Lung Cancer in Nepal

Ramila Shilpakar, MD, DM,[a,*] Bishnu Dutta Paudel, MD,[a] Rajeev Sharma, MD,[a] Sudhir Raj Silwal, MD,[b] Ranjan Sapkota, MS, MCH,[c] Prajowl Shrestha, MD, DM,[d] Soniya Dulal, MD, DM,[e] Madan Kumar Piya, M.B.B.S., MHCM,[f] Sampurna Man Tuladhar, MS, MRCS,[g] Prakash Neupane, MD,[h] Meghnath Dhimal, MSc, PhD,[i] Abesh Niroula, MD,[j] Dipesh Uprety, MD[k]

Background

Nepal is a beautiful, landlocked country located between India and the People's Republic of China, with rich cultural heritage and diverse nature. Nepal, with an area of 147,516 km^2, occupies 0.03% land area of the world and has a population of approximately 30 million.[1] Although small geographically, the topography extends from the flat Terai plains in the south to central hills and high Himalayas in the north. Nepal is home to people of 126 different caste or ethnic groups, speaking 123 different languages.[2] The gross domestic product per capita in 2020 is $1155.[3] Nepal is a low middle-income country with the gross domestic product growth rate of 2.27%. Approximately one-fourth of the population (25.16%) lives below the poverty line. The average life expectancy at birth is 66.6 years.[1] The health care delivery system in Nepal consists of both public and private systems. Public health care delivery provides services to most of the population. Only 61.8% of the Nepalese households have access to health facilities within 30 minutes, with considerable urban (85.9%) and rural (59%) discrepancy.[4]

Epidemiology

Cancer accounts for 9% of total annual deaths and is the third leading cause of noncommunicable disease death in Nepal.[5] According to the GLOBOCAN 2020 statistics, the number of new cases of cancer is 20,508 and cancer-related deaths are 13,629 for Nepal. The age-standardized rates (AARs) in cancer incidence and mortality per 100,000 were estimated to be 80.9 and 54.8, respectively. Age-standardized incidence and mortality rates of cancer in Nepal as compared with neighboring countries are depicted in Table 1. Lung cancer is the most common cancer in men (18% of new cases diagnosed) and third most common cancer in women (7.7%) in Nepal.[6] Nevertheless, the true magnitude of the disease in terms of incidence, prevalence, and mortality is still unknown because Nepal did not have a population-based cancer registry (PBCR) until recently.

Hospital-based cancer registry was initiated in 2003; there are now 12 such registries in the country as found in Figure 1, which is the main source for cancer registry in Nepal.[2] The Nepal Health Research Council has started PBCR since January 1, 2018. Currently, three PBCRs have been established in nine of 77 districts of the country covering 20% of the population of the country. The reports from the PBCR reveal a significant difference in the cancer incidence and mortality between males and females and the urban and rural areas of Nepal.[7,8] Lung cancer is one of the most common cancers in all the geographic areas of Nepal with an AAR ranging from 2.6 to 23.7 per 100,000.[9] Comparison of AARs of lung cancer with other neighboring registries is found in Figure 2.

*Corresponding author.

[a]Department of Medical Oncology, Bhaktapur Cancer Hospital/National Academy of Medical Sciences, Kathmandu, Nepal, [b]Department of Radiation Oncology, Bhaktapur Cancer Hospital, Bhaktapur, Nepal, [c]Department of Cardiothoracic and Vascular Surgery, Manmohan Cardiothoracic Vascular and Transplant Center, Kathmandu, Nepal, [d]Chest Unit, Department of Medicine, National Academy of Medical Sciences, Bir Hospital, Kathmandu, Nepal, [e]Department of Medicine, BP Koirala Institute of Health Sciences, Dharan, Nepal, [f]Department of Medical Oncology, National Hospital and Cancer Research Center, Jawalakhel, Lalitpur, Nepal, [g]Department of Cardiothoracic Surgery, Nepal Cancer Hospital, Lalitpur, Nepal, [h]Department of Medical Oncology, The University of Kansas Medical Center, Kansas City, Kansas, [i]Research Section, Nepal Health Research Council, Kathmandu, Nepal, [j]Department of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, Georgia, and [k]Department of Medical Oncology, Karmanos Cancer Institute, Detroit, Michigan.

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Address for correspondence: Ramila Shilpakar, MD, DM, Department of Medical Oncology, Bhaktapur Cancer Hospital/National Academy of Medical Sciences, Dudhpati, Bhaktapur, Nepal. E-mail: ramilashilpakardangol@gmail.com

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Table 1. Comparison of Age-Standardized Incidence Rate and Mortality Rate of All Cancers and Lung Cancer in Nepal With Neighboring Countries

Variable	Nepal	India	People's Republic of China	Bangladesh	Bhutan
Age-standardized incidence rate (all cancers)	80.9	97.1	204.8	106.2	81.9
Age-standardized mortality rate (all cancers)	54.8	63.1	129.4	75.3	66.6
Lung cancer, % (new cases)	12.2	5.5	17.9	8.3	8.2
Lung cancer rank by cases	First	Fourth	First	Fourth	Second
Age-standardized incidence rate (lung cancer)	10.4	5.4	34.8	9.5	7.5
Age-standardized mortality rate (lung cancer)	9.5	4.9	30.2	8.8	6.9

Data from GLOBOCAN 2020. The Global Cancer Observatory (https://gco.iarc.fr/today/data/factsheets/populations).

Squamous cell carcinoma has been the predominant subtype.[10,11] Nevertheless, there is an increased incidence of adenocarcinoma subtype in recent years.[12]

Tobacco Use

According to the WHO 2018 report, tobacco kills 27,137 people each year in Nepal, which accounts for 14.9% of all deaths. Tobacco use is reported in 30.8% of the adult population (48.1% in males and 14.1% in females). The mean age at initiation is 18.2 years, and the estimated smoking prevalence is 18.5% for ages 15 to 64 years. In addition, 36% of adults and 54.1% of youth (13–15 y) are exposed to secondhand smoking at home.[13] Given this alarming picture, the government of Nepal has implemented national tobacco control strategic plan and action as per the WHO Framework Convention on Tobacco Control, such as increasing tax on tobacco products, informing people of tobacco risk through large tobacco package warnings and information campaigns, making all public places smoke-free, and imposing a comprehensive ban on tobacco advertising and promotion in national television, radio, and print media.[14] Nevertheless, there is also the need for strengthening the smoking cessation campaigns as there are neither quit helplines nor smoking cessation clinics or smoking cessation drugs available. Strict tobacco control and smoking cessation policy should be the most important national priority along with raising awareness for reducing the burden of lung cancer.

Screening and Early Detection

Although the two large phase 3 studies, the National Lung Cancer Screening Trial and the Dutch-Belgian NELSON trial, have revealed an improved survival with the use of low-dose computed tomography (CT) screening in high-risk individuals,[15,16] there is no formal lung cancer screening program in Nepal. Because of the lack of screening programs, more than two-thirds of patients with lung cancer present with advanced or metastatic disease.[10,11] In addition, many other factors contribute to this late presentation, including a lack of access to health care facilities in rural areas, a long lag time from symptom onset to physician consultation, empirical use of antitubercular regimen by the health care providers owing to a higher prevalence of pulmonary tuberculosis, and delay in performing diagnosis testing, including CT scans and biopsy.[17,18]

Diagnosis and Staging

The histologic confirmation of lung cancer requires biopsy of the tissue either by means of bronchoscopy or transthoracic samplings. Accurate nodal staging is important for prognosis, to dictate therapy and limit unnecessary surgical interventions. Staging of mediastinal lymph nodes with noninvasive testing, such as positron emission tomography (PET)-CT, has sensitivity of 80% which increased to 92% when staging is done by endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration.[19,20] In addition, staging with EBUS has higher or comparable sensitivity and negative predictive value compared with cervical mediastinoscopy.[21] Hence, availability of resources and expertise for transthoracic needle aspiration biopsy or advanced diagnostic bronchoscopy tools for biopsy of pulmonary nodules/mass in addition to ability to perform noninvasive and invasive mediastinal staging is of utmost importance in lung cancer care. Bronchoscopy is used in the diagnosis for a central lung lesion and is done in few centers. EBUS-guided transbronchial needle aspiration is a novel technique that started recently in Nepal in 2019 and is done in four tertiary academic centers. Transthoracic sampling is usually performed under image guidance (ultrasound or CT) by interventional radiologists, and this facility is also available in limited tertiary centers. Likewise, mediastinoscopy is practiced only in very few tertiary centers. Histologic subtyping and molecular profiling are very important in lung cancer for identifying appropriate therapy. Immunohistochemistry (IHC) is available only in two academic institutions and in one private laboratory. Even in these facilities, the scope of IHC services remains very limited. Most of the requests for IHC are managed by private laboratories, and the samples are then outsourced to India with a turnaround time of approximately 2 weeks, which further delays the diagnosis. Very few private laboratories, mostly in the capital city, have started doing molecular diagnostic study. Nevertheless, most samples are sent to the neighboring country India for

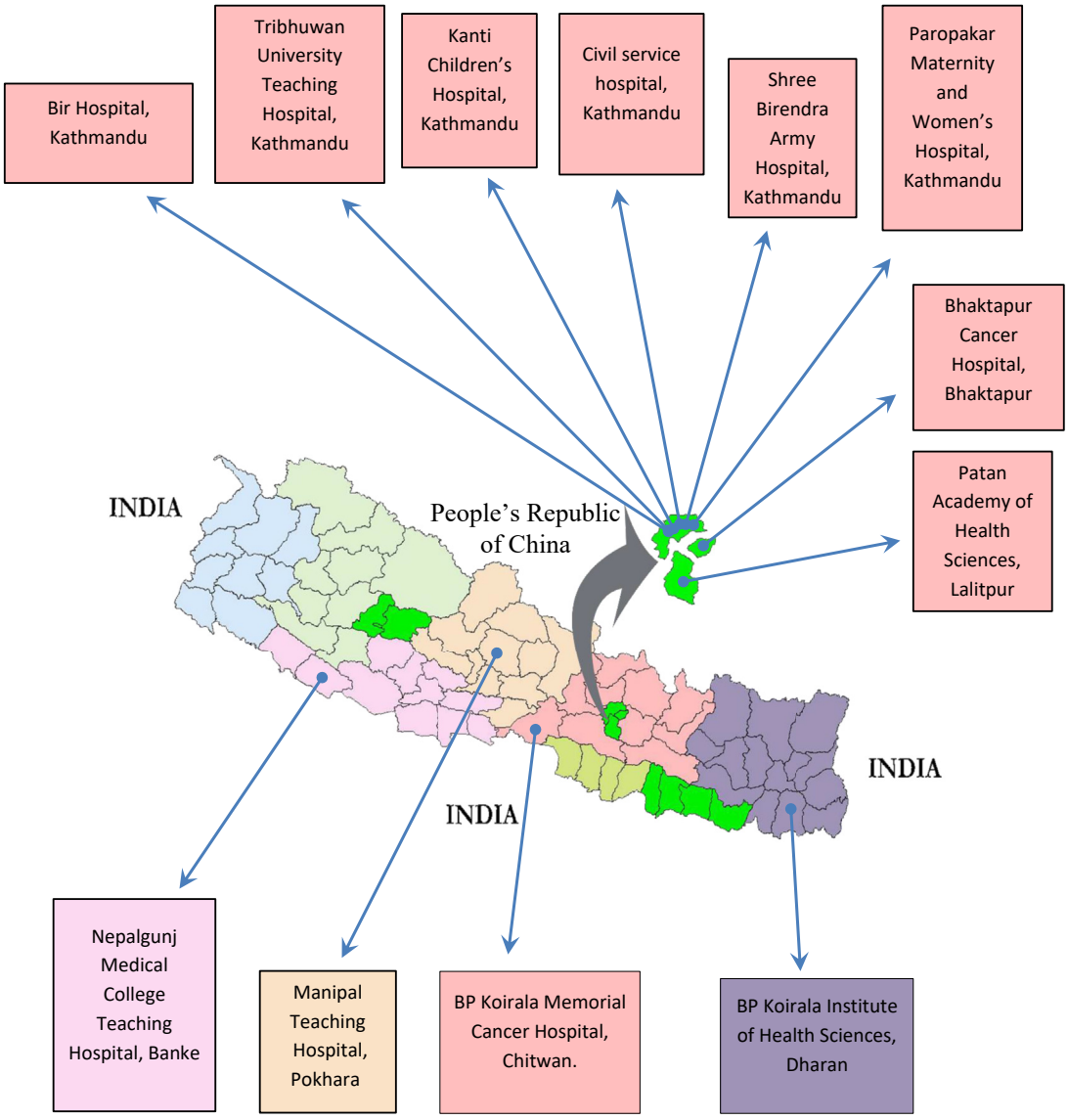

Figure 1. Map of Nepal. Sites for hospital-based cancer registry are found in the boxes. The districts in green are the districts where population-based cancer registry has been pilot started since January 1, 2018.

analysis. Because the expenses are mainly from out of pocket, molecular testing is usually recommended in patients with advanced nonsquamous histology or in never smokers or those with mixed histology and is usually tested for sensitizing *EGFR* mutation and *ALK* or *ROS-1* alterations. The incidence of *EGFR* mutations in Nepalese population is approximately 29% to 36% with exons 19 and 21 being the common mutation, which is comparable with other Asian studies.[22,23] Next-generation sequencing testing is limited to a small number owing to unavailability and cost of the testing.

Staging is an important aspect of lung cancer management for proper planning of treatment. CT scans and magnetic resonance imaging of the brain are often performed for staging. These services are available only in urban settings in both public and private settings. Although public facilities can obtain the scans at subsidized rates, there may be a significant delay in obtaining the scans owing to the high volume of patients. PET scan is now widely used for more accurate staging. In Nepal, PET scans are only available in two private centers that are both located in the capital city. The PET isotopes are obtained from India, and owing to the nationwide lockdown from coronavirus disease 2019 pandemic, PET services are currently not available in Nepal owing to the lack of isotopes. Efforts are being made for starting PET scans in tertiary public cancer centers soon, which will be a huge benefit in staging of lung cancers.

Surgery

Surgery remains the principal curative modality in patients with early stage lung cancers but resection rates

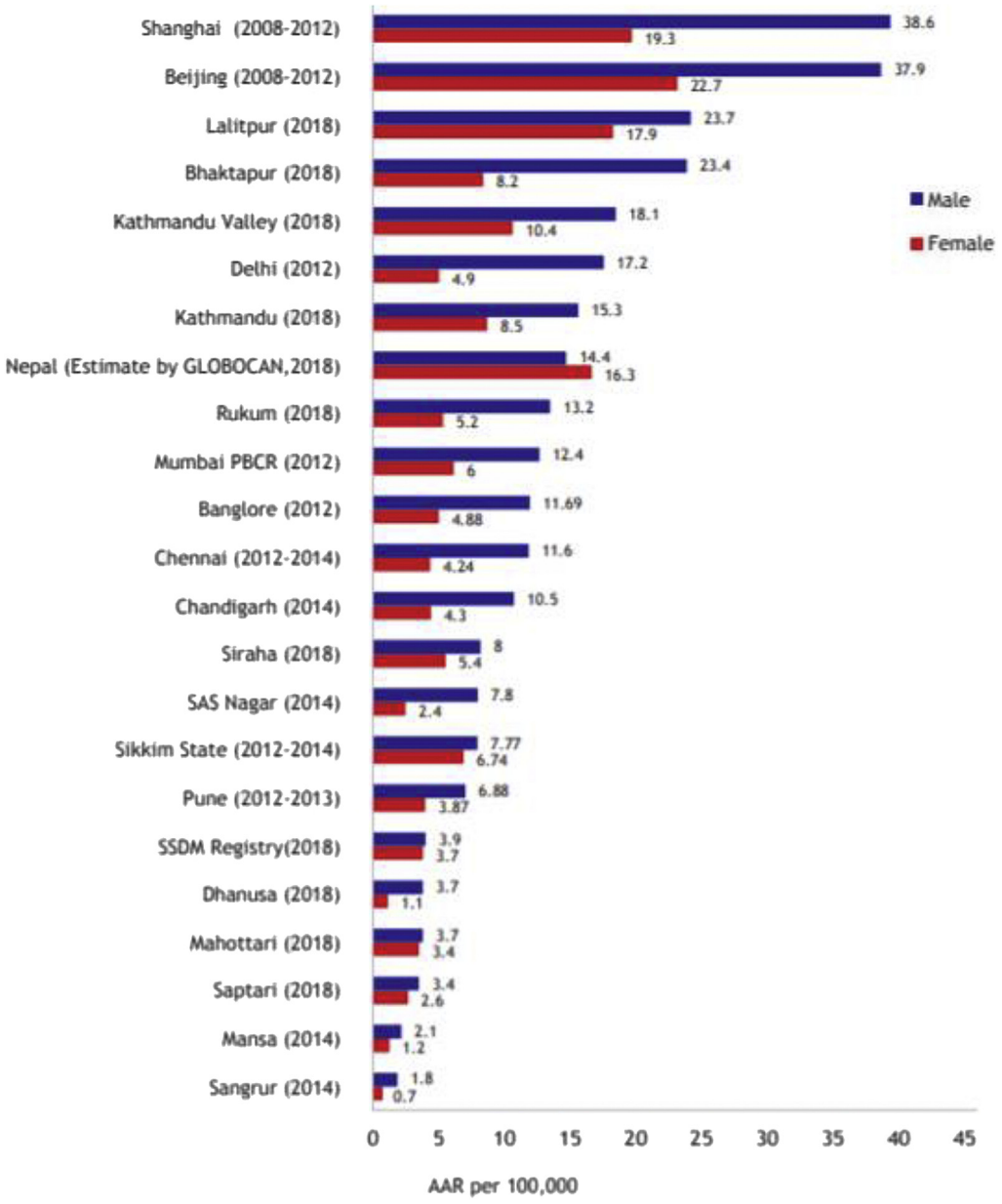

Figure 2. Comparison of AARs of lung cancer with other neighboring registries. Data from Jha AK, Chapagain S, Dhimal M, Subedi R, Kafle U, Thakur C, Khadka K, Budukh A, Dikshit R. Population Based Cancer Registries at Kathmandu, Bhaktapur, Lalitpur, Siraha, Saptari, Dhanusha, Mohattari, West Rukum and East Rukum Districts, Nepal—2018. Nepal Health Research Council; 2018. AAR, age-standardized rate.

are very low owing to advanced stage at presentation, lack of surgeons in rural settings, and poor general condition of patients at the time of presentation (3%–6.7%).[18,24] Anatomical surgical resection in the form of lobectomy (or sometimes pneumonectomy) either by open surgical approaches (most cases) or video-assisted thoracoscopic surgery along with mediastinal lymph node dissection is the preferred surgical approach. There is no robotic surgery available in Nepal. There are challenges to video-assisted thoracoscopic surgery in Nepal owing to cost, limited number of skilled thoracic surgeons, and high prevalence of tuberculosis and infectious diseases leading to dense pleural adhesions in many cases. Invasive mediastinal staging by means of mediastinoscopy is performed before the actual resection. In some cases, EBUS is used for mediastinal staging preoperatively. Forced expiratory volume in 1 second, 6-minute walk test, and stair climbing tests are done as a part of preoperative assessment. Diffusion capacity for carbon monoxide, perfusion scan, and measure of V_{O2}

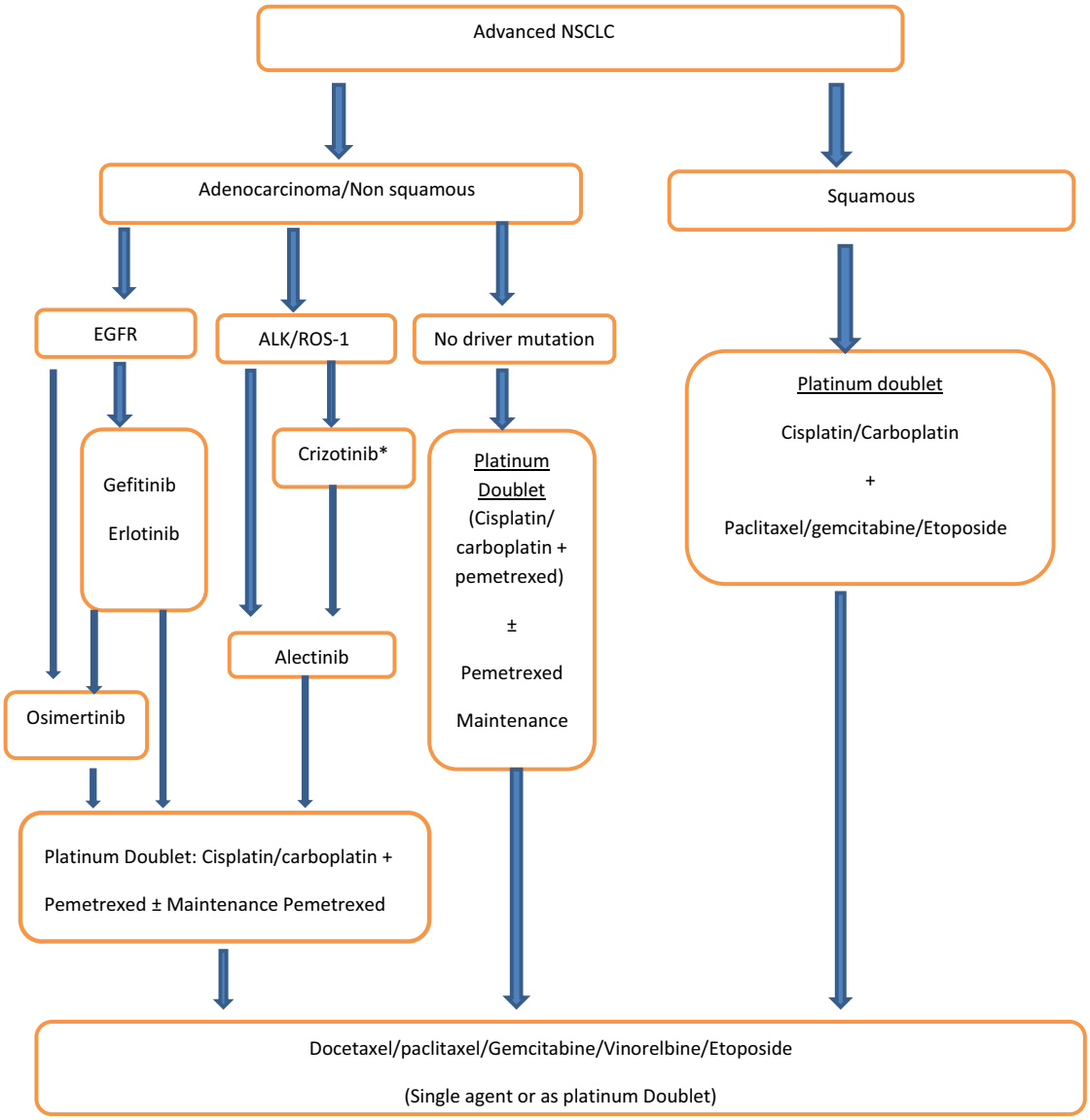

Figure 3. Systemic therapy for advanced NSCLC in a public setting. Note: Because there is no compassionate or expanded access to newer TKIs such as osimertinib/alectinib, osimertinib and alectinib available in Nepal are both generics made in Bangladesh prescribed for affording patients only. *Crizotinib is a free supply from access through The Max Foundation (Seattle, WA). TKI, tyrosine kinase inhibitor.

max (maximal oxygen consumption) are not routinely available. Despite these limitations, mortality associated with surgery is only approximately 2% (5.5% for pneumonectomy and 1.5% for lobectomy).[24]

Radiation Services

Radiation therapy (RT) is indicated in all stages of lung cancer, including postoperative RT for positive surgical margin, definitive RT for patients with early stage disease who are not candidates for surgery, concurrent or sequential chemo-RT for locally advanced disease, and palliative RT for a metastatic disease. In Nepal, RT services started from Bir Hospital in 1991 with a cobalt teletherapy machine using two-dimensional treatment planning. Currently, there are five radiation centers in the country (two public and three private) providing RT services with two cobalt teletherapy and six linear accelerator machines. Nepal, at present, is far below the WHO recommendation of one megavoltage machine per million populations for a population of approximately 30 million.[25]

Although all centers provide conformal RT (CRT), such as three-dimensional CRT and intensity-modulated RT, only a couple of them are equipped for image-guided RT and volumetric-modulated arc therapy. More

Table 2. Resources in Various Cancer Centers in Nepal: Public Cancer Centers

Resources	BP Koirala Memorial Cancer Hospital	Bhaktapur Cancer Hospital	Bir Hospital	Sushil Koirala Prakhar Cancer Hospital
Human resources				
Radiologists	6	4	17	2
Pathologists	6	5	5	1
Thoracic surgeons	2	1	6	0
Pulmonologists	0	0	3	0
Medical oncologists	3	5	0	0
Radiation oncologist	7	6	4	1
Radiation services available	Yes	Yes	No	No
Dedicated palliative care unit	Yes	Yes	No	No

advanced technology such as stereotactic body RT requires four-dimensional CT with appropriate motion management, which will be soon available in the country. For patients with lung cancer, three-dimensional CRT with CT-based planning is the preferred technique, whereas intensity-modulated RT is used only when necessary, to ensure adequate coverage of the planning target volume while satisfactorily achieving the dose constraints for organs at risk. Image-guided treatment verification is done using orthogonal electronic portal imaging devices and/or cone-beam imaging, on the basis of its availability.

The common RT schedule is to deliver 60 Gy in 30 fractions, using 2-Gy fractions daily in 6 weeks. Hypofractionation schedules are used when clinically indicated and include 55 Gy in 20 fractions, 40 Gy in 15 fractions, 30 Gy in 10 fractions, and 20 Gy in five fractions, on the basis of the intent of treatment and patient's general condition. Long waits in public facilities (approximately 2 wk to 2 mo) for RT have not only negatively affected the disease outcome but have also led to financial toxicity owing to the need for treatment in private facilities for quick service.

Systemic Therapy

Although there have been significant changes in the systemic treatment of NSCLC with the advent of targeted therapy and immunotherapy, new systemic therapies are almost nonexistent in oncological practice in Nepal because of lack of universal health coverage by the government exerting an enormous financial burden directly on the patients. Because there is no uniform national guideline, international guidelines such as the National Comprehensive Cancer Network and the European Society of Medical Oncology are often followed for the management of both SCLC and NSCLC. Comprehensive molecular testing with next-generation sequencing for driver mutations and programmed death-ligand 1 status is rarely done because of the high cost and need for sending the sample to India owing to unavailability within the country. Limited panel of targetable mutations for the available drugs is done for management of patients practically. So, the common genetic mutations in lung cancer in Nepalese population still remain unknown.

The mainstay of systemic therapy in SCLC is platinum-etoposide doublet. Cisplatin-etoposide is often

Table 3. Resources in Various Cancer Centers in Nepal: Private Cancer Centers

Resources	Nepal Cancer Hospital	National Hospital and Cancer Research Center	Kathmandu Cancer Hospital	B and C Medical College
Human resources				
Radiologists	5	1	2	4
Pathologists	5	1	2	2
Thoracic surgeons	1	0	0	1
Pulmonologists	1	1	1	0
Medical oncologists	7	2	1	2
Radiation oncologist	6	2	5	2
Radiation services available	Yes	No	Yes	Yes
Dedicated palliative care unit	Yes	Yes	Yes	Yes

used for limited-stage disease and is given concurrently with radiation. Carboplatin is substituted for cisplatin in extensive-stage disease, for older frail patients, and when potential toxicity from cisplatin use is a major concern. Immunotherapy, such as atezolizumab or durvalumab, is rarely used because of the financial constraints. In second-line settings, irinotecan, paclitaxel, and CAV (cyclophosphamide + adriamycin [doxorubicin] + vincristine) regimens are often used.

Platinum doublet remains the standard of care in advanced NSCLC; however, the choice of drugs depends on the characteristics of the patient and the tumor subtype. The chemotherapeutic agents, such as cisplatin, carboplatin, pemetrexed, taxanes (paclitaxel, docetaxel), gemcitabine, etoposide, and vinorelbine, are often available chemotherapeutic agents for lung cancer. The summary of treatment in a public setting is found in Figure 3.

Gefitinib and erlotinib are often used tyrosine kinase inhibitors for *EGFR*-mutant NSCLC whereas crizotinib is used for *ALK* and *ROS-1*–rearranged NSCLC (available free of cost through The Max Foundation, Seattle, WA). Generic drugs are frequently used for their lower costs. Nepal still has no access to even a single oncology clinical trial that would otherwise have been a great benefit for most patients.

Challenges and Future Direction

Despite several limitations with cancer care delivery, there has been improvement in lung cancer management in Nepal.[26] The government of Nepal provides financial subsidies of nearly $1000 to every person diagnosed with having cancer, which, even if insufficient, provides some relief to patients. Expansion of health insurance and a proper health policy should be the priority action of the government. This should include provision for essential anticancer drugs available and affordable for all patients with cancer and a priority-based cancer drug authorization. High prevalence of tobacco consumption is a major risk factor for lung cancer, and thus more efficient tobacco control acts along with tobacco and smoking cessation programs should be implemented for control of lung cancer-related morbidity and mortality. Delay in diagnosis leading to advanced stage at presentation is contributed largely by lack of oncology exposure and knowledge among general practitioners, so health education on early recognition and context-appropriate screening programs may improve early diagnosis and survival for lung cancer.

There is very limited manpower in oncology with approximately 35 certified radiation oncologists, 27 medical oncologists, 12 thoracic surgeons, and 16 designated Nepali medical physicists in the country.[2] Tables 2 and 3 reveal the available resources across few major public and private cancer centers in Nepal. Building the infrastructures, including pathology, surgery, and RT facilities, and having more trained oncologists across the country are high priority for improving cancer care in Nepal. There are insufficient local data on the epidemiology, stage at diagnosis, treatment outcome, and genetics of lung cancer. So, there is an urgent need to tailor and accelerate cancer research from the government and joint partnership with the international community.

Steps for benefits to the patients through clinical trials should be explored. With the concept of global oncology emerging, the benefit of newer anticancer drugs should be made available to patients with cancer in low- and middle-income countries such as Nepal as well either through compassionate use or generic or biosimilars. In addition, collaboration and coordination with institutions from developed countries facilitate many aspects of cancer care, including treatment, patient advocacy, and research.

CRediT Authorship Contribution Statement

Ramila Shilpakar, Bishnu Dutta Paudel, Rajeev Sharma, Sudhir Raj Silwal, Ranjan Sapkota, Prajowl Shrestha, Soniya Dulal, Madan Kumar Piya, Sampurna Man Tuladhar, Prakash Neupane, Meghnath Dhimal, Abesh Niroula, Dipesh Uprety: Conceptualization, Validation, Investigation, Writing—original draft, Writing—review and editing.

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