special articles

Augmented Package of Palliative Care for Women With Cervical Cancer: Responding to Refractory Suffering

Eric L. Krakauer, MD, PhD[1,2,3]; Khadidjatou Kane, MD[1,4]; Xiaoxiao Kwete, MD, MPH[5]; Gauhar Afshan, MBBS[6]; Lisa Bazzett-Matabele, MD[7,8]; Danta Dona Ruthnie Bien-Aimé, RN[9,10,11]; Lawrence F. Borges, MD[12]; Sarah Byrne-Martelli, DMin[1]; Stephen Connor, PhD[13]; Raimundo Correa, MD[14]; C. R. Beena Devi, MD[15]; Mamadou Diop, MD[16]; Shekinah N. Elmore, MD, MPH[17]; Nahla Gafer, MD[18,19]; Annekathryn Goodman, MD[20,21]; Surbhi Grover, MD[22,23]; Annette Hasenburg, MD[24]; Kelly Irwin, MD[25]; Mihir Kamdar, MD[4,26]; Suresh Kumar, MD[27]; Quynh Xuan Nguyen Truong, MPH[28,29,30]; Tom Randall, MD[20,21]; Maryam Rassouli, RN, PhD[31]; Cristiana Sessa, MD[32]; Dingle Spence, MBBS[33,34]; Ted Trimble, MD[35]; Cherian Varghese, MD, PhD[36]; and Elena Fidarova, MD[36]

abstract

The essential package of palliative care for cervical cancer (EPPCCC), described elsewhere, is designed to be safe and effective for preventing and relieving most suffering associated with cervical cancer and universally accessible. However, it appears that women with cervical cancer, more frequently than patients with other cancers, experience various types of suffering that are refractory to basic palliative care such as what can be provided with the EPPCCC. In particular, relief of refractory pain, vomiting because of bowel obstruction, bleeding, and psychosocial suffering may require additional expertise, medicines, or equipment. Therefore, we convened a group of experienced experts in all aspects of care for women with cervical cancer, and from countries of all income levels, to create an augmented package of palliative care for cervical cancer with which even suffering refractory to the EPPCCC often can be relieved. The package consists of medicines, radiotherapy, surgical procedures, and psycho-oncologic therapies that require advanced or specialized training. Each item in this package should be made accessible whenever the necessary resources and expertise are available.

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INTRODUCTION

Cervical cancer, the fourth most common cancer in women globally and the most common cause of cancer-related death in sub-Saharan Africa,[1] is associated with suffering that is more prevalent, complex, and severe than that associated with other malignancies.[2,3] Elsewhere, we reported that women with cervical cancer have a higher prevalence of moderate or severe pain, anxiety, and depression than patients with cancer on average.[2] They also suffer from a high prevalence of moderate or severe malodorous vaginal discharge, bleeding, sexual dysfunction, and financial distress, and more than 40% are abandoned by their intimate partners.[2] In light of this extraordinarily prevalent, severe, and complex suffering, we convened a panel of experts in treatment and palliative care of women with cervical cancer to devise an essential package of palliative care for cervical cancer (EPPCCC).[3]

The EPPCCC, described elsewhere and summarized in Table 1, is designed to be the minimum package that can safely and effectively prevent and relieve most suffering associated with cervical cancer, to be applicable by any clinicians with basic palliative care training, and to be inexpensive enough to be made universally accessible free of charge to the patient even in the lowest-income settings.[3] However, both available evidence and expert opinion suggest that cervical cancer frequently results in suffering too severe, complex, or refractory to be adequately relieved by basic palliative care.[8-11] A variety of anatomic, physiologic, psychological, and social factors appear to contribute to this phenomenon. For example, the proximity of major nerve plexuses to the cervix makes them susceptible to tumor invasion that often results in severe or refractory neuropathic pain.[8,12] The large blood supply to the uterus and vagina puts patients with cervical cancer at risk of difficult-to-control hemorrhage,[13-15] and disruption by necrotic tumor of the vaginal microbial environment often results in difficult-to-treat, psychosocially disabling vaginal discharge.[15,16] The proximity of the cervix to bowel and bladder puts patients at risk for bowel obstruction with resultant intractable vomiting; rectovaginal, vesicovaginal, and enterovesical fistulae with distressing leakage of stool and urine; and hydronephrosis with resultant renal failure. These distressing problems may

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Existing evidence indicates that patients with cervical cancer, more often than patients with other cancers, experience suffering that is refractory to basic palliative care such as what can be provided with an essential package of palliative care for cervical cancer. Therefore, a panel of experts in all aspects of cervical cancer treatment and palliation created an augmented package of palliative care for cervical cancer intended to make possible relief even of refractory suffering.

Knowledge Generated

The augmented package of palliative care for cervical cancer consists of carefully selected medicines, radiotherapy, nerve blocks, surgical procedures, and psycho-oncologic therapies that require advanced or specialized training. Each item in this package should be made accessible whenever the necessary resources and expertise are available.

Relevance

The augmented package of palliative care for cervical cancer will make possible relief of many types of severe, refractory suffering due not only to cervical cancer but also any cancer or serious illness.

be palliated best by surgical procedures.[17] Severe psychosocial suffering that is difficult to relieve may result when invasive cervical cancer or its treatment injures the genitals and causes sexual dysfunction.[18,19]

These data suggest that women with cervical cancer often experience suffering too severe, complex, or refractory to be controlled by basic palliative care. Thus, the group of experienced experts in cervical cancer treatment and palliation from countries of all income levels that created the EPPCCC agreed that an augmented package was necessary as a supplement to the EPPCCC. The augmented package includes the following:

1. Palliative radiotherapy
2. Advanced medical therapies
3. Nerve blocks for pain control
4. Palliative surgery
5. Psycho-oncology.

Governments should assure that the EPPCCC is universally accessible before approving even partial insurance coverage of expensive elements of the augmented package for which the poor may be unable to afford the co-payment. However, all governments should aspire to make accessible as much as possible of the augmented package as soon as possible. Implementation of each element of the augmented package requires advanced or specialist training in one or more of several disciplines: palliative care, radiation oncology, pain medicine, surgery, or psychiatry. Thus, the effort to make the augmented package accessible must entail efforts to create capacity for training in these disciplines wherever it is inadequate or nonexistent. Implementation of both packages will benefit not only women with cervical cancer but also patients with any serious illness.

PALLIATIVE RADIATION THERAPY

Patients with cervical cancer in low- and middle-income countries (LMICs) frequently present with locally advanced disease and associated symptoms.[20,21] For these patients, palliative external beam radiation therapy (EBRT) often can provide rapid relief of vaginal bleeding or discharge and of pain because of the primary lesion, nodal disease, or metastatic disease in the mediastinum, neck, bone, or brain.[22] Yet radiotherapy often is difficult or impossible to access in LMICs. Thus, making EBRT universally accessible with simple, reliable machines is crucial to fulfill the human right of patients with cancer to the highest attainable standard of health.[23]

The most common palliative EBRT regimens for symptomatic pelvic cancers are shown in Table 2. They are ordered from most commonly used to least commonly used globally. Choice of regimen should be based on the patient's prognosis, specific symptoms, performance status, ability to attend the radiotherapy center, and capacity of the treating center.[22,26,32,33] Short regimens, such as 3.7 Gy twice daily for four fractions and up to three courses or 4-5 Gy daily for five fractions, are favored to balance effective symptom palliation with minimum logistical burden for patients, particularly when the prognosis may be limited. Conventional palliative regimens, such as 3 Gy for 10 fractions, are also safe and effective. However, they may be more burdensome for both patients and treatment centers and do not offer better symptom response. Single treatment regimens, such as 10 Gy for one fraction, offer convenience but have higher toxicity.

Ideally, radiotherapy clinics should be distributed widely enough to assure universal access and should be officially and operationally integrated with comprehensive palliative care services.[34-36] Living accommodations should be made available for patients who must spend one or more nights at the radiotherapy facility. All radiation oncologists should have intermediate-level palliative care training, at least 60 hours per WHO recommendation, to promote this integration and to help assure an appreciation for the full spectrum of palliative interventions.[37] Conversely, all levels

TABLE 1. Essential Package of Palliative Care for People Affected by Cervical Cancer

Interventions	Medicines[a]	Equipment	Social Supports[b]	Human Resources[c]
1. Prevention and relief of pain or other physical suffering,[d] acute or chronic 2. Prevention and relief of psychological suffering,[e] acute or chronic 3. Prevention and relief of social suffering, acute or chronic 4. Prevention and relief of spiritual suffering	Amitriptyline, oral Bisacodyl (senna), oral Dexamethasone, oral and injectable Diazepam, oral and injectable Diphenhydramine (chlorpheniramine, cyclizine, or dimenhydrinate), oral and injectable Fluconazole, oral Fluoxetine (sertraline or citalopram), oral Furosemide, oral and injectable Haloperidol, oral and injectable Hyoscine butylbromide, oral and injectable Ibuprofen (naproxen, diclofenac, or meloxicam), oral Lactulose (sorbitol or polyethylene glycol), oral Loperamide, oral Metoclopramide, oral and injectable Metronidazole, oral (for both oral use and vaginal insertion) Morphine, oral immediate release and injectable Naloxone, injectable Omeprazole, oral Ondansetron, oral and injectable[f] Oxygen Paracetamol, oral Iron and multivitamin supplement (oral) Petroleum jelly	Pressure-reducing mattresses Nasogastric drainage and feeding tubes. Urinary bladder catheterization kits. Roller gauze for vaginal packing Elastic compression bandages Opioid lock boxes Flashlights with rechargeable batteries (if no access to electricity) Adult diapers or cotton and plastic	Cash transfers or resource allocation for housing, children's school tuition, transportation to health care facilities, or funeral costs. Other resource allocation (in-kind support): food packages, blankets, sleeping mats, shoes, soap, toothbrushes, and toothpaste	Doctors and clinical officers (with basic palliative care training) Nurse practitioners, midwives, or feldshers (with basic palliative care training) Nurses (with basic palliative care training) Social workers, psychologists, grief counsellors, or trained and supervised lay counsellors CHWs (if available) Peer supporters Local spiritual counsellors (after vetting)

NOTE. Adapted.[4-6]

Abbreviations: CHW, community health worker; PTSD, post-traumatic stress disorder.

[a]On the basis of the WHO Model List of Essential Medicines 2019.[7] Acceptable alternative medicines are in parentheses.

[b]At least for patients living in extreme poverty and for one caregiver per patient.

[c]Doctors may be oncologists, gynecologists, surgeons, general practitioners, family doctors, clinical officers or assistant doctors, or others.

[d]Other physical suffering includes breathlessness, weakness, nausea, vomiting, diarrhea, constipation, incontinence, malodorous vaginal discharge, and bleeding.

[e]Psychological suffering includes anxiety, depressed mood, PTSD, confusion or delirium, sexual dysfunction, and complicated grief.

[f]Only in hospitals that provide cancer chemotherapy or radiotherapy.

of palliative care training should include instruction on indications for radiotherapy.[38] Available evidence indicates good economic return on investment in radiation therapy in LMICs, especially for cervical cancer.[36,39]

ADVANCED MEDICAL THERAPIES

In addition to the medicines in the EPPCCC, several others can significantly improve comfort of women in specific clinical situations such as advanced-stage kidney disease or neuropathic pain refractory to all other medicines in the EPPCCC.[4,6] Some of these medicines are more expensive than those in the EPPCCC, and others are not as well-studied, but they should be made accessible whenever possible for patients with these conditions. However, morphine in oral fast-acting and injectable preparations should be accessible to everyone in need before any more expensive opioid preparations are made available.[40]

Lidocaine, Injectable

For moderate or severe pain that is refractory to opioids, or when opioids cause intolerable adverse effects, particularly near the end of life, an intravenous bolus (1-2 mg/kg over 30 minutes) can be given.[41,42] If the bolus provides relief, a continuous infusion can be started (0.5-2 mg/kg/h) to maintain

TABLE 2. Comparison of Palliative External Beam Radiation Therapy Regimens for Pelvic Cancers With Reported Rates of Symptom Control

Regimen	Repeated Treatments	Modality	Symptom Control Rates
3.7 Gy twice a day × 4 fx, once every 2-4 weeks × up to three courses[24,25]	Yes, 59% compliance on trial	2D or 3D	ORR 45% Bleeding 58%-75% Pain 98%
4-5 Gy × 5 fx[a,26]	No	2D or 3D	Bleeding 94% Pain 67%
4.5 Gy twice a day × 4 fx[27,28]	No	3D	ORR 89% Bleeding 100% Pain 93%
3 Gy × 10 fx[a,29]	No	2D or 3D	Bleeding 88% Pain 65%
10 Gy × 1 fx, monthly × up to 3 fx (10-by-3)[30,31]	Yes, 47% compliance in LMICs	2D or 3D	ORR 62% Bleeding 100% (third fx) Pain 41% (second fx) Vaginal discharge 29% (second fx)

Abbreviations: fx, fraction (treatment); LMICs, low- and middle-income countries; ORR, overall response rate.
[a]Retrospective study.

analgesia. The common side effects are usually mild or self-limited and dose-related and include perioral numbness, sedation, confusion, lightheadedness, and headache. Cardiac arrhythmia is a potential serious but low-risk adverse effect. Lidocaine can be combined with opioids as needed.

Ketamine, Oral or Injectable

For moderate or severe pain that is refractory to opioids, or when effective opioid doses cause intolerable adverse effects, ketamine can be added to enable reduction of opioid dose and improve analgesia.[8,43-51] A typical starting dose is 2.5 mg orally or intravenously every 8 hours. If there is no benefit and also no adverse effect, the dose can be doubled on day 2 and again on day 3. The maximum dose is 0.5 mg/kg/dose. It can also be given as an intravenously infusion at 0.05-0.3 mg/kg/h. Contraindications include uncontrolled hypertension or high stroke risk. There is some evidence that ketamine can be used safely in patients with increased intracranial pressure and psychiatric illness.

Slow-Release Oral Morphine

For patients with moderate or severe cancer pain that is frequent or constant who can take oral medicines, slow-release oral morphine can reduce pill burden and provide more steady relief.

Fentanyl Transdermal Patches

This opioid preparation generally is better than morphine to treat moderate or severe cancer pain in noncachectic patients whose opioid requirement is stable and who are unable to take oral medicines or who have renal failure.

Fentanyl, Injectable

This is useful as a continuous infusion, with rescue bolus doses as needed, for moderate or severe pain that is frequent or constant in patients with renal failure or cachexia who are unable to take oral medicines. It is also useful for dose finding in noncachectic patients before applying fentanyl transdermal patch. Because of the rapid onset of action and short duration of action of injectable fentanyl, bolus doses alone are a good choice for preventing pain from brief procedures or dressing changes.

Injectable lidocaine, ketamine, and fentanyl are for use mainly in hospitals, but they can be provided in the home by palliative care specialist doctors if permitted by law and if clinically indicated.

Besides morphine and fentanyl, the other strong opioid on the WHO Model List of Essential Medicines for Pain and Palliative Care 2019 is methadone.[7] Although methadone often can provide better relief for neuropathic pain than other opioids, we did not include it in the augmented package because opioid-refractory neuropathic pain can also be treated with other medicines in the essential and augmented packages, because of the relative complexity of its safe use, and so as not to risk complicating extremely important efforts in LMICs to use it to treat opioid use disorder.

NEUROLYTIC PROCEDURES FOR RELIEF OF SEVERE OR REFRACTORY PAIN

Pain impulses from the pelvic region are transmitted via somatic nerves from muscle, bone, skin, and connective tissue and via sympathetic and parasympathetic nerves and plexuses from visceral organs. Neurolytic procedures, and in some cases also neural stimulation, often can interrupt or modulate pain impulses transmitted within this neural network.[52-54] However, because of the complexity of this pain network, adequate relief often requires multimodal treatment such as with both a neurolytic procedure and systemic pharmacotherapy.

Nerve Blocks

Neurolysis is the targeted destruction of a nerve or nerve plexus with chemical agents (alcohol or phenol), heat

(radiofrequency ablation), or cold (cryoablation). If the appropriate and adequately trained staff member(s) and necessary equipment are available, these procedures should be considered when pharmacologic pain treatment results in inadequate pain control or intolerable side effects. Typically, neurolytic blocks should be performed with fluoroscopic, ultrasonographic, or computed tomography guidance. Although these procedures are not effective for every patient, they usually provide some degree of analgesia, from partial to complete, that lasts from days to several months and reduces the opioid requirement.[55-57]

Neurolysis of the superior hypogastric plexus is the most common block for pelvic cancer pain. The superior hypogastric plexus lies anterior to the L5/S1 disk and innervates the cervix, uterus, bladder, and rectum. Complications such as neural injury, bowel perforation, retroperitoneal bleeding, bowel and bladder dysfunction, infection, and diarrhea are rare.[30,55-57]

Ganglion impar block is a safe and relatively easy procedure to treat visceral pelvic, perineal, and anal pain. The ganglion impar lies in the presacral space near the sacrococcygeal ligament and provides innervation to the perineum, distal rectum, distal urethra, vagina, and vulva. Image-guided neurolysis of the ganglion impar appears to be a generally safe and effective procedure.[58-60]

Intrathecal drug delivery systems infuse analgesics directly into the spinal fluid at the appropriate spinal level via a subcutaneous catheter connected to an implanted, refillable drug pump. This method of analgesia can be very effective but is expensive, requires specialized equipment and well-trained staff members, and should not be initiated during an infection.[61-63] Because of the risk of permanent neurologic injury, intrathecal saddle neurolysis of the sacral nerve roots should be considered only as a last resort for severe refractory pain in a patient near the end of life.[64-66]

Neurosurgical Procedures

Where a skilled spine surgeon and the necessary support staff and facilities are available, transmission of pain impulses from pelvis to brain can also be interrupted by surgical intervention in the spine or brain.[67] Chemical rhizotomy (severing of spinal nerve roots) by injecting alcohol into the lumbar subarachnoid space can be combined with percutaneous cordotomy,[68] but skill and expertise are necessary to minimize risk of injury to other nerves. Another surgical option is to open the lumbar dura and cut the dorsal roots to the pelvis.[69] For pelvic pain mainly on one side, the spinothalamic tract on the contralateral side of the spinal cord can be interrupted by an open surgical or percutaneous cordotomy. Cordotomy usually is performed only unilaterally because bilateral cordotomy has a high risk of permanent motor weakness.[70-72]

A visceral afferent nociceptive pathway is located between the dorsal columns of the spinal cord and can be interrupted by surgical laminectomy and midline myelotomy.[73,74] This requires opening the spinal dura, usually at the T10 level, direct incision into the dorsal midline of the spinal cord between the dorsal columns over 1-2 cm in length, and extending within the spinal cord to the level of the central canal—about 5 mm deep. An operating surgical microscope is required to guide the incision and minimize damage to the dorsal columns, which are essential for balance and ambulation.[75-78] There is some risk of meningitis with this procedure, and it should be performed only by well-trained and experienced neurosurgeons.

The neural pathways that interpret pain in the brain can also be interrupted by performing a stereotactic cingulotomy.[79] This procedure requires access to a stereotactic frame and imaging to target the appropriate region of the brain. Good pain relief at three months has been reported in 64% of patients. Spinal cord stimulation, used primarily for non-cancer pain, can also be used for cancer pain. However, stimulators require surgical implantation and are expensive, and the wire leads tend to break.[53,80]

Palliative Surgical Procedures

Women with locally advanced or recurrent invasive cervical cancer may benefit from surgical procedures to palliate physical symptoms and emotional distress related to compromise of the urinary tract, intestinal tract, or vasculature. However, when deciding whether to intervene surgically, the potential benefits of the surgery must be weighed carefully against the risks and potential discomforts of the procedure itself in the context of the patient's values and likely prognosis. Women who are medically fragile or are late in the course of their illness may be better served by non- or less-invasive interventions.

Ureteral obstruction often causes pain and acute kidney injury and can lead rapidly to destruction of function of one or both kidneys. If possible, this should be treated with placement of ureteral stents or, if necessary, percutaneous nephrostomy tubes. Fistulae of the distal urinary tract to the vagina or rectum may develop either because of direct tumor infiltration or as a complication of radiotherapy. Placement of flexible percutaneous nephrostomy tubes, ideally with simultaneous placement of coils in the ureters, can decrease or eliminate leakage of urine via a fistula from the vagina or rectum. However, provision must be made for urostomy bags.

The sigmoid colon or rectum can also become obstructed because of infiltration or compression by tumor, and fistulae can develop to the vagina or bladder. Colostomy can relieve large bowel obstruction and may decrease or eliminate fecal incontinence because of leakage via a fistula. It also may help prevent abscess formation or enable an existing abscess to heal after drainage and antibiotic treatment. In addition, some women may experience ulceration of the rectum as a complication of radiotherapy,

and colostomy may bring relief from any resulting pain, fecal frequency, or incontinence. Access to training in colostomy care and to an adequate supply of colostomy bags should be assured if colostomy is offered.

Local progression of cervical cancer may lead to catastrophic hemorrhage from compromise of major vessels or from tumor neovasculature. If the goal of care is not solely comfort but (also) to sustain life to some extent, emergent selective pelvic vessel embolization should be considered if experienced operators and adequate equipment are available.[14] If this is not an option, emergent palliative radiotherapy should be arranged, if possible. If neither embolization nor radiotherapy are available, tranexamic acid can be given, and the vagina can be tightly packed with simple roller gauge in a lithotomy position, with or without sedation or short general anesthesia depending on expected pain. A bladder catheter is needed while the pack is in place.[81] If the only goal of care is comfort and the patient appears to be exsanguinating, pain, dyspnea, anxiety, or any other symptoms should be treated aggressively, even to the point of sedation if necessary to assure comfort.

Psycho-Oncology

Any doctor with basic palliative care training should be able to diagnose and treat uncomplicated anxiety or depressed mood with medicines in the EPPCCC, described elsewhere,[3] and in LMICS, nurses, psychologists, social workers, and community health workers can be trained to provide simple, culturally appropriate supportive counseling and psychotherapy for uncomplicated depression.[82-84] However, psychiatric or psycho-oncologic consultation is recommended for severe or refractory symptoms, for patients taking multiple psychoactive medicines, and for more complex psychiatric disorders such as bipolar disorder and psychotic disorders.[85,86]

Psycho-oncology, a subspecialty of psychiatry and psychology, addresses the psychological, social, behavioral, and cognitive problems related to cancer and cancer treatment. Psycho-oncologists collaborate with oncologists and palliative care providers to assess severe, complex, or refractory psychological and social suffering of patients with cancer and their family members and to plan and implement efforts to relieve this suffering.[87,88] Specific competencies include diagnosis of psychological distress and comorbidities such as anxiety disorders, posttraumatic stress disorder, major depression, and sexual dysfunction; recognition of drug interactions and adverse psychological effects such as delirium; planning and implementing evidence-based psychopharmacologic and nonpharmacologic interventions; assistance with difficult discussions with patients or family members; and identification of optimum goals of care.[85-87]

Standard open-access measures used by psycho-oncologists to identify and diagnose psychosocial distress include the Distress Thermometer,[89] the Patient Health Questionnaire Anxiety and Depression Scale,[90] and the PROMIS emotional distress scales for cervical cancer.[91] Treatment is tailored to the specific clinical situation. Evidence-based nonpharmacologic interventions for anxiety and depression include cognitive behavioral therapy, acceptance and commitment therapy, psychoeducation, and mindfulness and relaxation.[87,92] Some patients benefit from existential interventions, such as dignity therapy, that promote meaning making, foster hope, and support expression of feelings at the end of life.[93] Psycho-oncologists who are psychiatrists (medical doctors) can provide advice on the best pharmacologic interventions in a specific situation. Specialized psycho-oncologic consultation can be made accessible in LMICs via mobile phone or internet either as needed or as part of regular virtual tumor board conferences.

In conclusion, cervical cancer and its treatment sometimes result in suffering that is refractory to basic palliative care with the EPPCC. Therefore, we propose an augmented package of palliative care for cervical cancer that can prevent or alleviate even refractory suffering. Some elements require special training or experience, and some medicines or equipment are expensive and will not be widely available in low-income settings. However, we propose that each element should be implemented as soon as possible by at least one referral center in a region, province, or state, in a manner that makes relief of refractory suffering accessible by all.

AFFILIATIONS

[1]Division of Palliative Care & Geriatric Medicine, Massachusetts General Hospital, Boston, MA
[2]Departments of Medicine and of Global Health and Social Medicine, Harvard Medical School, Boston, MA
[3]Department of Palliative Care, University of Medicine & Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam
[4]Department of Medicine, Harvard Medical School, Boston, MA
[5]Harvard School of Public Health, Boston, MA
[6]Department of Anaesthesiology, Aga Khan University Medical College, Karachi, Pakistan
[7]Department of Obstetrics and Gynecology, University of Botswana, Gaborone, Botswana
[8]Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT
[9]Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA
[10]Université Episcopale d'Haiti, Port-au-Prince, Haiti
[11]Faculté des Sciences Infirmières de Leogane, Léogâne, Haiti
[12]Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA
[13]Worldwide Hospice Palliative Care Alliance, Fairfax, VA
[14]Gynecologic Oncology Unit & Palliative Care Service, Clínica Las Condes, Santiago, Chile
[15]Normah Medical Specialist Centre, Sarawak, Malaysia
[16]Cancer Institute of Cheikh Anta Diop University, Dakar, Senegal

[17]Department of Radiation Oncology University of North Carolina School of Medicine, Chapel Hill, NC
[18]Radiation and Isotope Centre, Khartoum Oncology Hospital, Khartoum, Sudan
[19]Comboni College of Science and Technology, Khartoum, Sudan
[20]Division of Gynecologic Oncology, Massachusetts General Hospital, Boston, MA
[21]Department of Obstetrics and Gynecology, Harvard Medical School, Boston, MA
[22]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[23]Botswana-UPenn Partnership, Gaborone, Botswana
[24]Department of Gynecology and Obstetrics, Johannes Gutenberg University Medical Center, Maine, Germany
[25]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA
[26]Division of Palliative Care and Geriatric Medicine, Department of Anesthesiology, Critical Care & Pain Medicine, Massachusetts General Hospital, Boston, MA
[27]Institute of Palliative Medicine, Medical College, Kerala, India
[28]College of Public Health Science, Chulalongkorn University, Bangkok, Thailand
[29]School of Social Work, Boston College, Newton, MA
[30]University Medical Center of Ho Chi Minh City, Ho Chi Minh City, Vietnam
[31]Shahid Beheshti University of Medical Sciences, Tehran, Iran
[32]Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
[33]Hope Institute Hospital, Kingston, Jamaica
[34]University of the West Indies, Kingston, Jamaica
[35]National Cancer Institute, Bethesda, MD
[36]Department of Non-communicable Diseases, World Health Organization, Geneva, Switzerland

CORRESPONDING AUTHOR

Eric L. Krakauer, MD, PhD, Division of Palliative Care & Geriatric Medicine, Massachusetts General Hospital, 55 Fruit Street/Founders 600, Boston, MA 02114; e-mail: ekrakauer@hms.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Eric L. Krakauer, Khadidjatou Kane, Xiaoxiao Kwete, Gauhar Afshan, Danta Dona Ruthnie Bien-Aimé, Lawrence F. Borges, Raimundo Correa, Cristiana Sessa, Cherian Varghese, Elena Fidarova
Collection and assembly of data: Eric L. Krakauer, Xiaoxiao Kwete, Nahla Gafer, Annekathryn Goodman, Kelly Irwin, Annette Hasenburg, Mihir Kamdar, Lawrence F. Borges, Shekinah N. Elmore, Quynh Xuan Nguyen Truong, Suresh Kumar, Maryam Rassouli, Elena Fidarova
Data analysis and interpretation: Eric L. Krakauer, Xiaoxiao Kwete, Lisa Bazzett-Matabele, Sarah Byrne-Martelli, Stephen Connor, C. R. Beena Devi, Mamadou Diop, Shekinah N. Elmore, Nahla Gafer, Annekathryn Goodman, Surbhi Grover, Annette Hasenburg, Kelly Irwin, Mihir Kamdar, Quynh Xuan Nguyen Truong, Tom Randall, Cristiana Sessa, Dingle Spence, Ted Trimble, Elena Fidarova
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Eric L. Krakauer
Employment: (I) My wife is employed by Inform Diagnostics and Foundation Medicine

Xiaoxiao Kwete
Employment: Yaozhi Co Ltd
Stock and Other Ownership Interests: Expat Inc
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Travel, Accommodations, Expenses: Expat Inc

Shekinah N. Elmore
Stock and Other Ownership Interests: Teladoc
Consulting or Advisory Role: Best Doctors Inc, Wildtype

Annette Hasenburg
Honoraria: AstraZeneca, Med Update, Pfizer, Roche, Streamedup!, Tesaro, MedConcept, LEO Pharma
Consulting or Advisory Role: PharmaMar, Tesaro, Roche, AstraZeneca, LEO Pharma, GlaxoSmithKline/MSD
Travel, Accommodations, Expenses: AstraZeneca, MedConcept, Roche, Streamedup!, Tesaro, MedUpdate, Pfizer

Mihir Kamdar
Leadership: Amorsa Therapeutics
Stock and Other Ownership Interests: Amorsa Therapeutics
Consulting or Advisory Role: Medtronic, Fern Health

Cristiana Sessa
Consulting or Advisory Role: Basilea

Ted Trimble
Consulting or Advisory Role: Merck, GlaxoSmithKline, Inovio Pharmaceuticals
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