Disparities in Cancer Care: The Example of Sarcoma—In Search of Solutions for a Global Issue

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Overview

Disparities in health care have an adverse effect on the outcome of disadvantaged patients with cancer. Patients may be at a disadvantage because of geographic isolation; insurance status; or racial, ethnic, or other factors. In this article, we examine how disparities affect the care of patients with sarcoma in the United States, Canada, and the Asia-Pacific region. Because of the rarity of sarcomas and their challenging diagnosis and complex treatment patterns, some professional or national guidelines stipulate that patients with sarcoma should be treated at centers of expertise by multidisciplinary teams. This recommendation, based on published evidence, is not always applicable because of various sociopolitical or patient-related factors. We are proposing solutions to overcome these obstacles in a practical and patient-centered way while acknowledging that disparities exist among countries as well as within any country.

INTRODUCTION

Sarcomas are rare cancers arising from mesenchymal tissue. Bone and soft tissue sarcomas encompass at least 175 distinct histologic subtypes, with varying clinical behaviors and oncologic outcomes. Their rarity and histologic heterogeneity pose a great challenge in diagnosis and management.[1] For instance, although patients diagnosed with extremity sarcoma present relatively early in the disease process, those diagnosed with retroperitoneal sarcoma present later, because the course of disease is indolent and involves marked growth before notable symptoms. These diseases require an approach by a multidisciplinary team "with extensive expertise and experience in the treatment of sarcoma," according to the National Comprehensive Cancer Network.[2] This recommendation comes from data that fairly consistently show improved sarcoma outcomes at a center with expertise,[3,4] although studies are hampered by accounting for case mix and confounding variables and by trouble defining expertise. In this article, we review disparities in sarcoma care in North America (Canada and the United States) and provide some remarks about the Asia-Pacific region.

Referral Centers and Regionalization of Care

Given the challenges in the diagnosis of sarcoma and the complexity of its treatment, it is crucial to obtain the input of experienced radiologists, pathologists, surgeons, medical oncologists, and radiation oncologists in the setting of a multidisciplinary tumor board. Sarcomas should ideally be treated at a high-volume referral center with the expertise to provide such care.[5] Multiple analyses of the National Cancer Database found that, in the United States, there were significantly improved oncologic outcomes in patients with soft tissue sarcoma undergoing treatment at high-volume centers,[6-8] even when this care necessitated travel.[9] Most studies have used case volume as a surrogate for expertise.[10] The definition of high-volume sites has varied; it is sometimes defined as sites in the 99th percentile for volume, but it generally includes sites that see more than five to 20 (de novo, surgical) cases per year. Regionalization of care and the establishment of clear guidelines are associated with improved outcomes in European countries, such as France.[11]

In Canada, there are established referral centers in each province to which all patients have access, and mandates in most provinces regionalize and establish corridors of care. Because of the oversight by provincial agencies, the care provided in these centers tends to be uniform, evidence based, and consensus driven. Moreover, thanks to organizations such as the Canadian Cancer Trials Group, many regional centers offer patients enrollment in high-quality trials, facilitating access to cutting-edge treatments.

However, access to treatment can be geographically and economically challenging, especially in Canada, where distance traveled to a referral center is extremely variable. In the United States, where centralized sarcoma care is not mandated, most patients with sarcoma are still treated at low-volume sites. National Cancer Database analyses estimate this proportion to be between 83% and 95% (depending on the sarcoma

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PRACTICAL APPLICATIONS

- Because not all patients with sarcoma can be treated at centers of expertise, it is necessary to find creative ways for them to benefit from these centers when they have no access.
- Benefits can be achieved by improving utilization of centers of expertise or improving decentralized care through collaboration.
- Telemedicine can be used as a tool to enhance national or international collaboration.

subtype and the definition of high-volume center).[12] Because the National Cancer Database only includes patients treated at Commission on Cancer–affiliated sites (approximately 30% of cancer cases), the percentage seen at high-volume sites is almost assuredly even lower. The concept of distance decay (i.e., the oncologic outcomes of patients decrease the farther away they live from a referral center) has been shown for several malignancies, including sarcoma.[13] If care and outcomes are better at specialized, regionalized centers of excellence, then patients with sarcoma who reside a distance from these sites are disadvantaged, either because they are less likely to travel for that care, or, if they do travel, because they will bear greater associated financial and psychosocial burdens. Clearly, issues remain with regard to ensuring access and receipt of care at these centers. To remove this disparity, two approaches can be taken.

Improve Utilization of Centers of Excellence

Clarify definition of centers of excellence Given the low number of sites that meet the criteria of high volume, there is opportunity to clarify and expand the definition of centers of excellence. The Sarcoma Alliance for Research through Collaboration has 85 U.S. institutions that are deemed centers with expertise, but there has been no assessment of whether treatment at one of these centers results in improved outcomes or whether they are accessible to a majority of the population. The sarcoma advocacy and professional communities should work together to analyze geographic disparities, such as has been done in France,[14] and creatively develop incentives that would create more accessible options for centralized high-quality care. In addition, efforts to further define and accredit centers of expertise may clarify guidelines that encourage referral, similar to the development of the Foundation for the Accreditation of Cellular Therapy in blood and marrow transplantation centers.

Educate primary care physicians about diagnosis and referral There is no screening test for sarcoma, so the timeliness of diagnosis depends on initial medical providers recognizing and appropriately working up the condition. Occurring in various forms throughout the body, sarcoma can present nonspecifically; the first symptoms are often misattributed to other musculoskeletal conditions or benign lesions (e.g., lipomas). Educating primary care providers to recognize the symptoms of sarcoma and to refer appropriately is a daunting task, given the number and variety of providers that patients with sarcoma may first see with symptoms. In the United Kingdom, a national sarcoma advocacy group has developed a provider awareness campaign and sponsored the development of an open-access training module.[15]

Promote patient awareness and study patient-reported barriers It is likely that many patients with sarcoma are never made aware of the possible differential outcome benefits of care at a center of excellence, although it is not clear that this knowledge overcomes preference for local care. A few studies in the United States have presented hypothetical vignettes to patients, asking whether they would be willing to travel to improve outcomes; the results suggest that factors other than raw outcome differences are considered.[14,16,17] Receipt of care in a distant site requires financial and other costs that can be considered unaffordable: travel time and expense, possible need for lodging and food, reliable transportation, additional time away from work, and additional time away from childcare responsibilities. These burdens may be prohibitive or, even if overcome, may leave the remote patient with unequal financial hardship, not to mention other psychosocial stress. In the United Kingdom, where guidelines have increasingly mandated centralization of care, a 2015 patient experience study,[18] in which 90% of patients were treated by a sarcoma specialist team and half of patients had to travel more than 20 miles for treatment, found that 90% of patients did not mind traveling. However, a robust survey of patients with sarcoma who have not traveled to be treated by specialists would be required to fully understand the patient values and preferences needed to overcome logistic and financial issues. Programs offered by charities, such as the Canadian Cancer Society, help Canadian residents with transportation and housing while they receive lengthy chemotherapy and radiotherapy treatments away from home.

Improve Decentralized Care to Those Who Do Not Travel

The disparities noted here can be mitigated by strengthening the seamless transfer of care of patients with sarcoma. Constant communication with primary care physicians, as well as access to telemedicine, can improve access to care even more and limit the pecuniary burden of care in referral centers.

There is a need to improve care when the patient does not physically receive all care at the center of expertise. Although this approach may be perceived as mixed

messaging, because guidelines promote centralized care, it is a reality that, given the substantial and real barriers, not all patients will be able or willing to receive any or all of their care at these centers, and efforts should be made to minimize compromised outcomes. The most practical approach in these cases is to pursue a hybrid approach, finding a way to support the patient by delivering the most important components of care at the center of excellence and facilitating the quality delivery of remaining therapy closer to home. An important finding of one study, by Bagaria et al,[19] in extra-abdominal soft tissue sarcoma was that, although high-volume hospitals more often adhere to treatment guidelines (significantly so for stage III tumors), low-volume hospitals that followed national guidelines achieved comparable outcomes.

Centralized pathology review Many studies have identified difficulties with accurate pathologic diagnosis in sarcomas. On expert review, up to 40% of cases were considered incorrectly diagnosed[2,20]; errors involved underestimating and overestimating the malignant nature, resulting in the risk of inadequate treatment. National Comprehensive Cancer Network guidelines recommend that "pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist."[2] Centralized or expert pathology review is a relatively feasible procedure that does not require patient travel and is likely cost saving.[21] Barriers include insurance coverage or out-of-pocket cost for uninsured patients, delay in the start of treatment, and pathologist reluctance, but other countries can be models of successfully overcoming these barriers. In addition to the French experience, England has established designated Specialized Sarcoma Pathologists who take part in external quality-assurance schemes and have an informal network for slide and peer review.[22]

Centralized surgery for appropriate cases Because appropriate surgical resection is such a powerful predictor of outcome for soft tissue sarcoma, it is not surprising that patients having surgery at low-volume sites have worse outcomes.[11] Studies have shown that rates of complete (R0) resection are lower at remote or low-volume centers. Soft tissue sarcoma can be resected by a variety of general and specialty surgeons. Fewer than 10% of suspicious lumps will be malignant; if all these were initially referred to a sarcoma surgeon, the burden on the patients and the specialist would be onerous. Some studies have been done to delineate an algorithm that would appropriately flag likely malignant soft tissue tumors (size $>$ 5 cm, rapid increase in size, location deep to fascia, pain). Efforts should be made to improve, disseminate, and test the efficacy of such diagnostic algorithms for community surgeons. It is unclear whether there is a threshold of cost savings or patient outcomes that would influence practice policy or changes to insurance coverage in the United States or other countries.

Support and education of local oncologists Care and case discussion via a multidisciplinary team or a tumor board are believed to be essential to sarcoma outcomes.[23,24] Improving the expertise and comfort of remote oncologists is likely best accomplished with ongoing, case-based support. The wider acceptance of telemedicine and teleconferencing in the last year, as a result of the restrictions imposed by the COVID-19 pandemic, should open large doors for remote dissemination of sarcoma expertise,[25] especially because the benefit has already been proven in other settings. In the United States, the Extension for Community Healthcare Outcomes,[26] which was initially developed to support remote physicians treating hepatitis through monthly case conferences and education by a centralized expert gastroenterologist, has now been expanded and proven effective in multiple other fields and settings and could be the platform for supporting sarcoma care in remote areas.

Psychosocial support and resources for remote patients Sarcoma therapy may be offered or attempted locally, but the patient may not have access to appropriate psychosocial support to start or complete therapy. Multiple studies have shown that geographic barriers disproportionately affect patients of low socioeconomic status, racial minorities, or those who lack private insurance—so those with perhaps the greatest needs cannot access the support services of a tertiary center.[27] Without multidisciplinary ancillary services, such as social work, therapists, and navigators, patients may not be aware of or access resources that would make treatment financially, pragmatically, or emotionally feasible. Efforts to provide decentralized psychosocial support to patients with sarcoma have been successful in England and Australia by placement of remote "key workers" or nurse navigators.[28] Some ancillary services, such as fertility preservation or prosthetic shops, are also centralized; presumably, remote patients with sarcoma have less access to these services that can improve quality of life. Again, the COVID-19 pandemic has resulted in increased availability of technology benefiting remote patients with cancer, including access to telepsychiatry and an enormous increase in the utilization of online support groups. This availability should dramatically increase access to the resources and support needed to complete therapy.

Ethnic and Racial Disparities

Multiple population studies in the United States based on the Surveillance, Epidemiology, and End Results program or the National Cancer Database have identified racial disparities in sarcoma-specific survival and other oncologic endpoints. In Canada, given the rarity of these tumors and the comparatively smaller population, racial and ethnic disparities have not been identified in the context of sarcoma care specifically. However, disparities and health inequities have been identified in high-risk populations with

regard to other, more common cancers, such as lung, breast, and ovarian cancers,[22] and they are likely present for sarcomas as well. Indeed, the Indigenous population has decreased access and utilization of health care services, leading to decreased survival in 14 of the 15 most common cancers, even after accounting for socioeconomic status and rurality.[28] Community partnerships are key in improving these outcomes; Ontario, for example, has established a three-phased Aboriginal Cancer Strategy to improve cancer-control strategies with tailored programs.

Another high-risk health disparity group is immigrants, who, as an example, constitute approximately 20% of the Canadian population and significantly underutilize the health care system, especially cancer-screening programs, with an impact on cancer survival.[29,30] This underutilization can be due to a language barrier, education level, or poor socioeconomic status. Additional research must address these issues in sarcoma care in Canada and elsewhere.

INSURANCE STATUS

In countries with a predominance of privately insured care, patient outcomes can vary according to insurance status. A recent study of the Surveillance, Epidemiology, and End Results program database of patients with extremity sarcoma identified that disparities in insurance status were associated with an increased risk for metastatic stage at diagnosis, decreased rate of limb-salvage procedures, and decreased disease-specific survival.[31] The Canadian health care system is based on universal access for all Canadian citizens and permanent residents, free of charge. Health care is a provincial mandate; thus, each province allocates resources and establishes its own guidelines in terms of resource management. Yet, disparities can occur when it comes to access of novel systemic treatments that are not provincially reimbursed and, thus, must be covered by the patient's medication insurance, which is mandatory in many provinces.

The great advantage of such a health care system is the improved access to treatment and to optimal care independent of the patient's age, employment status, or financial situation. Although one might be concerned about the delays that can be incurred at every step of the diagnosis in a fully public-funded system, provincial health agency requirements ensure that each component of care is performed within a timely fashion according to pre-existing guidelines.

THE ASIA-PACIFIC REGION

The Asia-Pacific region, comprising 45 countries, is the most diverse and populous on earth. Much of this diversity is relevant to health outcomes, including cancer. The following data were extracted from the World Health Organization[32] and the World Bank.[33] It is critical to note that the quality of data collection varies by country. For example, there are no data recorded on gross domestic product for the World Bank for Afghanistan between 1982 and 2002 or from North Korea at all.

The Asia-Pacific region comprises more than 4.2 billion people, or 54% of the global population. The subregions range in population size from 11,650 people (Tuvalu) to 1.4 billion (China). Population growth in the region has been among the highest on the planet, and the Asia-Pacific region contains the three largest populations globally: China, India, and Indonesia. Populations vary in size as well as in ethnicity. Government types vary from autocracy through single-party systems to parliamentary democracies. The per capita gross domestic product also varies strikingly across the Asia-Pacific region from low-income Micronesia (US $631) and Nepal (US $1,071) to middle-income India (US $2,099), Papua New Guinea (US $2,434), and China (US $10,261) and high-income Singapore, Australia, Japan, and South Korea (more than US $44,671; 2017 data).

These demographic, political, and economic features are immediately relevant to health outcomes, which also vary enormously across the region. In 2018, life expectancy in Papua New Guinea was 64.3 years, compared with 83.1 years in Singapore. Among low-income countries, life expectancy is 63.5 years, compared with 80.7 years for nations with high-income status. However, life expectancy is changing rapidly, increasing in Nepal from age 62.3 in 2000 to age 70.5 in 2018. Unsurprisingly, the contribution of cancer to health outcomes and life expectancy also varies enormously. Among low-income countries, six of the top 10 causes of death are infectious (HIV, tuberculosis, malaria), whereas communicable, maternal, and perinatal causes of death account for 65% of mortality. Cancer is not in the top 20 causes of death; it accounts for 3.9% of deaths. Among high-income countries, cancer accounts for four of the top 10 causes of death (lung, bowel, breast, and stomach), and infectious illness (lower respiratory tract infections) accounts for only one of the top 10 causes. Communicable, maternal, and perinatal causes account for 6.6% of deaths in higher-income countries, whereas cancer accounts for 25% of deaths. Indeed, cancer is now the leading cause of death in high-income countries.[34] These factors determine the priorities for health systems in addressing the challenge of cancer.

The patterns of cancer vary strikingly across the Asia-Pacific region, as determined by poorly understood genetic and environmental differences. For example, although breast, bowel, and lung cancers are among the leading types of cancer in Australia and New Zealand, in the Western Pacific region, liver and stomach cancers are important causes of cancer mortality. Many cancers associated with infectious diseases are more common and more lethal in the

Asia-Pacific region; examples include nasopharyngeal cancer (Epstein-Barr virus), liver cancer (hepatitis B and C viruses), bladder cancer (schistosomiasis), and cervical cancer (HPV). In Papua New Guinea, cervical cancer is more common than breast cancer as a leading cause of death in women younger than age 50.[35] This fact reflects social determinants of the transmission of HPV, the absence of public health measures (Papanicolaou screening, vaccination), and limited resources for cancer treatment. Other distinctive cancer patterns appear genetically determined. For example, *EGFR* mutation–positive non–small cell lung cancer in young, nonsmoking Asian women appears linked to distinct loci in genome-wide association studies.[36]

Disparities in cancer outcomes exist within countries in the Asia-Pacific region as well as between them. Within Australia, a high-income nation with excellent overall cancer outcomes, Indigenous populations are 40% more likely to die from cancer than are non-Indigenous Australians.[37] In New Zealand, Maori populations have poorer outcomes for 23 of 24 of the most common causes of cancer death.[38] The excess mortality is partially attributed to persistent social disadvantage, despite the efforts of the relevant health systems.

Rare cancers, including sarcomas, represent particularly problematic challenges to health care, including in the Asia-Pacific region.[39] Concentrated expertise in diagnosis, imaging, surgery, radiotherapy, and systemic therapy for sarcomas are essential for optimal outcomes. Molecular pathology and genomics are only partially accessible in high-income countries. In countries such as Papua New Guinea, simple histologic diagnosis of osteosarcoma is performed by a limited number of laboratories for the entire country, often not in a timeframe consistent with optimal treatment. Volume-dependent, sarcoma-specific surgical expertise, including the intraoperative, anesthetic, and postoperative support resources to perform limb-salvage procedures, is limited by context in low-income countries. Low-income countries have limited access to linear accelerators and may depend on older cobalt machines, without access to advanced planning and simulation. The affordability of systemic therapies is a persistent issue, driving the use of generic agents and affecting the choice of agents. In addition, the ability to record outcomes accurately is a key feature of quality-driven outcomes and is likely limited by income status. In countries without single-payer, government-supported health care, access to optimal care may be affordable privately, creating issues of equity of access. The global trend for rare cancers toward personalized medicine, with its progressive dependence on genomics and access to targeted therapies, is likely to exacerbate differences between countries in the Asia-Pacific region in particular.

Research is fundamental to state-of-the-art care for patients with sarcoma. There are active cooperative clinical research organizations focused on sarcoma in the Asia-Pacific region, including the Australian and New Zealand Sarcoma Association and the Asian Sarcoma Consortium, which have broad membership of oncologists from higher-income countries in the Asia-Pacific region.[40]

Economic and population growth in the Asia-Pacific region will dominate the global landscape in the 21st century. Among global giants, China has increased its per capita gross domestic product more than 10-fold since 2000, and India's has increased almost 4.8-fold. Health is a fundamental human good; as the per-capita wealth of countries expands, it will likely drive investment from and engagement with the global pharmaceutical industry. However, this engagement is also determined by politics and international law. Economic and population growth may increase the likelihood of major conflicts in the Asia-Pacific region, which will have adverse effects on health systems. Drug development globally depends on international patent law and trade agreements. Low- and middle-inome countries have to balance protecting intellectual property rights and satisfying the health needs of their populations. An example of this balance was the Indian patent office's rejection of the Novartis patent for imatinib, a decision upheld by the Indian Supreme Court in 2013.[41] This balance will shift as the economic development of countries, such as India and China, incorporates vibrant pharmaceutical and high-tech industries.

CONCLUSION

Improvement in cancer-treatment outcomes requires increasingly complex diagnostic and treatment procedures, which have variable availability between countries and even within countries. The best outcomes are obtained through treatment given by multidisciplinary teams in centers of expertise, especially for rare tumors, such as sarcomas. This ideal model is not always possible because of sociopolitical or patient-related reasons, whether in high-income or low-income areas. Even in countries with uniform universal health care and accessible regional centers, disparities in care can still occur secondary to distance, education, and socioeconomic status as well as racial and ethnic factors. Several solutions have been tested in different countries and can be applied to help patients take advantage of that expertise, even partially, to reduce disparities. The current trend of telemedicine could facilitate these exchanges at a national or an international level.

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