health literacy, insufficient health service coordination, and limited diagnostic and treatment services [40].

Treatment Options

Treatments for renal cell carcinoma (RCC) depend on the stage of the disease, whether localized or metastatic. In localized RCC there are three widely accepted approaches: radical nephrectomy, partial-nephrectomy, and thermal ablation [41]. While robotic-assisted operations for radical and partial nephrectomies are now commonplace in the developed world (decreasing morbidity, hospital stays and improving quality of life), they are scarce in LMIC [42]. Since 2019, there has been 5,582 Da Vinci Surgical Systems® installed across the globe. Of these, 63% were in the United States, and 17% was in Europe, while only 14% was in Asia, and the rest 6% were in other countries [43]. A recent study from Pakistan analyzed 119 patients (both male and female) who underwent a Da Vinci robotic surgery and determined that patients had short hospital stays (mean of 3 days) and minimal complications (17/119 patients) [44]. However, the authors noted that the cost of machine maintenance and the cost of surgery is a major obstacle in a LMIC, where the gross domestic product per capita is $1,188 and the cost of a robotic surgery is $2,156 [43,44].

Regarding treatments for metastatic RCC, a study by Bergerot *et al* compared the trends in first (1L), second (2L) and third (3L) line treatments in patients with metastatic RCC in a Brazilian health system to a previously studied cohort in the United States [45]. The authors noted substantial variability in chemotherapeutic use among different countries. Specifically, in 1L there was higher use of Pazopanib in Brazil vs US (21.7% vs 13.2%) and in 2L, Everolimus was used more in Brazil vs the United States (37.3% vs 27.8%, respectively) [74]. This variation may reflect lack of access to targeted treatments and/or physician education [45].

Barriers in LMIC

Current and future burden of urologic cancers in LMIC is an issue that must be recognized globally. As the world population continues to grow, this burden will only lead to a greater mortality-incidence ratio in LMIC.

Although it is encouraging to see few studies assessing the burden of cancers in LMIC, there continues to be sparse data investigating the reasons behind mortality rates of urologic oncological diseases in LMIC. Additionally, there are only few randomized clinical trials (RCT) in LMIC. For example, in South America and Asia the incidence rate of penile cancer is 13.8% and 56.3%, respectively, but only two RCTs originated from these regions addressing the outcome of this disease [46]. This scarcity of RCTs may prevent patients from receiving potentially beneficial experimental treatments [46]. A study analyzing the difficulties of RCTs in LMIC have outlined potential barriers, such as enrollment issues, where patients in LMIC may be hesitant to participate due to unfamiliar terms (like “randomization”) or cultural resistance towards foreign documents [47–49]. These findings highlight the importance of physician-to-patient education when describing the potential benefits of RCTs. In order to facilitate the education Wong *et al* suggest increasing the leadership role of physicians in LMIC to participate in RCTs [50]. In their analysis of RCTs in LMIC, from 454 publications only 19% involved authors from a LMIC and 17% had a first or corresponding author from an LMIC [50]. With this knowledge, it is imperative to broaden LMIC physician involvement in RCTs in order to increase patient education. Treatments are also evolving in HIC, precision and molecular medicine is now a leading contender in therapies. Currently HIC have small sample sizes from ethnic groups within their cities. These small sample sizes make the development of precision medical treatments for other ethnicities who make up the majority of LMIC, and who are non-white or Caucasian, challenging. This again supports the need for increased representation of RCTs from LMIC.

In addition, there is lack of research regarding the reasons of delayed presentation, which frequently leads to more advanced stage at diagnosis. Regarding medical treatment and availability, a limitation in LMIC is the access to a urologist. In Nigeria and Ghana, the ratio of urologist in a

 doi:10.20944/preprints202407.0771.v1

population is 1:3.8 million and 1:2.5 million, respectively [46]. This is a much lower availability to urologists when comparing ratios in the United States and United Kingdom, 1:27,000 and 1:90,000, respectively [46]. This access to a trained urologist is a critical rate limiting factor leading to delays in presentation. Albeit the sparsity of data from LMIC, it is evident that there are disparities in access to healthcare. Initiatives tailored to the specific needs in each region, such as targeting risk factors (i.e., smoking rates in LMIC) or increasing patient education, can help affect incidence and mortality.

Conclusions

LMIC face significant challenges regarding the incidence and mortality of urological cancers. Increased use of imaging modalities or PSA screening saturation can lead to an increase of incidence. While delays in presentation to a healthcare provider decreases early stage at diagnosis and limited access to resources may make access to top notch therapies difficult, in turn leading to an increase of mortality. Overall, it is important to understand issues facing LMICs, however, the lack of data from these countries must be addressed in order to make substantial changes.

Author Contributions: Conceptualization, Sami E Majdalany and Firas Abdollah. <ethodology, Sami E Majdalany and Mohit Butaney software, Sami E Majdalany and Shane Tinsley. Writing—original draft preparation, Sami E Majdalany.; Writing—review and editing, Sami E Majdalany, Mohit Butaney, Nicholas Corsi, Shane Tinsley, Firas Abdollah. Supervision, Firas Abdollah, and Craig G Rogers. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflicts of interest.

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