Tropical Hemato-Oncology

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Preface

Tropical hematology and oncology. So, what is special about it? It may not be obvious at first sight. There are excellent textbooks of hematology and oncology. Yet, these textbooks do not take completely into account the tropical perspective. Never before, to our knowledge, has a book specifically dedicated to this subject ever been published. Therefore, it appeared to be an interesting topic to some of us. This was enough to undertake this work. We want to tell its story. It is first a personal story. It later became a collective story.

Late in 2009, I had retired from my medical oncologist activity in Comprehensive Cancer Centers, specifically the Institut Gustave-Roussy (Villejuif) and the Centre Léon-Bérard (Lyon) and from professorship of medical oncology at the Claude Bernard Lyon 1 University (Lyon). The Hospital of Cayenne (French Guiana) needed reinforcement in medical oncology. I worked at this hospital for almost a year and for periods of 15 days every 2 months until now, in collaboration with a colleague from Lyon. French Guiana is a French territory with the same administrative organization as in mainland France. The health system is the French one; the European rules apply as in metropolitan France. I discovered different pathologies from those seen in Lyon and Paris, a different distribution of cancers. But mostly I discovered other cultural visions, problems related to distance and geographical characteristics. In addition, the hospital had a strong orientation toward tropical medicine (including traditional medical disciplines). These observations led a small group of friends and professors of medicine to agree about the idea of editing a book dedicated to tropical hematology and oncology. It is this small group that formed the editorial board of this book.

We wanted this book to be built on several principles:

- To consider all aspects of the subject: organization, public health, cultural diversity, specific mechanisms of carcinogenesis, etc.
- To not take into account the major principles of hematology and oncology, which are developed in high-quality textbooks.
- To try to discuss specific issues related to the occurrence of these diseases in a particular area: the tropics.

- To have a panel of authors as wide as possible. We tried to find author pairs from the north and the south. This has not always been possible, but the effort succeeded for many chapters.
- To be quite short and, as much as possible, to be practical. In particular, we asked the authors to highlight the management adjustments based on local opportunities and to try to answer the question "what can we do when we have few resources?"

We thank all the authors who have answered this challenge. We were very pleased to invite well-known friends of the hematological and oncological communities, but even more to get to know colleagues from different disciplines and from different countries. We tried, according to our readings, references, and acceptances, to write, to bring authors from all backgrounds and from as many countries as possible. We sometimes had to make difficult choices. For example, we planned a chapter on the biological characteristics of carcinogenesis in the tropics. Eventually it became clear that it was treated across the different chapters and, therefore, that some subjects were redundant. We have not included a chapter on CLL, Hodgkin's disease, and myeloma. In fact, there was no real specificity for these diseases, but the treatment of myeloma is discussed in the chapter on medical treatments. Other concepts have been treated several times in different chapters. We nevertheless kept these repetitions because they may allow giving different perspectives on the same subject. During the 6 months of preparation of this work, we have had many exchanges with the authors. Special thanks to Ian Magrath who agreed to write a foreword. We had a lot of discussions together to finalize the objectives and perspectives on this book. We also thank Springer who accepted the challenge. In particular we thank Nathalie Lhorset-Poulain who accompanied us during the preparation of this book.

This book aims to be a resource to help practitioners in the tropics; we hope it will be useful in this regard. We warmly thank the authors who have agreed to participate; nothing would have been possible without them.

Professor Jean-Pierre Droz
and members of the editorial team:
Professor Bernard Carme
Professor Pierre Couppié
Professor Mathieu Nacher
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Foreword

It was not until the end of the nineteenth century that academic institutions' focus on tropical medicine arose, the first being the Liverpool School of Tropical Medicine in 1898, with the London School of Hygiene and Tropical Medicine (LSHTM) being opened the next year. The schools in the Netherlands and in Belgium were established in 1910 (Amsterdam) and 1931 (Antwerp), respectively. It is no coincidence that each of these schools was located in a port city, for this was where the seamen suffering from diseases picked up in the tropics were to be found. Sick seamen meant that ships could not sail on schedule, with consequent loss of revenue by the trading companies. Given the large profits to be made by trading in exotic spices, cotton, silks, tea, and opium (at one time the East India Company accounted for half the world's trade), it is not surprising that international trade was largely conducted by joint-stock private companies owned by wealthy European merchants and the nobility. The East India Company, for example, at one time accounted for half of all the world trade and between 1757 and 1858 controlled large areas of India by means of its own private army and administrators. It was not until technological advances made in the nineteenth century – particularly improvements in microscopy – and Pasteur's final proof that "germs" cause infectious diseases that research could be conducted on the major tropical infections, although at that time there was little that could be done to alter the course of the debilitating diseases from which so many inhabitants and visitors suffered. One exception was malaria, which had for long been known to respond to treatment with cinchona bark, thanks to Peruvian Indians who passed on their knowledge to Jesuit priests in the early seventeenth century. The active constituent of cinchona bark was later shown to be quinine. So it was that in relatively quick succession, Sir George Manson and Sir Ronald Ross (particularly known for their work on the transmission of malaria), Sir Aldo Castellani (who showed the association between sleeping sickness and trypanosomiasis), Robert Leiper (a helminthologist noted for his discovery of the life cycle of the guinea worm), Carlos Chagas (who first recognized the American form of trypanosomiasis and established its transmission by triatomid bugs), Theodor Bilharz (who discovered schistosomiasis in Egypt), and Pirajá da Silva (who established its life cycle), among others, were able to rapidly move forward the understanding of tropical

diseases, a term which was particularly applied to the diseases caused by parasites, which were largely, though by no means exclusively, confined to tropical regions for reasons discussed below and about whose life cycles considerable evidence was accumulating. There was little if any discussion of cancer, although some cases must have been seen. Presumably, this was because the classification of cancer was in its very early stages, and signs and symptoms may have been misinterpreted. Cancer accounted for a relatively minor fraction of sick people in the tropics, and treatment was extremely limited, even in Europe, until well into the twentieth century. Cancer may also, in some cultures, be stigmatized (e.g., women with breast cancer) and hence hidden from other family members to the extent possible. However, although not foreseen at the time of the research, understanding the life cycles of various parasites, especially trematode worms, proved to be important to the development of measures designed to prevent certain cancers that in tropical regions have been responsible for a large proportion of cancers in the past and, in Africa particularly, may still be seen (e.g., schistosome-related bladder cancer). The availability of funding from the companies that made enormous profits from the high demand (at least in the upper echelons of society) for the products available from tropical countries was more than enough to establish schools of tropical medicine, which focused also on public health and epidemiology as the mechanisms of parasitic infestation were gradually uncovered. Cancer was not a major item on their agendas, and the cancer burden, both in the tropical colonies and among those who returned from the colonies, was small. Nonetheless, there are differences in the distribution of various cancers throughout the world and in different socioeconomic subgroups, and a book focused entirely on tropical cancers may well serve a valuable purpose in emphasizing the importance of environment and lifestyle in the causation of cancer. Moreover, chronic infection as a cause of cancer remains important in certain populations. There is, for example, a Schistosomiasis Control Initiative focused on schistosomiasis in Africa, since, unlike Egypt, whose efforts to control schistosomiasis extend back to early in the twentieth century, some countries in which schistosomiasis is common have only recently developed control programs.

Since anemia is widespread and carries with it important social and economic implications due to poor development in children, an inability to learn, and a predisposition to infectious diseases, some hematologists focused on hematological diseases that occurred predominantly in tropical reasons, such as the inherited thalassemia and sickle cell disease. These diseases were shown to lessen the severity of malaria, the distribution of which, prior to eradication programs, was remarkably similar to that of thalassemia, such that patients did not die, but neither were they in full health. Tropical hematology, however, was primarily focused on nonmalignant diseases, and the inclusion of malignant hematological diseases in this book stems from the editor's desire to cover the full spectrum of malignant diseases in tropical countries. But are there differences between the spectrums of malignant diseases in the tropical regions compared to temperate climates? Before addressing this question, it is important to know what is meant by "tropical" and how a tropical environment might influence the spectrum of cancers and approaches to their prevention and control.

The Tropics Precisely Defined

The tropics comprise – as will be reiterated in multiple chapters of this book – the region between the two imaginary lines of latitude that presently encircle the globe at 23°26′14.3″ north and south of the equator, respectively (the precise positions are drifting slowly toward the equator). The northern latitude is called the Tropic of Cancer or Northern Tropic, and the southern, the Tropic of Capricorn or Southern Tropic. This region has a number of unique characteristics. It is the hottest part of the planet, being closest to the sun, and the temperature does not fall below 18 °C (64 °F) throughout the year. This means that the four seasons (spring, summer, autumn, and winter) that occur in all other parts of the planet do not occur in the tropics. The tropical sun remains high in the sky throughout the year and is directly overhead at its "culmination" (approximately noon) on 2 days of the year at the latitudes of the tropics and the regions between them. Necessarily, from this observation, the point at which the sun sets (or rises) appears to move between the latitudes of the Tropic of Cancer and the Tropic of Capricorn throughout the year. This is the result of the plane of the Earth's axis not being at right angles to the plane of the ecliptic, i.e., the plane of the Earth's orbit round the sun. The axis is inclined at an angle of approximately 24.4° which is fixed in relationship to the stars, such that as the Earth orbits the sun, the degree of tilt presented to the sun varies between 0 and 24.4°. As a result, the point on the horizon at which the sun rises or sets moves back and forth between the two tropics as the Earth traces its orbital path, reaching its most northerly point in June, precisely on the Tropic of Cancer, and its most southerly point in December, precisely on the Tropic of Capricorn. The days on which the rising or setting of the sun appears to stand still before reversing its direction are known as *solstices* (*Latin for* "*sun*" *and* "*to stand still*"). The June solstice is the longest day of the year and the first day of summer north of the Tropic of Cancer. It is the shortest day of the year and the first day of winter in the southern hemisphere south of the Tropic of Capricorn.

The climate in the tropics is of three main types – tropical rainforest, tropical monsoon, and savanna, the last of which has a pronounced dry season. These climatic zones result in a broad range of ecosystems, some of which change little throughout the year. Tropical regions account for 80 % of the world's biodiversity, 40 % of its population, and 20 % of its economy. Using the World Bank's classification of countries into low-, middle-, and high-income countries, only Singapore and Hong Kong – now a part of China – are among the 30 countries ranked as high-income countries by the World Bank. Thus, the cancers of these countries, and the cancer services, with the two exceptions mentioned, are similar to those in other low- and middle-income countries. According to Jeffrey Sachs (National Bureau of Economic Research, working paper 8119), the GNP per capita in the tropical zone in 1820 was approximately 70 % of that in the temperate zone, but this had fallen to 25 % by 1992, reflecting the difference in economic growth throughout this period. The major reason for this was the difference in the development of technology, particularly that related to agriculture and health, but difficulty in mobilizing energy

resources in tropical zones was also important. Sachs also recounted that in 1995, productivity per hectare of grain in tropical zones was 50 % of that in temperate zones. This is a result of soil formation and erosion, losses related to various pests and parasites, the availability of water, and the effects of tropical climates on plant respiration. Poor agriculture gives rise to poor nutrition and poor health. Poor health results in a reduced ability to learn and a lower capacity for work. This feeds back into the more limited development of technology, and correspondingly low economic growth rates, although it must be said that many colonies have only achieved their independence in the mid-twentieth century and part of the lack of concern about technological growth may have related to the colonial plan to maintain the less developed countries as the providers of raw materials and their colonial masters as the producers of the end product – a means of ensuring that the wealth of a country was, to a large extent, concentrated in the hands of the colonialists. Although some hospitals and schools were built, most of the very sick colonialists were sent back to their own countries. These remarks apply particularly to the French and British colonies since the Spanish and Portuguese colonies (except for Cuba and Puerto Rico) had gained their independence by 1826. A third reason for the poorer performance of tropical countries is the fact that many of them are considerable distances from the sea – particularly African colonies – which tend to disadvantage them from the perspective of exporting goods to the rich countries. In the context of health care, this also meant that as more technology developed, the delivery of medicines and equipment became an increasing challenge, for not only do the poorest countries produce few drugs but importation offers many opportunities for taxation (official and "nonofficial"), e.g., in Africa, where the cost of many generic drugs, especially those for cancer, can be several times higher than in the country of manufacture! In the context of new drugs, most patents provide for 20 years of monopoly and, therefore, during this time, a lack of market competition except by completely different compounds which have similar activity. The less developed countries, with their small pharmaceutical industries (if they exist at all), therefore have limited access at best to many of the newer drugs, which are usually priced too high for them to afford, although special circumstances may sometimes apply, such as the provision of imatinib free of charge by Novartis to the 40 poorest countries in the world. They must, however, demonstrate the presence of the relevant translocations, such as the 9;22 translocation in chronic myeloid leukemia and a subset of acute lymphoblastic leukemia, in order to receive the drug free of charge.

Poor health in low- and middle-income countries is not solely the result of lower agricultural yields. Tropical countries have a larger burden of disease even after controlling for GNP per capita. The infant mortality rate is 50 % lower in temperate-zone countries and life expectancy 8 % higher. Due to constantly improving technology pertaining to disease control in temperate zones, coupled with improved housing, nutrition, public sanitation, and the introduction of immunization, infectious diseases which had affected all parts of the world in the nineteenth century were more readily controlled in temperate-zone countries (e.g., tuberculosis and malaria). In general, the more limited health workforce of tropical countries led to much slower progress with respect to vaccination of children against the common,

but potentially, serious infections. Further, many infections in the tropics are caused by vectored parasites and viruses, and these, along with helminthic infections, some of which are listed below, have proved to be difficult to control. Arthropod vectors have the advantage in the colonies that they have no winter to survive, and their adult forms continue to spread disease throughout the year. The difficulties in controlling these diseases, however, are in considerable part due to their neglect at an international level during a period when health technology was growing rapidly in temperate-zone countries. The World Health Organization, for example, lists 17 neglected tropical diseases. It is likely that the lack of a winter season favors the maintenance of insect vectors, some of which may be confined to the tropical regions, such that appropriate vectors for some diseases do not exist outside the tropics, but there are often multiple possible insect vectors as has been shown by the occasional appearance of tropical virus infections in temperate countries. Malaria, for example, now considered a tropical disease, was once a disease that was present almost everywhere in the world. Although only transmissible to humans by female Anopheles mosquitoes, there are some 430 species of Anopheles which overlap in distribution such that vectors for malaria are available everywhere. The parasite develops more rapidly in the mosquito at higher ambient temperatures – it requires 10–18 days to complete its production of sporozoites in the mosquito (the infectious particles injected into a new host when a female mosquito takes a blood meal), such that it may be somewhat more readily eradicated in temperate regions. Malaria is not known to cause cancer, but there are reasonably strong data that indicate a role for it in Burkitt lymphoma in Africa. The enormous difference in geopolitical power between temperate and tropical countries is clearly also a major factor in the poorer economic performance of the latter. Huge challenges face tropical nations, such as environmental degradation. Tropical forests, for example, are either overharvested or cut down to make room for large international agricultural corporations – or small homesteads for subsistence farmers, who clear the forests in order to create agricultural lands from which they can eke out an existence. Population growth, although slowing, is markedly higher in tropical countries which already lack the resources to ensure good nutrition and the health of their citizens. These socioeconomic circumstances have a considerable impact on the health of the people who live in the tropics who, to a large extent, are dependent upon natural resources for their livelihood.

Destruction of the Rainforests

Some 90 % of the 1.2 billion people living in extreme poverty worldwide live in the vicinity of rainforests and depend upon the forests for their livelihood (57 % of all rainforests and almost all tropical rainforests are located in developing countries). While the judicious use of *renewable* sources provides wood (an energy source) and foods (various plants and animal species) and protection of the land against erosion, flooding, and drought, the permanent destruction of large regions of the tropical

rainforests will lead to the loss of countless species of animals and plants (estimated at the present time as 5–10 % per decade) and, quite probably, to lost opportunities to develop new medications due to the elimination of the valuable resources mentioned. The destruction of the rainforests results in flooding in the rainy season and drought in the dry season, creating enormous hardships for the vulnerable people living in or near the forests (i.e., people with very limited or no reserves that can carry them through difficult periods) and resulting in markedly decreased productivity in these regions. Long periods of drought in the arid savanna regions have a similar effect on the pastoral way of life, a lifestyle that is absolutely dependent upon the animals herded by the pastoralists. When sources of water dry up, the animals die, leaving their owners with no source of nourishment. They have little choice but to move to the cities – only to find they cannot make a living there either.

Urbanization

While we associate the word "tropics" with a rural lifestyle, the cities that are within the tropical zone are undergoing rapid expansion as a result of the population growth resulting from the demographic changes caused by the industrial revolution – or those parts of the industrial revolution that people in poorer countries can take advantage of. According to John R Wilmoth, director of the population division of the UN, many countries are urbanizing at lower levels of development than in the past. People who leave the countryside are by no means assured of a livelihood because many cities will not have an industrial economy that can provide jobs and an infrastructure that would allow new residents to live in acceptable conditions. The result is large slum areas and dumping grounds for waste of all kinds, particularly on the vaguely defined peripheries of such cities, because the city does not have sufficient equipment to remove waste. This has a major effect on the development of new housing, clean water, education, electricity, transportation, and health care which, because of the density of the population, would normally be more efficiently provided in cities than in rural regions. Already, many of the largest cities in the world are in tropical regions, such as Delhi, Kolkata, and Mumbai in India, Manila in the Philippines, Jakarta in Indonesia, Guangzhou and Shenzhen in China, Lagos in Nigeria, and Mexico City, Lima, and Rio de Janeiro in Latin America. All of these cities are among the largest 30 cities (in terms of population) in the world and suffer from massive pollution, mostly due to the high volume of traffic occupying a space not designed to contain it and lax regulations on industrial discharges into rivers, the sea, or the air. Many respiratory diseases ranging from asthma to lung cancer result, and more health services are almost certainly required than was the case in the past, where tropical environments were exclusively rural. In these megacities the slum dwellers often live, quite literally, on the detritus of their wealthier fellow citizens, but the latter, although vastly better off, may still have higher rates of cancer due to smoking coupled with air pollution, although they may have some respite from the massively polluted air in

their air-conditioned offices. But worse still, low- and middle-income countries are undergoing urbanization at an increasing rate. The UN estimates that presently, 22 % of the world's population lives in urban regions, but this will increase to 27 % by 2030. In a word, the unique climates and habitats of tropical regions are being destroyed with major consequences for the world. As these regions are degraded, and urbanized, there is a loss of environmental stability and changes in lifestyle patterns and in the diseases which are associated with them. Even the ancient myths that bound tribes together no longer provide the psychological support and "cultural glue" that make people feel part of a community that, whatever the myths used, gives meaning to people's lives. The loss of these cultural ties may be as devastating psychologically as the physical consequences of disease – particularly complex diseases, such as cancer, that usually require complex impersonal treatment by highly trained personnel as well as expensive equipment for imaging and treatment (e.g., radiation therapy machines). Modern myths must be created, which teach illiterate people something about cancer and more gently lead them toward a world that at least resembles the technological world in which the wealthier societies live – although not all that the rich have to offer is good, and care must be taken to differentiate the good from the bad (smoking, drinking, overeating, and lack of exercise should become the evil spirits that must be exorcized).

Infection and Infestation as Causes of Cancer in Tropical Regions

In spite of the growth of cities and the frequent loss of traditional lifestyles in rural regions of the tropics, chronic infectious diseases, e.g., human papillomavirus (HPV) infection, human immunodeficiency virus, *Helicobacter pylori*, or parasitic diseases (trematode worms or flukes in particular), account for a much higher fraction of cancer than in temperate regions. It should be understood that there is no sharp boundary from the biological perspective around tropical regions, and some of the diseases, and certainly the problems encountered by LMIC populations, are similar in many nontropical countries. It is also necessary to beware of "averages" and global figures if the true picture is to emerge. For example, the International Agency for Research in Cancer (IARC), which collects cancer registry data from all over the world, estimates that in 2008, approximately 16 % of cancers worldwide were associated with infections. However, in LMIC, the fraction of cancers associated with infections was estimated to be 23 %, with high-income countries accounting for only 7.4 %. Even these figures remain composite, i.e., the average of many countries. In Australia, for example, it is estimated that only 3.3 % of cancers were caused by infection in 2008, while in the Gambia, approximately 62 % of new cancer cases in males were diagnosed in the same year with hepatocellular carcinoma – caused by hepatitis B and aflatoxin – and there can be no doubt that some other cancers are also related to chronic infection, suggesting a figure slightly higher than 70 % for the

fraction of cancers in males caused by infection in the country. In women the annual incidence rate of hepatocellular carcinoma was lower and accounted for 24 % of cancers, but cervical cancer, caused by HPV, was estimated to be 38 % of new cases, so that the fraction of infection-related cancers in both sexes was similar, but much higher than the average fraction in all LMIC combined. Interestingly, the incidence of gastric cancer, once the most common cancer in the world, was quite low. These findings are important, since they suggest that the majority of cancers in the Gambia are preventable by affordable vaccines. Cervical cancer can also be effectively controlled by simple screening techniques, particularly if they involve the detection of HPV in cervical secretions. In Egypt, there is a high prevalence of schistosomiasis (both hematobium, causing severe chronic bladder damage, including fibrosis and progression to squamous carcinoma of the bladder, and mansoni causing granulomata of the bowel and, again, the possibility of progression to colon cancer, although the data for this are less compelling than carcinogenesis relating to *S. hematobium* and *S. japonica*, a fluke that occurs predominantly in China). The Egyptian government has attempted for decades to prevent schistosomiasis. Attempts to poison the intermediate host, a water snail, failed, but eventually, a nationwide policy of selective therapy with praziquantel, provided free of charge to individuals diagnosed as having schistosomiasis, had a major impact, such that the incidence of schistosomiasis countrywide is believed to be less than 3 %. Some years after these efforts, it was also thought that the incidence of bladder and bowel cancer caused by schistosomiasis has been markedly reduced, but there is insufficient registry data to be sure. Bladder cancer at one time was thought to be the commonest cancer in Egypt (although this was based on data from the National Cancer Institute in Cairo (NCIC) and not population-based). At that time, squamous bladder cancer accounted for 80 % of bladder cancer cases, but the proportion of squamous cases has been falling at the NCI and a few years ago accounted for approximately 50 % (the remainder being transitional). In support of the role of schistosomiasis in bladder cancer is the observation that most cases are in farmers or their families, while patients with transitional bladder cancer usually work in Cairo.

In equatorial Africa, the case is still that 80 % of the people live in rural regions in which a higher fraction of cancers are caused by infections or infestations that can be prevented or treated. Incidentally, there are a number of other flukes, mostly found in SE Asia or China, such as the so-called “food flukes” that are believed to cause liver or biliary tract cancers. They infect an additional intermediate host (a fish or crustacean) which, when eaten, spreads the disease.

Challenges in Cancer Control in the Tropics: The Epidemiological Transition

The industrial revolution resulted in major changes in lifestyle and had major social, economic, and demographic impacts. Populations of countries (e.g., the UK) moving through the epidemiological transition that it precipitated first began to grow

rapidly due to improved living conditions and hygiene. Premature deaths (less than 70 years) are reduced, so that the population also ages. Then a gradual reduction in the birth rate follows which does not initially slow population growth since people live longer. During this period the burden of cancer increases, since on average the population is larger and older. All LMIC, which account for 85 % of the world population, appear to be going through a period of rapid increase in the cancer burden – they accounted for an estimated 8 million (57 %) of the 14.1 million cancer cases that occurred in 2012 (IARC) and 65 % of the cancer deaths. The age-adjusted incidence rate is 267.2 and 147.7 for more and less developed countries, respectively, so that the incidence of cancer is higher in more developed countries. However, death rates are quite similar, indicating that treatment results are worse in the less developed countries as expected. In the UK following the Industrial Revolution, the population size stabilized as the birth rate and death rate found a new equilibrium but at a much lower level than prior to the transition. While this pattern is not invariably followed and, indeed, can hardly be said to be following an industrial revolution in the less developed countries, the increase in the cancer rate in LMIC is presumably due to improving standards of living. Population growth and aging appear, as would be expected, to be invariable in such a time, but there is uncertainty about when and to what degree the growth rate will slow and the cancer burden stabilize. It may well differ in different countries, but the IARC predicts that in 2030 the number of cancer cases will be 7.6 million in more developed regions and 13 million in less developed regions. Thus, the less developed regions will need to be prepared to cope with a much larger increase in cancer patients in this 15-year period. In fact, the increasing cancer burden is likely to cause major catastrophes in the poor countries, which cannot take care of their present cancer burdens because of the lack of facilities (including radiation therapy units, skilled surgeons, and medicines) and well-trained pathologists and oncologists. A number of countries (e.g., the emerging economies) have been able to overcome the problems caused by the demographic changes and resultant epidemiological transitions, however, and now manufacture sophisticated goods such as motor vehicles and electronic goods and often take high market shares because they can produce high-quality goods more cheaply. Such countries are able to create enough wealth to be able to care for their cancer patients who, in turn, are generally supported by health insurance, which is, for the most part, lacking in LMIC, where patients must pay for most or all of their care out of pocket. Even now, many patients in LMIC cannot afford even the relatively cheap medicines or procedures available and die. Sometimes they return home having had no or partial therapy because of financial costs or the fact that there is no one to look after their children. Families are frequently large, such that although the parents can support the family by subsistence farming, or other source of livelihood, they are extremely vulnerable to crises such as cancer in the family because they have little or no money (they often barter for goods) or other forms of support. Unfortunately, all too often, the necessary treatment is not available. Large family sizes increase the vulnerability because the parents have more children to look after – and if and when the economic situation improves, more elderly parents to care for too.

Countries at a low level of scientific development who do not make major investments in scientific education will continue to compete poorly and have an ever

greater task in catching up with those countries whose economies are largely built upon manufacturing, particularly complex goods such as motor cars, computers, etc. To reach this stage, however, sound investments in education and good leadership are essential. In countries that have undergone an epidemiological transition, infectious diseases have largely come under control, and the major diseases are noncommunicable, such as diabetes, heart disease, lung disease, and cancer. A reasonably high fraction of such diseases are caused by unhealthy living, and if education and policy are able to modify behavior, the number of premature deaths (less than 70 years) will be reduced. However, at the other end of the spectrum, an increase in the elderly members of the population also creates a heavy financial burden unless universal health insurance has been implemented. In many European countries, their own populations are shrinking, and people from other countries (usually LMIC) must be recruited in order to carry out the tasks necessary to maintain and even improve services provided. While some of these may be uneducated, they may obtain an education in the country to which they have migrated (possibly because they could not obtain an education at home) and often remain in their adopted country. Unfortunately, the technical and scientific skills of such individuals are, for the most part, not available in their own country. The less developed countries have both the least amount of resources for health care and are likely (as per the IARC predictions) to have far greater cancer burdens by 2030 than the more developed countries. In addition, they may still have significant levels of infectious diseases and possibly still some cancers associated with infectious agents. Thus, the less developed countries will be even less able to cope with the ever-increasing cancer burden, short of a major new discovery relating to the control of cancer. Since the health systems prior to the epidemiological transition evolved largely to manage acute problems (e.g., trauma and short-term infectious diseases), they are ill placed to deal with the sudden marked increase in chronically ill people (not just cancer, but all NCDs) who require multiple visits to doctors, including specialists who, in the poorer countries, are in very short supply. In addition, the number of young people sufficiently educated to attend university is far fewer in more developed countries than less developed countries because of the limitations in the education of children at secondary school. The extent to which increased efforts to educate more specialists will offset these predictions is unclear. In addition, the predictions are based on demographic factors only – increased exposure to risk factors, especially tobacco, will make the situation even worse.

Cancer Prevention and Control

Prevention entails the avoidance of risk factors which can be achieved only by changing behavior through education of the public and creating policy that encourages them to do so and/or screening to detect premalignant or early-stage disease. The common risk factors for cancer and noncommunicable diseases include being overweight, obesity, lack of exercise, abuse of alcohol, and, most important of all,

the use of tobacco. The common risk factors tend not to apply to the poorer members of society, who are often undernourished, have little saturated animal fat in their food, undertake physical rather than sedentary jobs, and cannot afford alcoholic drinks or cigarettes. The growing middle class, however, in attempting to emulate their peers in higher-income countries, tend to have poor diets (i.e., rich in fats) and smoke cigarettes. Increasing their awareness of risk factor exposure can be greatly aided by education and policy. Given the broad nature of the common risk factors described, policy must be multisectorial at the government level, while its implementation must involve a broad range of stakeholders.

While prevention, for the most part, takes place in the community, effective treatment planning at country level requires a sound health system built on knowledge of the number and types of cancers and, ideally, knowledge of their distribution in the country coupled with efforts to ensure that referral is early (education of those who refer patients for further investigations as well as the public will be required) and the necessary treatment modalities available along with needed equipment and necessary specialists. Such resources are rarely available in the less developed countries today, and to create institutions and hospitals will be an expensive process, almost certainly out of the range of possibilities of most of the less developed countries. The assessment of the number of cases and trends is usually made via cancer registries at a population level, but there are still too few registries in poorer countries, especially in the rural areas. Registries can also be used to measure the impact of interventions designed to prevent or treat cancer, including mortality and survival rates, but accurate information requires high coverage rates of the population in question. Unfortunately, it is difficult to imagine that the needs will be met, and there is little evidence that much is being done about the enormous gaps that must be filled.

This book covers the entire gamut of cancer prevention and treatment and the characteristic features of the most common cancers as well as general topics such as clinical trials, training, and education. It addresses issues of insurance and socioeconomics of cancer control. It also deals with each of the main cancers individually. Within its pages one can only hope that there are potential answers to the serious questions raised with respect to the predictions of the cancer burden in 2030. Of one thing, we can be certain. Without a scientific approach, none of these problems will be overcome. That must be its ultimate message. Prof Droz is to be congratulated for bringing together an elite group of authors and creating a solid framework for discussion of cancer control in the tropics and in other LMIC.

Brussels, Belgium Ian Magrath

Contents

Oncology in the Concept of Tropical Medicine: To Be or Not to Be?

Bernard Carme

1 A Definition of Tropical Medicine

The first thing to do to introduce the concept of tropical medicine is to define the term. The easier might be to say that it is the practice of medicine, all medicine, in tropical areas. It is then up to clarifying the concept of tropical area and surprisingly this is not obvious. It must first integrate the equatorial regions to cover the regions between the two tropics. But where are the north and south bounds and how to consider the so-called subtropical areas? For someone subtropical areas include temperate regions until the 40th degree of latitude and for others it would stop at the 30th parallel, knowing that the tropics are more precisely at 23°27' latitude. Let geographers care to agree and define concerned territories and populations. But we must go beyond this boundary.

The concept of tropical medicine must remain intuitive and variable in geometry because it is necessary to combine purely geographical criteria with development criteria, however, provided that a high level of development, that is to say, higher incomes, will tend to leave this framework regardless of their geographical location. Tropical medicine primarily concerns low-/intermediate-income countries and/or developing and emerging countries. It is conventional to say that tropical pathology decreases with development. Singapore, although located in the equatorial zone, does not match these criteria.

There is no need to set a rigid framework especially as fields of medical practices with other names can find their place in tropical medicine. This is the case of travel

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medicine, development medicine/international health, humanitarian medicine, and disaster medicine that are considered specialties; they have their own teaching programs, learned societies, and specific conventions.

Trips with medical concerns, that is to say, not ubiquitous, are primarily those taking place in the South for people from the North or the reverse if we consider the Southern Hemisphere. Development medicine primarily concerns the countries that have not yet acquired a good level of health, primarily tropical countries. The impact of natural disasters and/or those caused by human activity is always more pronounced.

Hurricanes, other storms, and earthquakes have greater impact because buildings are frail constructions and not secured (low-cost construction and/or non-seismic) and the settlements are exposed to natural hazards (flooding, landslides, etc.). Here the physical geography reasserts itself. Haiti, the Philippines, and Pakistan are countries whose human toll and economic consequences of climate disasters were the heaviest in 2012 [1]. There are fears in the future of an increase of these phenomena related to climate changes, the growth of urban populations with a higher density, conflicts, terrorism, etc.

2 The Scope of Tropical Medicine

But regardless of the level of economic development, there are strong relationships between diseases, geographical areas by including the features of wildlife reservoir of infection which are sources of microorganisms and/or communicable disease vectors, and the human societies. Tropical medicine retains marked peculiarities. First of all is the importance of infectious diseases which is still dominant.

This is due to the persistence of old diseases that have specific or strong tropical polarity; they can be caused by parasites (malaria, leishmaniasis, schistosomiasis, amebiasis, trypanosomiasis (human African trypanosomiasis [HAT], Chagas disease)), bacterial infections (cerebrospinal meningitis, salmonellosis, shigellosis, etc.), or viral infections (severe measles, dengue, yellow fever, etc.).

Additionally to these diseases are new and/or reemerging infectious diseases which are more frequently found and have a greater impact in the tropics: SARS (severe acute respiratory syndrome), avian flu, retroviral infections (HIV/AIDS, HTLV), viral hemorrhagic fevers (Lassa, Marburg, Ebola, etc.), chikungunya, cholera, and tuberculosis. Their importance (incidence, severity) is also a function of environmental conditions, not only climate but also social and economic settings.

This is also true for the "cosmopolitan" infections but also to greater exposure to certain environmental pollution and poisoning linked to physical agents: venoms, poisons, and toxins.

Difficult living conditions increase individually the impact, frequency, and severity, due to lack of resource hygienic constraints (fecal peril, personal hygiene, food storage), precarious housing (promiscuity promoting interhuman contamination and/or contamination from animal reservoirs), and faulty power supply causing nutritional deficiencies.

Finally, there are other general diseases whose impact can be particularly important in the tropics as hematology with hemoglobinopathies and in particular, to come to our concerns, oncology.

3 The Emergence of Oncology in Tropical Medicine

A low level of development will impact a part of the population with the impossibility or extreme difficulty to access curative but also preventive cares; lack of financial resources, both individually and collectively, results in deficient sanitary equipment. Poverty is indeed the first of diseases, in the South as well as in the North.

Schematically, the so-called Northern pathologies are essentially cosmopolitan diseases a long time neglected or hidden and therefore much ignored in poor countries; in these countries the scene was occupied by infectious and nutritional diseases. The reduced life expectancy was of course an element masking the importance of disorders related to aging. The lack of efficient equipment, both in terms of diagnosis and therapeutics, and lack of medical supervision with an expected low demand for care explained the situation. It is therefore logical that the consequences of hypertension, diabetes, and malignant diseases, cancer and blood disorders, were otherwise ignored, at least neglected in poor-income countries. This should not be the case today. Nowadays physical inactivity and dietary overload do not necessarily reflect a true enrichment of the people, and they are aggravating factors. This trend will not spare a more and more important part of the Southern populations. Addictions such as high consumption of tobacco and alcohol as well as the use of harder drugs are rapidly developing in the context of uncontrolled urbanization; they preferentially strike the poor peoples of the great cities of the poorest and/or less structured countries. This is just as the public road, domestic life, and work accidents for which lack of legislation and of preventive measures is constant. It is also in this context that it is observed an increase of mental disorders related to acculturation, rejection of the old traditional structural models. Unemployment makes young people receptive to different destructive pressures or indoctrination leading directly or indirectly to the trafficking of all kinds, prostitution, and delinquency. Thus, the classical scheme which has been defined for three decades to present the "traditional" dominant pathological settings in the Northern and Southern Hemispheres was based taking into consideration rich and poor countries and must be changed. There are rich countries in the Southern area, either formerly or now emerging. There are also privileged groups in poor-income countries of the South. Conversely the islets of poverty are far from negligible and will instead become more pronounced in the North, which is mostly rich. Economic development and its corollaries (urbanization, industrialization) cause the emergence of the "Northern pathologies" in the Southern area. Moreover labor migrations, legal or illegal, and leisure exchanges from the South to the North increase less obviously in the Northern areas, Southern pathologies; however, environmental conditions are less favorable to their development. Certainly global climate warming could lead to the development of vector-borne diseases such as dengue, chikungunya, or malaria in some temperate countries, but it should remain at the margin.

4 International Health Objectives

The WHO slogan reflecting a goal, not to speak of promise, "Health for all by the year 2000" was regarded as intrinsically unrealistic but was still useful to raise the willingness to organize the health strategy worldwide and to secure funding to provide substantial support for the poorest countries. International bodies do not want to give up and put forward ambitious goals such as ending poverty by 2030 [2]. Given the progress of medicine, it is clear that it is poverty that remains the disease. While progresses have been made, it remains as access to essential medicines, vaccines, and a favorable environment is by itself a difficult goal to reach for more. Cancer cure appeared under these conditions as a health luxury aimed only to the population in rich countries because in poor-income countries there were targets a priori easier to achieve because there management was possible due to effective, available, and relatively inexpensive means. But everything is connected and progresses must be made in all areas.

Oncology must now be a priority because cancer is of increasing importance in both relative and absolute terms. In addition, opportunities both therapeutic and preventive are now well codified. According to data reported by the WHO, cancers were responsible for 8.2 million deaths in 2012. Almost a third of cancer deaths are related to five behavioral and feeding risk factors that are increasing in importance everywhere but more in the Southern countries [3]: smoking, excessive alcohol consumption, lack of exercise, high body mass index, and an unbalanced diet with a low consumption of fruits and vegetables.

In low- and middle-income countries, 20 % of cancer deaths are attributed to viral infections, particularly hepatitis B and C (liver cancer) or human papillomavirus (HPV) (cervix uteri cancer) [4]. Over 60 % of new cancer cases occur in Africa, Asia, and Central and Latin America. These regions account for 70 % of cancer deaths worldwide. Especially, their importance should increase over the next two decades.

Aging is an essential factor in the development of cancers which is due to the accumulation of specific hits and progressive loss of efficiency of cellular repair mechanisms. The impact is increasing worldwide. In addition, there is a probability that specific risk factors in the South should be added to those of the industrialized countries due to the negative aspects of development and population westernization. Inadequate legislation or difficulties in implementation, lack of supervision, and corruption processes are possible contributing factors. Anyway, we can and must reduce the impact of cancer by applying prevention strategies, early detection, and clinical management of patients.

5 Lessons from the Past to Prepare the Future

The future could take a lesson from the past while staying in a historic setting of tropical medicine. Dr. Emile Jamot, French military doctor of colonial troops, sets up in 1917, in Oubangui-Chari on the banks of Fafa river in the area of Ouham, the first traveling team for systematic screening and treatment of sleeping sickness [5].

The principle can be summarized as follows: go to the front of the patients without waiting for patients to come to us. They had the double curative (for patients) and preventive (for the surrounding population) objectives. Transported in 1922 in Cameroon where HAT took considerable proportions, this principle allowed, if not to eliminate, at least to contain this plague before the end of the 1920s. A century later, these principles (detect early, closer to populations, and treatment without delay) remain valid for HAT, always present in Africa but also for all the diseases both in rich- and poor-income countries. This applies perfectly to cancer.

With this rule, and having also an active policy in the area of prevention, the fight against cancer would be optimized. In this setting the implementation of vaccination against HBV and HPV, together with educational efforts to health, is warranted. In 2013, the WHO launched its Global Action Plan for the prevention and the fight against non-transmissible diseases from 2013 to 2020. The aim is to reduce by 25 % premature deaths from cancer, cardiovascular diseases, diabetes, and chronic respiratory diseases.

But if the status of the tropical oncology and reasoning in absolute terms must improve, it is logical to see cancer winning in the hierarchy of medical concerns. According to the WHO [6] in 2012, there were no cancers among the 10 leading causes of death in low-income countries when there were three in high-income countries: lung, colon-rectum, and breast cancers.

Historically, Shakespeare, with his pragmatic vision, wrote, a long time ago: “All that lives must die, passing through Nature to eternity” [7]. Thus, the overall mortality rate will remain 100 %, and the first cause of death and its following will never be vacant.

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Part I
Public Health Aspects

The Health Needs of People in Tropical Countries, Growth of Malignant Diseases and Coexistence of Extremes

Jeanne-Marie Amat-Roze

The tropical area is the hot and humid part of the world. It does not extend in latitude beyond the tropics (L. 23°27), but this does not mean that the tropical area is everything between the tropics, because a huge part of this space is occupied by hot deserts.

The region is home to nearly 80 % of the world's population, a figure likely to reach 90 % by the end of the century.

1 The Fragmentation of the *Third World*

Tropical countries were classified in the *Third World* group defined by Alfred Sauvy in 1952, but today, the tropical area contains the entire spectrum of forms of socialisation of space, from the simple dependence on nature's provision by the last hunter-gatherers to crowded cities with populations in the millions. The *Third World* has exploded, as illustrated by the contrasting health levels of its populations. Although some countries have made as much headway in the last 30 or 40 years as the industrialised countries made in a century, others have lagged behind [1].

Simple population health indicators such as mortality rates and life expectancy reveal this explosion, neatly summarising the condition and efficiency of states and throwing a spotlight on socio-economic conditions, social and public health policies and the effectiveness of development programmes (Tables 1 and 2).

World ranking on the Human Development Index (a statistical index created in 1990 by the UN Development Programme) gives a useful insight into the countries' development based on three criteria: life expectancy at birth, level of education, and standard of living. Out of 187 countries ranked by the UN, tropical countries now

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Table 1 Changes in life expectancy at birth, by international region

	Sub-saharan Africa	Middle East and Northern Africa	South Asia	East and Southeast Asia	Latin America and the Caribbean
1960[a]	40	47	44	47	56
2011[b]	53	72	65	73	74

[a]UNDP, 1990 World Report On Human Development
[b]PRB, World Population Data Sheet, 2011 [5]

Table 2 Comparison of mortality indicators for four regions in 2011

	Sub-saharan Africa	Northern Africa	Central and South Asia	South America
General mortality rate ‰	14	6	7	6
Infant mortality rate ‰	77	33	53	18

PRB, World Population Data Sheet, 2011

appear in all categories of the ranking. In 2014, Singapore is 7th, Cuba 44th, Malaysia 62nd, Sri Lanka 73rd, Brazil 79th and Thailand 89th. The countries of sub-Saharan Africa are disproportionately represented among the countries with the lowest indices—35 of the 43 [14].

The contrast in the evolution of the *Third World* has prompted international organisations to create categories of countries. To avoid the usual dichotomy whereby the world is divided into 'developing/developed countries', 'north/south' and 'rich countries/poor countries', it would be better at the beginning of the twenty-first century to speak of 'LDCs' (least developed countries), 'emerging countries' and 'formerly industrialised countries'. Talk of 'poor countries' is ambiguous because wealth does not necessarily produce development. Countries rich in natural resources – sources of economic wealth for human development – are ranked bottom in the UN's indices. Their populations are poor and vulnerable. Examples are Guinea and the Democratic Republic of Congo, which were listed 177th and 186th out of the 187 states on the United Nations' Human Development Index in 2014 [13].

1.1 The Least Developed Countries (LDCs)

The least developed countries (LDCs) are the least developed in socio-economic terms. They are ranked according to three kinds of criteria:

- Low standard of living, based on income per head over 3 years; this must be less than US$ 900 (2003 definition).
- Delayed human development based on a composite index made up of infant mortality rate, life expectancy, malnutrition and schooling.

- Economic vulnerability, also based on a composite index including population size (not more than 75 million inhabitants), remoteness (e.g. think Kiribati or Tuvalu in Oceania), the percentage share of each economic sector and the export concentration index.

There were 25 countries in this category when it was created in 1971. In 2014, they number 48, and of these 34 are in Africa, 9 in Asia, 4 in Oceania and 1 in the Antilles (Haiti). Their contribution to world output is marginal (less than 0.9 %).

1.2 Emerging Countries

The concept appeared in the 1980s based on the macroeconomic performance of developing countries that were no longer LDCs. These countries are stable and have a favourable business climate. Their GDP is less than that of a developed country, but their rapid economic growth means that their human development indicators are catching up with those of developed countries. Their contribution to the world economy is growing. According to the IMF, their share of world GDP rose from 27.4 % in 1992 to more than 40 % in 2011. Membership of the group is neither immutable nor unanimous (each international organisation has its own list). Some countries, such as the 'Asian tigers', have moved out of it; others, like Peru and the Philippines, are not regarded as emerging economies by all development experts, and still other countries are classified as 'high-potential countries', such as Nigeria, or 'future emerging' like Mexico.

Living standards in these countries are rising fast, producing an emerging middle class. The OECD [2] forecasts the worldwide middle class will expand from 1.8 billion people in 2009 to 3.2 billion in 2020 and 4.9 billion by 2030. This growth is driven by Asia (which by 2030 will have 66 % of the worldwide middle class), but there is a middle class emerging in Africa too. Hundreds of millions of people have come out of extreme poverty in the last three decades, but inequalities are growing. According to the 2014 UNDP Report, 1.2 billion people live on the equivalent of 1.25 dollars (the threshold of extreme poverty defined by the World Bank) or less a day, and 1.5 billion people in 91 countries live 'in a state of poverty marked by mutually aggravating inadequacies in terms of health, education and standard of living'.

When presented as national average figures, these indicators mask contrasts in health that are observed at every interregional scale: town-countryside, inter- and intra-urban and intra-rural. The contrasts are sometimes large and are particularly acute on the intra-urban scale. They are the outworking of the combined effects of living conditions, living standards and lifestyles of varying degrees of healthiness.

2 Health Needs as Varied as the Socio-Territorial Contexts

Good health is very much a relative value. Health is a multifactorial system that depends on the individual and the community. Care is only one component. The conjunction of political conditions (peace, conflict, post-conflict, quality of governance) and the choice by politicians to use economic resources to benefit human development (health, education, improving living standards) and socio-economic realities, including the changing status of women and their level of education, the reduction of poverty, medical advances, and their dissemination and access to them, explain the health improvements that have been observed. Countries that have applied this global approach have reduced infectious diseases, the great killers that stalked humanity for thousands of years, at an extraordinary rate [6].

The age structure of their populations is currently very favourable, with relatively young populations at the ages where they enjoy good health. With ageing, these countries will, like the formerly industrialised countries, have to cope with chronic non-communicable ailments, which leave people vulnerable to cardiovascular diseases and cancers. Controlling these risks and providing care require a new health policy quite different from combating infectious diseases. Notice also that care needs will change much faster than in the industrialised countries—due to the rapid demographic transition—and that this care will be needed by millions of people due to the current bulge in the numbers of young adults. What is more, these dynamics are playing out in countries where social security is limited or nonexistent and traditional support systems are disappearing. In France, it took 114 years for the proportion of 65s and older to rise from 7 to 14 %. In China, it took just 25 years, in Thailand 22 years and in Vietnam 17 years [15]. According to the UN, tropical countries already have 60 % of the world's entire population of 65-year-olds and older. In May 2011, the Population Reference Bureau estimated that there were 180 million people aged 65 or older in China and more than 60 million in India. Emerging countries possess excellent medical services, human resources and facilities, as evidenced by the success of medical tourism. It is up to their politicians to start taking the decisions today that will enable the majority to cope with this epidemiological transition and its consequences (Table 3).

The age pyramids of the LDCs still show a spectacular proportion of young people, but projections also agree on rapid ageing and the emergence of a middle class. Even so, the populations of the LDCs continue to be weighed down by the burden of communicable diseases. The WHO estimates that in sub-Saharan Africa, just under 64 % of the 11 million deaths are attributable to communicable, maternal, perinatal, and nutritional diseases, 27 % to non-communicable diseases and 7 % to trauma [9, 12]. This proportion is not found elsewhere, even though it is likely that there is less knowledge of non-communicable diseases due to lack of diagnosis and (or) under-reporting. The scourge of communicable diseases—some of which can be described as vulnerable diseases because they respond to cheap, effective treatments and to vaccines—keeps infant mortality pitifully high in these countries where death comes to the young. The African states which represent the majority of

Table 3 Indices of age and youth in tropical countries

Proportion aged 65 and older (%)		Proportion aged under 15 (%)	
World	8	World	27
Brazil	7	Niger	49
Indonesia	6	Angola	47
India	5	DR Congo	46
Nigeria	3	Burkina Faso	45
Kenya	3	Ethiopia	44
Burkina Faso	2	Senegal	44
Niger	2	Madagascar	43
Senegal		Côte d'Ivoire	41
Sub-saharan Africa[a]	3	Sub-saharan Africa[b]	44

PRB, World Population Data Sheet, 2011
[a]Western, eastern and central Africa. Southern Africa: 5 %
[b]Western, eastern and central Africa. Southern Africa: 31 %

LDCs have benefited over the last 10 years from big so-called 'vertical' programmes against AIDS, tuberculosis and malaria—programmes that have had a positive effect on care systems. However, the health improvements are not so much due to care as to improved living conditions, primarily access to clean water and waste water treatment, both for people living in the countryside, where numbers are higher than ever, despite the growth of cities, and for city dwellers living in districts with inadequate infrastructure. The register of chronic ailments shows a link with old burdens such as malnutrition and haemoglobinopathies, but their spectrum is expanding, which is symptomatic of the current demographic and social dynamics. Besides the risks associated with living conditions, we see increasing signs of lifestyle-related risks and the risks associated with rising longevity. Epidemiological data from one-off surveys repeatedly shows rising numbers of cases of diabetes and high blood pressure and inadequate diagnosis and treatment. These conditions are unfortunately silent, which makes them difficult to track [3].

3 Tropical Areas, Multiple Health Challenges

The sheer numbers of people create chain reactions that have multiple health impacts. The world population reached three billion in 1960 and passed the seven billion mark in 2011. Most of the growth is occurring in tropical countries due to the demographic inertia of having so many young adults and the high birth rate in sub-Saharan Africa. Densities are rising, which is a factor in increased frequency of contact between people, between towns, between town and country and between nature and society, amplified by urbanisation. Five billion people are projected to be living in cities by 2030. According to figures from the report of the World Urbanization Prospects, the 2014 Revision, of the world's 30 largest cities, half are

now tropical, and it is these that are growing fastest. The city, a place of innovation and emancipation and of ways of life that, though no longer unique to it, are much more frequent here than in the countryside, is an accelerator of the global etiological changes observable in the ratio of communicable to non-communicable diseases. Sedentary lifestyles, lack of physical exercise, overeating, an unbalanced diet, smoking, alcohol consumption, drugs, accelerated ageing of the population—these are fertile soil for the development of chronic and degenerative ailments. This epidemiological transition [8] forces us to bring about a health transition [4, 7] which requires human resources and targeted facilities. This in turn raises the question of whether people have access to the care: geographical access to where the care is offered, financial access to effective care and social and cultural access. You can't have one without the other. There are so many taboos still to be overcome for women suffering from gynaecological cancers! Extending universal medical cover may help them, but that immediately raises the big question: how is healthcare to be paid for? [11]. This is a worldwide problem, for city dwellers as well as those in the countryside, and we have solved it if we are to reduce the social and economic inequalities that are developing between people. Wherever they are, the poorest are disadvantaged by multiple synergistic factors. Poor health, poor education and social, sexual, and economic subordination confine the poor, and especially women and children, to lifelong vulnerability. Education is the first lever that can help a person to escape from this vicious circle.

4 The Challenges of Sub-Saharan in Africa

This region wins the record for progress in several areas. Demographic growth is as high as 2.5 % a year. The population is expected to grow from an estimated 1 billion in 2014 (15.5 % of world population) to 2.4 billion by 2050 (25 % of world population). Fifty-two cities have a population of a million or more, as compared with none in 1950. Lagos, with a population of 23 million, is now the sixth largest city in the world. Kinshasa and Abidjan have more than ten million. The economic growth of the region is the fastest in the world in 2014. But contrasts have never been so great between one area and another, between one person and the next, and between mass poverty and booming economies in places like Mozambique and Nigeria. Mozambique has manna from heaven in the world's second largest natural gas field, as large as that of Qatar. The challenge for the country is to raise the living standards of Mozambicans living in rural areas and slums and increase their income from 25 pence a day to three or four times that. Despite being one of the richest countries in Africa, Mozambique is placed just 178th out of 187 on the Human Development Index. The health needs of sub-Saharan African societies are torn between the demands of a rich, educated, urban, sophisticated population and a majority who still lack primary care and development infrastructure (drinking water, sanitation) and who live in the poorest parts of towns or in the countryside [10, 11]. In tropical countries, the two extremes rub shoulders to a greater extent than anywhere else in

the world and medicine is its observatory with a care system running on different levels, from efficient, profit-making private care institutions in the cities, to the hollow shell of a primary care centre in the village at the end of the track. Sub-Saharan Africa has less than 2 % of the world's health workers but is burdened with 25 % of the world's sicknesses. The flight of medical skills to foreign countries, at a time when health demands are increasing, undermines development. The current spread of the Ebola virus in Liberia and Guinea is no surprise given that these societies lack the prerequisites of health and have a history of poverty governments broken by years of civil war and, according to the WFP, between 1 and 2 doctors per 100,000 inhabitants. The wave of potential emerging countries appearing on the horizon, driven by economic growth, is another reality. Ghana, Botswana, Zambia, Mozambique, Nigeria and Angola have all been dealt hands that should mean growth will be used for the human development of the majority and investment in education and health will follow the demographic growth.

Malignant diseases are responsible for an increasing number of deaths. The phenomenon is worldwide. Tropical countries are experiencing this dynamic but with greater contrasts than elsewhere. In the least developed countries, communicable diseases still hold out—and some make fertile ground for conditions such as cancer and hepatitis B and C, whereas in the emerging countries, in the space of a few decades, malignant diseases have become a major national health focus.

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Epidemiology of Cancer in the Tropical Areas

Tristan Roué and Mathieu Nacher

Tropical countries are those that lie within the region called the tropics. This region is limited in latitude by the Tropic of Cancer in the Northern Hemisphere and the Tropic of Capricorn in the Southern Hemisphere. The tropics include a large section of the world. In the Western Hemisphere, tropical countries include Mexico, all of Central America, all of the Caribbean islands, and the top half of South America. In Africa, the only nations that cannot be called tropical countries are Morocco and Tunisia in the north and South Africa and Lesotho and Swaziland in the south. All the rest lie either entirely, or at least partly, in the tropics. While no European countries are tropical countries, the Middle East has four tropical countries: Yemen, which is entirely in the tropics, and parts of Saudi Arabia, Oman, and United Arab Emirates. India, in Southern Asia, lies mostly in the tropics, and all countries of Southeast Asia are tropical countries. Australia (partly), Micronesia, the Marshall Islands, Kiribati, and most of the other island nations of Oceania in the South Pacific are tropical countries, as well.

Overall, about 4–5 % of the population of developing countries is covered by routine registration of mortality statistics. Cancer registries are another important source of data on cancer occurrence but also cover only limited geographic areas—about 3 % of the population of developing countries—although they provide information on the current cancer profile and its evolution over time [1]. Based on these

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limited data, it is possible to obtain working estimates of the burden of cancer in tropical countries and elsewhere. All the estimates below are available from the GLOBOCAN database at http://www.iarc.fr [2].

1 All Cancers

There were 14.1 million new cancer cases and 8.2 million cancer deaths for women in 2012 worldwide. 31 % (4.3 million) of new cancer cases and 20 % (2.8 million) of cancer deaths occurred in tropical countries. There is no significant difference in cancer incidence by sex in tropical countries with an overall age-standardized cancer incidence rate of 122 and 126 per 100,000, in men and women, respectively. The overall age-standardized cancer incidence rate in men ranges from 78.7 per 100,000 in Western Africa (70 per 100,000 in Guinea-Bissau), with high rates of prostate and liver cancer, to around 200 per 100,000 in Caribbean and Micronesia (330.7 per 100,000 in New Caledonia within Melanesia), with high rates of prostate, lung, colorectal, and liver cancer. For women, incidence rates range from 112.4 per 100,000 in Western Africa (63.4 per 100,000 in Niger), with high rates of breast, cervix uteri, and liver cancer, to 182.1 per 100,000 in Melanesia (269.3 per 100,000 in New Caledonia) with high rates of breast and cervix uteri cancer.

In terms of mortality, in men, the rate ranges from 53.7 per 100,000 in Niger to 152.7 per 100,000 in Uganda. In women, the rate is lowest in Namibia with 45.6 per 100,000 and highest in Kenya with 133.3 per 100,000. There is less regional variability than for incidence.

In the developed world, cancers of the lung, breast, prostate, and colorectum and hematologic malignancies predominate, whereas in the developing world, the pattern differs. While cancers of the lung and breast remain frequent, cancers of the cervix, liver, and stomach are also relatively common, reflecting differences in the prevalence of underlying causal factors [3].

1.1 Lung Cancer

Lung cancer is the most common cancer in the world. In the tropics, incidence rates are high in Micronesia (47.5 incident cases per 100,000 men and 22.9 per 100,000 women) and very low in Middle and Western Africa (around 2.0 per 100,000 men and 1 per 100,000 women). Lung cancer is the most common cause of death from cancer worldwide. Because of its high fatality and the relative lack of variability in survival in different regions, the geographical patterns in mortality closely follow those in incidence [2].

The most important discovery in the history of cancer epidemiology is the carcinogenic effect of tobacco. Lung cancer incidence increases rapidly among continuing smokers, so the risk is greatest in those who begin to smoke when young

and continue throughout life [4]. Stopping smoking at any age has a rapid beneficial effect on cancer risk. Indeed, in some developed countries, reductions in tobacco consumption have been associated with declining incidence of certain cancers, such as lung cancer. However, cigarette consumption is increasing markedly in developing countries [3].

1.2 Breast Cancer

Breast cancer is the most common type of cancer and the most common cause of cancer-related death in women worldwide. In the tropics, incidence rates range from 26.8 per 100,000 in Middle Africa to 48.8 per 100,000 in Micronesia. The standardized mortality rate is highest in Western Africa with 20.1 deaths per 100,000 and lowest in Central America with 9.5 deaths per 100,000. Although the standardized incidence rate is lower in Middle Africa than in Micronesia, the standardized death rate is higher in Middle Africa (14.8) than in Micronesia (10.4). Thus the prognosis of breast cancer in Middle Africa is worse than in Micronesia with 55 deaths per 100 incident cases against 21 per 100 in Micronesia.

Known risk factors for breast cancer include early age at menarche, older age at first childbirth, low parity, and late age at menopause. Many of these reproductive factors suggest that cumulative exposure to estrogens during a woman's lifetime increases the risk of breast cancer [3]. It is now known that high estrogen circulation levels are directly associated with breast cancer risk, at least in postmenopausal women [3]. Hormonal and reproductive factors play an important role in the etiology of breast cancer.

Women of African ancestry experience a disproportionate burden of breast cancer. The age-adjusted mortality rate of this cancer is more than 40 % higher in women of African ancestry than in populations of European ancestry [5]. Women of African ancestry tend to be diagnosed with breast cancer at a younger age and with more aggressive types of the disease, such as ER− (estrogen receptor negative) and ER−/PR−/HER2− (estrogen receptor negative, progesterone receptor negative, HER2 expression negative) breast cancer than in populations of European ancestry [5]. Genome-wide association studies have also identified a few differences in breast cancer risk variants between populations of European and African ancestry [6]. The combination of these factors may explain much of the geographic variation in the incidence of breast cancer in tropical countries.

Cancer is also commoner in those who are overweight. The evidence for the deleterious effect of weight is strongest for postmenopausal breast cancer [4]. Breast cancer incidence is much higher in most developed countries than in many developing countries, and this is partly accounted for by these dietary factors combined with delayed first childbirth, lower parity, and shorter breastfeeding duration [4]. These factors vary in prevalence under different social and economic conditions and may thus also explain the differences in incidence of breast cancer in tropical countries.

1.3 Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide. In the tropics, there is up to 8 orders of magnitude in incidence variation between countries. Incidence rates range from 11.2 per 100,000 in Southeastern Asia to 79.8 per 100,000 in the Caribbean. The standardized mortality rates range from 6.7 deaths per 100,000 men in Southeastern Asia to 29.3 deaths per 100,000 men in the Caribbean.

Measurement of serum prostate-specific antigen (PSA), a biomarker for prostate cancer, is useful for the detection of early prostate cancer. Nevertheless, the effect of PSA-based screening on prostate cancer mortality remains unclear [7]. Numerous observational studies have reported conflicting findings regarding the benefits of screening [7]. As a result, the screening recommendations of various countries differ [7] and may explain much of the geographic variation in the incidence of prostate cancer in tropical countries. Mortality rates are generally high in predominantly black populations (the Caribbean), very low in Southeastern Asia, and intermediate in Central America.

1.4 Liver Cancer

In the tropics, hepatocellular carcinoma is a common tumor in Western Africa and Southeastern Asia (16.4 per 100,000 men and 22.2 per 100,000 men, respectively), where it parallels the high incidence of chronic hepatitis B virus (HBV) infection. In women, the incidence rates are generally much lower than in men, the highest being in Western Africa for women (8.1 per 100,000) and Southeastern Asia for men (21.4) and the lowest in Micronesia for women (1.6) and Eastern Africa for men (4.6).

Chronic infection with the HBV is responsible for causing about 60 % of all primary liver cancer across the world [3]. The unrelated hepatitis C virus is also involved in the etiology of hepatocellular carcinoma. Alcohol probably plays a role in the cirrhosis in many cases. However, other factors are also incriminated in tropical areas. These include the carcinogen aflatoxin, a metabolite of the fungus *Aspergillus*, which frequently contaminates grain such as maize, cereals, and spices that represent major staple foods in many parts of the tropics.

1.5 Stomach Cancer

Age-standardized incidence rates range from 3.3 per 100,000 in Western Africa to 10.6 per 100,000 in Central America for men and from 2.6 per 100,000 in Western Africa to 8.2 per 100,000 in Central America for women. In both sexes, high mortality rates are observed in Central America (6.7 per 100,000 women and 8.8 per

100,000 men), whereas low mortality rates are observed in Western Africa (2.5 per 100,000 women and 3.2 per 100,000 men).

The etiology of gastric tumors is complex. Dietary factors (smoked or preserved food, nitrates, and high salt intake increase susceptibility) and socioeconomic conditions, especially related to chronic infection with the bacterium *Helicobacter pylori*, are important factors [8].

1.6 Cervical Cancer

As with liver cancer, a large majority of the global burden occurs in the less developed regions. High-risk regions include Eastern Africa (42.7 per 100,000 women), Melanesia (33.3), and Middle (30.6) and Western Africa (29.3), the lowest incidence rate being in Micronesia (8.7). The standardized mortality rates range from 2.7 deaths per 100,000 in Micronesia to 27.6 deaths per 100,000 in Eastern Africa.

Invasive cervical cancer is caused by a persistent genital infection by oncogenic human papillomaviruses (HPVs). More than 50 HPV genotypes are responsible for infection of the genital area. Socioeconomic development, HPV prevalence, and the importance of cervical cancer screening in the population are the main factors influencing the heterogeneous geographic importance of this cancer in the world [9].

1.7 Colorectal Cancer

Age-standardized incidence rates range from 4.5 per 100,000 in Western Africa to 24.8 per 100,000 in Micronesia for men and from 3.8 per 100,000 in Western Africa to 16.6 per 100,000 in the Caribbean for women. In terms of mortality, in men, incidence rates range from 3.5 per 100,000 in Western Africa to 10.5 per 100,000 in Micronesia. In women, the rate is lowest in Western Africa with 3.8 per 100,000 and highest in the Caribbean with 9.1 per 100,000.

The familial colon cancer syndromes are associated with a variety of extracolonic cancers. Inflammatory bowel disease, especially ulcerative colitis, and occasionally Crohn's disease may lead to focal dysplasia and develop into areas of flat adenocarcinoma [8]. Dietary factors are the most obvious candidate risk factors for colorectal cancer and may explain the differences in incidence in tropical countries.

2 Hematological Malignancies

Burkitt lymphoma is the archetypal tropical cancer. Its seminal epidemiological contribution plotted an African "lymphoma belt" across tropical Africa [8]. The disease is also endemic in Papua New Guinea. Indeed, Burkitt lymphoma is

associated with both Epstein-Barr virus (EBV) and malaria and is the commonest childhood cancer in many tropical areas.

Another EBV-related tumor, with a defined geographical distribution, is the nasal form of angiocentric NK/T-cell lymphoma occurring in Southeastern Asia and part of South America [8].

Kaposi's sarcoma-associated herpesvirus (KSHV or HHV8) is related to the EBV and is the principal cause of Kaposi's sarcoma [3]. KSHV is a frequently encountered skin tumor in tropical Africa [2]. In areas of sub-Saharan Africa where HIV infection is highly prevalent, the incidence of Kaposi's sarcoma has increased about 20-fold with the spread of HIV.

Adult T-cell leukemia is a subacute lymphoproliferative disorder, mainly confined to Caribbean countries [2]. However, it also occurs in South America, West Africa, and India. It is caused by human T-cell leukemia/lymphoma virus (HTLV-1).

3 Discussion

Cancer is a heterogeneous mix of diseases with different types of cancers more common in some populations than in others, sometimes substantially so. Many types of cancer vary in incidence by more than an order of magnitude between different populations, and every type is rare in some parts of the world [4].

Tropical countries include a wide diversity of socioeconomic and demographic aspects with numerous ethnic groups expressing a profusion of social and cultural practices, and many tropical countries are part of the developing world. In both high-human development index (HDI) and very high-HDI regions, four cancers (cancers of the female breast, lung, colorectum, and prostate) explain almost half the overall cancer burden. In medium-HDI regions, lung and female breast cancers remain among the most common types of cancer along with stomach and liver cancers, which are both associated with infectious causes. In low-HDI regions, female breast and liver cancers are also common, but two additional infection-related cancers—cervical cancer and Kaposi's sarcoma—are also prevalent [10]. Figure 1 shows the incidence of the top cancers per HDI.

The lifestyles in many developing countries in the tropics are in a state of transition from traditional to "modern," with its associated industrialization, urbanization, and cultural readjustment. Infectious diseases are giving way to noncommunicable diseases, such as cardiovascular diseases, adult-onset diabetes, cancers, trauma, and noninfectious respiratory diseases, as major causes of morbidity and premature mortality [11].

The cancer transition can be regarded as an extension or a completion of Omran's theory on epidemiological transition. In analogy with the third stage of epidemiological transition—a shift from infectious to noncommunicable diseases—the theory of cancer transition sees a shift from a predominance of cancers linked to infections to cancers associated with risk factors that are mainly noninfectious and possibly related to a so-called western lifestyle [12].

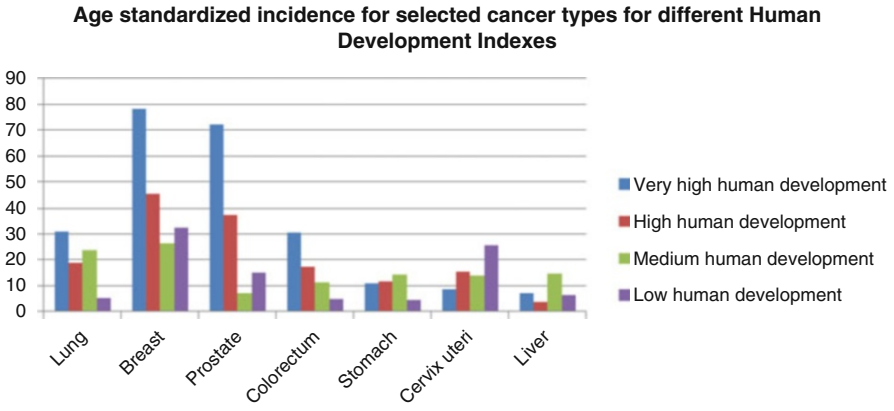

Fig. 1 Incidence of the top cancers per HDI

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Cancer Control in the Tropical Areas, Access to Expensive Treatments, and Ethical Considerations

Twalib A. Ngoma

1 Introduction

Cancer is a disease which results from the development of multiple genetic changes that, with occasional exceptions, occurs after birth and is not heritable. These genetic abnormalities occur in a stepwise process in a single cell of almost any tissue or organ in the body and modify the behavior of the cell (and its progeny), creating precancerous lesions, some of which take on a "cancer phenotype," which consists primarily of deregulated cell growth. These cancer cells proliferate inappropriately, forming masses or sheets of cells, and sometimes may circulate in the bloodstream and become progressively more able to invade adjacent tissues. At a variable point in its evolution, cancer disseminates, through a process known as metastasis, via lymphatic vessels to regional lymph nodes and via the bloodstream to more distant sites in the body. The mix of cancers that occurs in tropical countries varies within countries, driven largely by environment, geography, and standard of living. In tropical countries, cancer is regarded as a painful death sentence, while in high-income countries, it is regarded as a preventable and often curable disease. Cancer patients in tropical countries have very painful undignified death, scarring and negatively influencing the well-being of their families for life.

It is estimated that by the year 2020, one in three people in tropical countries, most of which fall under the category of low- and middle-income countries—the World Bank data 2005 Fig. 4.1—will develop cancer sometime during their life. Of great concern is the fact that in spite of the striking increase in the number of cancer patients mainly due to increasingly aging population and changes in lifestyles, national health

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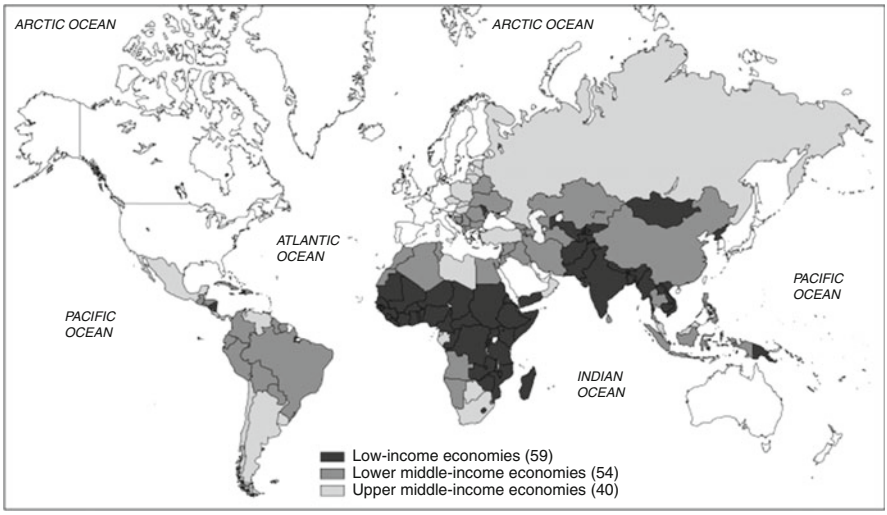

Fig. 4.1 Low- and middle-income countries by the World Bank income category, 2004—all tropical countries fall in this category (Source: Data from the World Bank (2005))

policy makers in tropical countries ignore cancer as a major cause of disability or death as well as economic loss. This should no longer be tolerated because without action mortality rates from cancer in tropical countries will reach catastrophic proportions with a resulting devastating effect on the economies of these countries. Tropical countries have no other choice than to seriously include cancer control in their health agenda and consider cancer as a vital component of health-care provision.

2 What Is Cancer Control

Cancer control describes the totality of activities and interventions intended to reduce the burden of cancer in a population, either by reducing cancer incidence or mortality or by alleviating the suffering of people with cancer [1, 2]. Prevention, early detection, diagnosis, treatment, psychosocial support, and palliative care are the components of cancer control that can reduce the cancer burden. Surveillance and monitoring are needed to understand the cancer burden and to track progress. All of these require commitments of financial and human resources, including training and education to build the required human resource base and information for the public to understand what they can do and the services available to them. It is important to understand that cancer control activities are not all conducted within the health-care system proper, nor do they always involve only health professionals [3]. Many effective tobacco control interventions (e.g., higher taxes, bans on advertising and promotion) are legal and regulatory in nature, while making morphine available for pain control necessarily involves narcotics control authorities as well as the health-care system. Other key interventions are allied to parts of the health-care system that otherwise are unrelated to cancer. For example, vaccination against hepatitis B virus to prevent liver cancer is conducted by childhood immunization

programs. Where cancer shares risk factors with other chronic diseases, tobacco being by far the most important but also including diet control measures will produce benefits for a number of diseases. Within the health-care system, some aspects of cancer control can be integrated into primary and higher health-care levels (e.g., vaccinations for HBV and human papillomavirus [HPV]), and others require specialized practitioners and equipment—especially aspects of treatment. The resources financial, human, and infrastructure required for cancer control interventions are huge. In tropical countries where those resources are not available, cancer control must build starting with interventions that are highly effective, cost-effective, and "resource-level appropriate." Additional steps can always be taken for incremental benefits once a cancer control culture exists and resources for cancer control grow.

3 Cancer Planning

Deciding on national cancer control priorities is best accomplished through a formal process of cancer control planning at the national or, if appropriate, the subnational level. Emphasizing the importance of this step, the 58th World Health Assembly (WHA) in May 2005 approved a resolution on cancer prevention and control that calls on all 192 WHO Member States to develop national cancer plans and programs [4]. Although they must eventually be embraced by government to be fully effective, national cancer plans may be developed outside of government, such as those spearheaded by NGOs. Regardless of how the effort is led, the process must involve a broad spectrum of stakeholders and interest groups. Steps in cancer control planning have been well described by WHO [5, 6] and additional guidance is available from the Union for International Cancer Control (UICC) with particular emphasis on the role of NGOs in the development of national cancer plans. The plan does not have to cover every aspect of cancer control: e.g., an initial focus on tobacco control and palliative care can lead to success in tropical countries and open the door to adding further goals later. It is important that after endorsement of the cancer control plan by the government, it should be promoted and supported financially and programmatically through both government action and public advocacy. In both the planning and implementation phases, development partners should provide necessary guidance and financial support. Periodic monitoring and evaluation during the implementation phase is very necessary, and every 3–5 years the plan should be updated through a process that involves all major stakeholders, public and private sectors, as described by WHO, UICC, and others [7].

4 Priorities for Cancer Control in Tropical Countries

4.1 Prevention

4.1.1 Tobacco Control

At a global level, tobacco causes more premature deaths from cancer and even greater numbers from other noncommunicable diseases than any other single agent. Experience in many high-income countries has proven that tobacco use and,

ultimately, its impact can be reduced substantially through a combination of policy measures. These policy measures include raising prices of tobacco products by increasing taxes on them, banning smoking in public places, banning advertising and promotion of tobacco products, requiring large and dramatic cigarette package warnings, and "counteradvertising" to publicize the adverse health effects of tobacco and the benefits of quitting. The top priority for cancer control is to convince the world's 1.1 billion smokers, most of whom live in tropical countries to quit. Cessation by today's smokers will lead to substantial health gains over the next five decades. Preventing children from starting smoking will have full benefits after 2050. The Framework Convention on Tobacco Control (FCTC), the first and only international public health treaty, includes the measures known largely from high-income countries to be effective. As provisions of the FCTC are implemented in tropical countries, it will be important to reevaluate their effectiveness under a range of economic and societal conditions. What is important is that every tropical country should sign and ratify the Framework Convention on Tobacco Control and implement its provisions, most importantly:

- Substantial increases in taxation to raise the prices of tobacco products (goal is to have taxes at 80 % or higher of retail price)
- Complete advertising and promotion bans on tobacco products
- Mandating that public spaces be smoke-free
- Large, explicit cigarette packet warnings in local languages (which also helps to reduce smuggling)
- Support of counteradvertising to publicize the health damage from tobacco and the benefits of stopping tobacco use

4.1.2 Liver Cancer and Hepatitis B Vaccination

HBV is the cause (often in conjunction with a cofactor) of most cases of liver cancer, taking 500,000 lives each year globally. A safe and highly effective HBV vaccine has been used in most high-income countries and some low-income countries since the 1990s, yet vaccination coverage is poor to nonexistent in many tropical countries with the highest rates of liver cancer. In 2001, the latest year for which complete data are available, fewer than 10 % of babies in Southeast Asia and Africa among the worst affected areas were vaccinated against HBV.

A three-dose series of HBV vaccines costs less than $2 through UNICEF, a cost that can be subsidized by the Global Alliance for Vaccines and Immunization (GAVI). The countries where children are not immunized are mainly those with inadequate immunization programs for the more traditional vaccines; thus, this is not a problem only for HBV vaccination. The future payoffs for HBV vaccination and other scheduled immunizations are enormous; vaccination should remain as high on the cancer control agenda as it is on the child health agenda.

Vaccination cannot help the 360 million people worldwide who are currently infected with HBV. However, limiting exposure to the most ubiquitous cofactor

aflatoxin can substantially lower the risk of liver cancer. Contamination of stored grain by aflatoxin a chemical produced by certain fungi under humid storage conditions can be reduced by using low-technology techniques such as drying crops in the sun, discarding moldy kernels, and storing crops in natural fiber sacks on wooden pallets. Such efforts may be worthwhile, although they are more complex than vaccination. Furthermore, about one-quarter of liver cancer is caused by hepatitis C virus (HCV) for which there is, as yet, no successful vaccine. What is important for prevention of liver cancer is:

- GAVI and other international partners should continue to assist countries to incorporate HBV vaccination into their childhood immunization programs as quickly as possible, with support from the global cancer community.
- Countries with a high liver cancer burden and significant aflatoxin contamination of foodstuffs should examine the options for aflatoxin exposure reduction. Development partners should help to implement those measures that are feasible and cost-effective.

4.1.3 Cervical Cancer Screening and Human Papillomavirus Vaccines

Nearly 300,000 women die from cervical cancer each year, 85 % of them in tropical countries with limited resources. The cause is persistent infection with one of several strains of the human papillomavirus (HPV). A century ago, cervical cancer was as common in the high-income countries as it is today in tropical countries. Improved living standards, effective treatment for early and somewhat advanced cancers, and screening using the Papanicolaou (Pap) smear are responsible for the steep decline in incidence and mortality in high-income countries. The strategies which could transform cervical cancer control in tropical countries are vaccines to prevent HPV infection and screening methods that are more compatible with situations where resources are very limited such as visual inspection methods as opposed to cytology-based methods such as Pap smear and a vaccine against the two most common carcinogenic strains of HPV entered the market in 2006. The initial market is in affluent countries; however, if adopted, the greatest impact of these vaccines will be in tropical countries with highest cervical cancer rates. They could prevent hundreds of thousands of deaths every year, starting several decades after establishment of a vaccination program. Governments and the international health community should take concrete steps now to develop HPV immunization policies and the means to pay for what is currently an expensive vaccine. Operational issues (e.g., developing immunization schedules, including the optimal age for immunization; deciding whether to immunize only girls or both girls and boys) also must be addressed.

For pre-vaccination generations of women, the vaccines cannot help. However, two new approaches to screening and treatment of precancerous lesions are available. Techniques for testing and treatment of precancerous lesions in a single visit, using “direct visualization” (either visualization with coloration with acetic acid

[VIA] or with Lugol's iodine [VILI]), have been piloted in trials in tropical countries like India, Tanzania, and Guinea with positive results. The treatment (for women without advanced disease) is by cryotherapy by freezing of abnormal tissue. Ongoing demonstration projects will provide a firmer information base on which to decide about the suitability and effectiveness of these techniques for broader use. The second technique involves testing for chronic HPV infection. HPV testing currently requires two visits if treatment is needed, but quick-reading tests have been developed that could eliminate the need for a second visit. While these screening methods may be feasible in middle-income countries settings, they can only be successful where a reasonable health-care infrastructure exists and care for detected cancers can be accessed, a requirement that, unfortunately, still excludes many tropical countries. Where they are feasible, the value of such programs can be great. It is widely believed that even one or two appropriately timed screenings in a lifetime could reduce the incidence of invasive cervical cancer by as much as 40 %. What is important for prevention of cervical cancer is:

- Tropical countries should actively plan for the introduction of HPV vaccination as more information becomes available about the vaccines and as they become affordable. The international community should support a global dialogue on HPV vaccine policy and pricing.
- Tropical countries and global partners should follow the evolving information on newer screening approaches and determine the feasibility of adoption, given local resources and infrastructure.

4.2 Cancer Management: Diagnosis, Treatment, and Psychosocial Support

In tropical countries with limited resources, most people with cancer have no access to potentially curative treatment. Where few or no services exist, the advice is that emphasis is put on establishing a core of expertise and limited cancer management that can be expanded as resources permit. Where some services are available but resources are stretched or inadequate, the emphases should be as follows:

- Ensuring that the most appropriate and most cost-effective measures are provided in well-equipped medical institutions and futile attempts at cure are avoided
- Ensuring that the stage is set for cancer services to expand

Along with clinical medical services, people with cancer and those around them benefit from psychosocial support to deal with the physical, psychological, and social impacts of the disease and improve quality of life. Psychosocial support can commence at diagnosis and continue through treatment and recovery or death. In tropical countries, psychosocial support can be offered by a wide range of health-care workers and lay people.

4.2.1 Resource-Level-Appropriate Treatments for Curable Cancers

The concept of "resource-level appropriateness" recognizes that effective interventions for the most curable cancers have progressed in high-income countries through more than one generation. The most appropriate choice for a tropical country with limited resources may not be the same as the current choice in London, Paris, New York, or Tokyo. For example, breast-conserving surgery for early-stage breast cancer requires treatment with radiotherapy. In tropical countries which have no radiotherapy facilities, women's lives can still be saved with more extensive surgery. The highly innovative effort, the Breast Health Global Initiative (BHGI) gives comprehensive information on the range of choices based on available resources [8]. The BHGI has produced a comprehensive set of resource-specific, stage-specific evidence-based guidelines, which will be updated biannually, for all aspects of breast cancer management. The BHGI model could be applied to other cancers for which highly effective treatments are available. The common cancers that fit this description are cancers of the breast, cervix, head and neck, and colon and rectum. A large proportion of cancers affecting children and young adults are also highly curable, in particular leukemias and lymphomas, retinoblastoma, and testicular cancer. A hurdle in organizing such efforts will be financial support. However, since the BHGI has successfully laid groundwork, this should make it easier for public sector sources, professional societies, advocacy organizations, and others to support efforts for other cancers. What is important for tropical countries with limited resources is:

- These countries should develop resource-level-appropriate guidelines for the overall management of major cancers for which treatment can make a substantial difference in a meaningful proportion of patients and for selected pediatric cancers.
- Use the BHGI model to develop resource-level-specific guidelines for cervical cancer, colon cancer, head and neck cancers, and selected pediatric cancers.
- Motivate professionals from high-income countries to work together with professionals in tropical countries to spearhead efforts to develop resource-level-specific guidelines, with financial support from a variety of institutions.

4.2.2 "Cancer Centers of Excellence"

Providing guidelines for cancer diagnosis and treatment is of no benefit without a medical institution and professionals who can apply them. Tropical countries should consider supporting at least one well-functioning government-supported cancer center where patients can go for diagnosis, treatment, palliation, and vital psychosocial services. The center should also undertake locally relevant research. Even if capacity is limited, such centers can act as focal points for national cancer control and as points of contact for the international cancer control and clinical oncology communities. In the poorest countries, and in small countries that wish to develop this

capacity, the center may be a unit in a hospital, focusing only on selected aspects of treatment or on specific types of cancer. In countries that already have one or more cancer centers, it may only require enhancing the functions of one or more centers. Financing to initiate and operate cancer centers in tropical countries can come from a variety of public and private sources, including taxes on tobacco products. Some international support is available for establishing or upgrading cancer centers. The IAEA Programme of Action for Cancer Therapy (PACT) is one such international organization. PACT intends to attract additional funding and collaboration from the United Nations Member States and other donors for cancer control. Another approach that can improve and expand cancer control in tropical countries is institutional twinning. Twinning involves long-term pairings of established cancer centers with new or existing centers in tropical countries. Hallmarks of successful twinning programs are regular exchanges of information and often personnel, attention to funding although not necessarily money flowing from the high-income partner, training, and technical issues. The oncology community is well organized in affluent countries and has the capacity to help to organize twinning programs. The treatment of children and young people with specific highly curable types of cancer should be a priority because a total number of children with cancer are small compared with cancers in adults; approximately 160,000 children and young adults get cancer every year, worldwide. Currently, 80 % of US children under age 15 with cancer are cured, but 80 % of the world's children who develop cancer live in countries with limited resources and most of them die because of late diagnosis and lack of treatment. What is important for cancer diagnosis and treatment in tropical countries is:

- Tropical countries to establish a government-supported cancer "center of excellence" that provides resource-level-appropriate services to the public and acts as a reference point for national cancer control. This center could be a new center or designation of an existing one.
- Tropical countries get assistance from international organizations to develop and improve cancer centers through twinning arrangements and other means. The Programme of Action for Cancer Therapy (PACT), established by the IAEA, could in collaboration with a range of partners take on this role. Financial contributions from national governments (research funding institutions and bilateral aid agencies) could be channeled into this effort as a means of progressively increasing the global donor community's investments in cancer control in tropical countries in ways likely to have the biggest impact.
- Tropical countries should aim to provide access to treatment and psychosocial services for children and young adults with highly curable cancers in pediatric cancer units in cancer centers or children's hospitals.

4.2.3 Radiotherapy

Since at presentation in tropical countries, 80–90 % have advanced disease beyond surgery and palliative chemotherapy is very expensive, palliative radiotherapy remains to be the most cost-effective and realistic treatment option. However,

radiotherapy services in many tropical countries are nonexistent, and when available, the way radiotherapy is practiced is substandard by international standards. The substandard practice leads to uncertainties of doses given to patients and poor outcomes. This situation should and can be improved even in tropical environments. In addition to good radiotherapy training programs tailored to the local situations and right choice of equipment, a change in the styles of thinking and the way of doing things is necessary to improve the practice of radiotherapy in tropical countries. Other things which can be done to improve the practice of radiotherapy in tropical countries are:

- Hiring staff who in addition to having excellent knowledge and technical competence are aware of limitations in their working environments.
- Ensuring good clinical practice is a norm in the radiotherapy department.
- Performing proper clinical evaluation of patients.
- Giving relevant information regarding the treatment to the patient.
- Enforcing daily minimum quality assurance programs.
- Planning treatments and reviewing patients while on treatment.
- Ensuring that radiotherapy technologists (RTTs) and radiation oncologists are well trained and are adequate in numbers.
- Ensuring that medical physicists check and countercheck all treatments given to patients.
- Introducing multidisciplinary meetings and chart rounds.
- Avoiding imitation of sophisticated high-tech radiotherapy.
- Making the right choice of equipment and accessories.
- Ensuring that there is always in-house technical/engineering support to minimize machine downtime.
- Developing local radiotherapy treatment protocol manuals.
- Encouraging multidisciplinary approach in the care of cancer patients.
- Avoiding underfunding of the radiotherapy services by proper accountability of the resources given versus expected outputs and outcomes.

4.2.4 Palliative Care

Late diagnosis of most cancers in tropical countries and a lack of treatment options even when diagnosis is early mean a large number of patients who need palliative care. The cornerstone of palliative care is pain control with oral morphine or other strong opioid analgesics. These medications are largely unavailable in tropical countries; in addition to medication, palliative care involves a range of other services to relieve and manage symptoms and to provide psychosocial support to patients and families in the communities where they live. The two major obstacles to palliative care in tropical countries are:

- Legal, societal, and educational barriers to opioid availability
- Lack of programs to deliver palliative care at the community level

A major barrier to making morphine available to cancer patients in severe pain is the irrational fear of opioids that continues to exist among policy makers,

regulators, law enforcement, health professionals, and the public. WHO and the International Narcotics Control Board (INCB) play key roles in educating relevant parties and encouraging governments to examine their national policies for unduly strict drug regulations. International collaborations and the provision of funding are vital to continued progress. Because people dying from AIDS require much the same palliative care as cancer patients do, building or adapting organizations to serve both types of patient presents a new set of opportunities.

4.2.5 Surveillance and Monitoring

Most tropical countries have no accurate vital and health statistics and/or recent data about their cancer burden or major risk factors for cancer. Estimates of cancer incidence and mortality by cancer type, age, and gender have been produced for every country by the International Agency for Research on Cancer (IARC). These estimates are useful for setting initial priorities, but cannot be used to track progress or to define priorities. Major improvements in vital and health statistics are long-term goals, but over the short term, modest improvements can be made. In particular, it is relatively inexpensive to gather information on the major risk factors for cancer and other noncommunicable diseases in periodic cross-sectional surveys. WHO has developed standardized survey instruments in "STEPS," a STEPwise approach to chronic disease risk factor surveillance. Questionnaire-based data gathering about tobacco use, alcohol consumption, diet, and physical activity constitutes the first "step." Steps 2 and 3 add physical and physiological measurements of risk factors for the other major chronic diseases: weight and blood pressure and blood glucose and cholesterol measurements, respectively. STEPS has the advantage of producing comparable information across countries as well as over time. More ambitious is measuring causes of death in a population. In countries with limited resources, this is difficult because many people die without medical care or at least without a diagnosis. Systems based on "verbal autopsies" can be developed in place of medical certification, as has been demonstrated in some tropical countries.

4.3 Cancer Registries

Cancer registries that record cancer cases and outcomes over time in specific hospitals or, more usefully, in defined geographic areas are important for understanding local cancer patterns of patients who come to medical attention and they provide useful data for research. Most tropical countries have no cancer registries because cancer registries require sustained commitments and trained personnel, which are in most tropical countries not available.

4.4 Access to Expensive Treatments and Ethical Considerations

Since there are no fixed criteria for determining when a cancer drug can be described as expensive or not, a threshold cost of treatment for 1 year that is 50 % or greater than the per capita GDP of the country will be considered as expensive. This means that based on the current costs of cytotoxic drugs, all cancer treatments are expensive in tropical countries. The evidence for this is the fact that it is not uncommon in tropical countries to see desperate families taking desperate measures to raise money to pay out of pocket for expensive cancer treatments. These families are forced to sell their homes, sell their land, work extra jobs, or rely on the charity of their family members, church, or community to secure specialty cancer drugs or other expensive treatments for a loved one. Although there is no health-care system which can provide every medical intervention that offers a prospect of health benefit to everyone, all of the time, equity should not be ignored. For example, how and on what basis can doctors deny potentially beneficial care to some patients and give the same treatment to other patients? This can be done by putting in place limits and rationing mechanism overseen by a committee of respected professionals, since in tropical countries the wealthy and ruling elite always circumvent whatever limits or rationing mechanism is in place in order to secure access to technologies that confer (or are perceived to confer) medical benefits, no matter how costly using tax payers' money—a situation which is morally and ethically undesirable. A sense of fairness is required by the committee of limits and rationing to address inequity.

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Precarity, Social Organization, and Outcome on Cancer Management in the Tropical Areas

Sandro Vento and Olof Ståhl

Precarity can be defined as a condition of existence without predictability or security, affecting material and/or psychological welfare; often, it is linked to and derives from unemployment. Precarity is a common everyday condition for the majority of healthy people living in tropical countries. A cancer diagnosis determines a condition of precarity even in those who have not experienced it before and obviously worsens the condition in people already affected; can the social organization in tropical, developing countries alleviate precarity or rather contribute to it?

Cancer management in the tropical areas faces several problems. Apart from the common clinical challenges shared globally, the task is further complicated by socioeconomic, cultural, and educational difficulties and shortcomings.

The healthcare systems in the tropical areas have, rightly so, focused on communicable diseases. In view of the increasing cancer burden also in the developing world, there is however a growing awareness of the healthcare problem of cancer [1]. The increasing focus on cancer has led to the development of cancer care programs including community education in prevention and self-examination, screening, diagnostics, treatment, and palliative care; such initiatives in the tropical areas share common challenges. To properly address cancer care, the disease burden needs to be known; unfortunately, in the vast majority of tropical countries, this knowledge is sparse. The lack of reliable cancer registries complicates the needed society efforts to improve cancer outcome; indeed knowledge of the epidemiology of cancer in general and of cancer in specific organs is essential to establish societal and medical community educational programs and to build medical facilities for both diagnostics (including imaging and pathology) and treatment, i.e., radio- and

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chemotherapy. The cancer demographics need to be known to identify possible region-specific risk factors, i.e., infectious, lifestyle related, or environmental, as well as to be able to address specific clinical issues for the various regions, e.g., triple negative breast cancer in African women. Ongoing efforts to establish cancer registries [1, 2] will hopefully allow to both define and meet the specific national/regional needs and shortages in cancer management in tropical countries.

Poor cancer awareness greatly contributes to the poor outcome in cancer in the developing world, as it is not limited to the public but extends to the medical community [3]. Lack of knowledge reduces the possibility of prevention and early detection, delays proper medical management, and opens up for traditional alternative treatments, ultimately resulting in a negative outcome due to advanced disease at presentation, delayed diagnosis and treatment, and probably premature cessation of prescribed therapy [3].

Improved awareness is also needed to increase the public's trust in western medicine. At difference with the western world, a major challenge in tropical countries is the culture and developed industry of alternative medical practices such as prayer camps, herbalists, and traditional healers. In rural areas of poor tropical countries, people have access only to "real" traditional healers who are the backbone of a particular "health system." Indeed in many countries the "complementary and alternative" medicine is the recently imported western medicine rather than the traditional medicine, based on herbs and spiritual healing (prayers and faith), which has been part of the everyday life of populations for millennia. The strength of the traditional healing system lies in its low cost, in its sharing of the world vision and belief system of its users, in being an alternative to an inefficient western-type healthcare system, in the privacy and absence of time limitations per consultation, and in treating patients psychologically. However, the traditional healing system often uses harmful treatment regimens, prolongs the search for more appropriate healthcare, and contributes to destroying interpersonal relationships of people with cancer through witchcraft accusations. Many patients in tropical areas continue to consider cancer as due to spiritual forces beyond the reach of biomedicine [4, 5], and the fact that most of those patients who manage to present to healthcare facilities and to receive conventional western medical treatment die gives people the impression that western medicine is not better for cancer.

Studies on breast cancer show that the disease is associated with social rejection and isolation and that it may represent a test on one's faith and thereby treated through intensified religious activities [3, 6]. Mastectomy has been shown to be associated with fears of death and of marital rejection [6, 7]. To fight established stigma of cancer and its treatments, knowledge needs to improve. First, to be able cope physically, psychologically, and financially with the burden of often toxic treatments, a basic understanding of the disease and of its management is needed. Secondly, the "success stories" of adequate oncology need to be told in order to attract patients from non-established treatments to scientifically proven western medicine. Fear, stigma, and traditional medicine have been shown, together with financial incapacity, to be major reasons not only for delayed diagnosis and treatment initiation but also for premature therapy cessation [3, 8]. Initial efforts are

being made to establish collaboration between practitioners of traditional medicine and western medicine, aiming at educating in signs and warnings of cancer and at the same time benefiting from the better availability of traditional medicine practitioners. Furthermore, medical practitioners have shown support for the role that traditional healers can play in providing emotional and spiritual support for patients, for example, in the palliative setting [6, 8].

In spite of the contribution of the above-discussed challenges, the overwhelming obstacle in improving cancer care in tropical countries is financial. On a society level, the financial incapacity contributes to the poor infrastructure in public and private healthcare systems. A professional medical workforce is lacking; for instance, it is estimated that approximately 120,000 physicians work in Africa with a ratio of 2.2 physicians per 10,000 people compared with a ratio of 33.2/10,000 people in Europe [1]. The general lack of medical facilities and staff is even more pronounced for specialized care such as oncology. Radiotherapy capacity is profoundly insufficient; over 50 % of the population in middle-income countries needing radiotherapy lack access, and for low-income countries the corresponding figure is above 90 %. Less than 40–50 % of the estimated need of radiotherapy machines is available; the geographical differences are big, with the worst situation seen in sub-Saharan Africa [9]. Apart from the shortage of technical equipment, the need of specialized, trained staff such as dosimetrists, medical physicists, engineers, and radiation oncologists is highly unmet.

Most cancer patients in developed countries cope with the financial burden of a very expensive treatment, thanks to their health insurance schemes which are of course unavailable to the overwhelming majority of the population in tropical areas where the common reality is a very serious economic family crisis. Furthermore, a study in Ghana showed that ignorance of the coverage of the national health insurance was a cause of incomplete treatment of breast cancer. Thus, even in settings where the public healthcare system does support cancer care, financial incapacity is an obstacle, due to lack of awareness of what the society actually pays for [8].

A diagnosis of cancer in one of the adult members not only generally determines the loss of a very important source of income but also often depletes the family's resources in seeking treatment. Unfortunately money is frequently spent by the family for treatments offered by unscrupulous subjects with the promise to cure advanced cancer by using totally unproven "therapies"; these individuals are often those who pretend to be traditional healers moving to towns and cities without having practiced as such before. Such practice not only drains the financial capacity of the patient, it is also likely to lead to a delayed diagnosis with a more advanced disease requiring more costly treatment compared to a disease at an earlier stage.

Considering the level of poverty and the trend of diminishing extended family support among communities in tropical countries and the often very long distance from centers where western medicine cancer treatment is available, it is clearly a serious challenge and a frequently impossible task to access western medicine therapy. Even when patients manage to reach the few centers where they could be treated, accommodation is a huge challenge for the patients and their relatives, with poor sleeping and eating conditions for already ill patients; overall, no more than

5 % of cancer patients in tropical areas reach oncology or radiotherapy centers, and even fewer are able to complete treatment regimens because of late presentation or financial constraints.

Needing to travel long distances on bad roads with poor transportation to cancer care centers is frequent in tropical areas. In those areas affected by wars and conflicts between groups, access to cancer care is further adversely affected as patients are not able to travel safely to get their therapy. The ability of doctors to reach treatment centers can also be impeded by the unrests.

Droughts and famines that can affect tropical countries can also cause displacement of individuals and families and consequently deteriorate the quality of cancer care. In addition, within tropical countries, there are millions of refugees, asylum seekers, internally displaced persons, or returnees, and these groups have generally little if any access to cancer care.

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Cancer Screening and Prevention in the Tropics

Mathieu Nacher and Tristan Roué

As much of the tropical world undergoes an epidemiologic transition from the preeminence of infectious diseases to that of noncommunicable diseases, cancer epidemiology also undergoes a transition from cancers due to infectious agents to cancers due to noninfectious, lifestyle factors. The accumulated knowledge of epidemiologic research on the causes of cancer, their burden, and the most cost-effective methods for prevention and early detection represents a precious compass for public health authorities in the tropics. Primary cancer prevention and screening for early detection in resource-limited tropical areas should be focused toward cancers causing the greatest burden of disease [1]. The tropics are characterized by differences in the epidemiology of infectious agents causing cancer (hepatitis B, helicobacter, HTLV1, HPV), in education levels, in behaviors that may prevent or promote cancer, and in the resources allocated to the health systems. In addition, rapid development leads to major changes in all the above aspects that greatly impact the epidemiology of cancer. The resulting interplay between development level, culture, and pathogen ecology leads to a range of situations that may be quite different within the tropics and in time [2]. Reliable data sources are costly and therefore not available in most of the developing world. About 40 % of the world population and 55 % of children under 5 years of age live in the tropics. However, fertility rates are decreasing and the populations are aging, thus increasing the number of persons at

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risk of cancer and modifying the incidence of different types of cancers. The majority of the poorest countries live in the tropics. Mortality data and cancer registry data are only available for an estimated 4–5 and 3 % of the populations living in the tropics, respectively [3]. The World Health Organization's mortality databank reports mortality data from death certificates over time for about 80 countries. Mortality is an imperfect surrogate for incidence when the case fatality rate varies in time or space. The cancer incidence in five continents (CI5) which selects the most reliable recent registry data only covers 6 % of the South American populations, 4 % of the Asian populations, and 1 % of the African populations. Nevertheless, these data can serve to estimate mortality and incidence of cancer in different parts of the world and prioritize the most pertinent and cost-effective targets and methods for cancer prevention and screening. The international agency for cancer screening releases estimates of the global cancer burden in the GLOBOCAN series [4]. These estimates rely on the best available data, country-specific data, when available, or on statistical modeling.

The populations living in the tropical areas are diverse and it is challenging to summarize the cancer trends and priorities in such an array of situations. One way of categorizing the tropical world is to use the human development index, which is often lower than in temperate countries [2]. Another way is to stick to geography and look within continents. Both lenses will be used to attempt to grasp the major

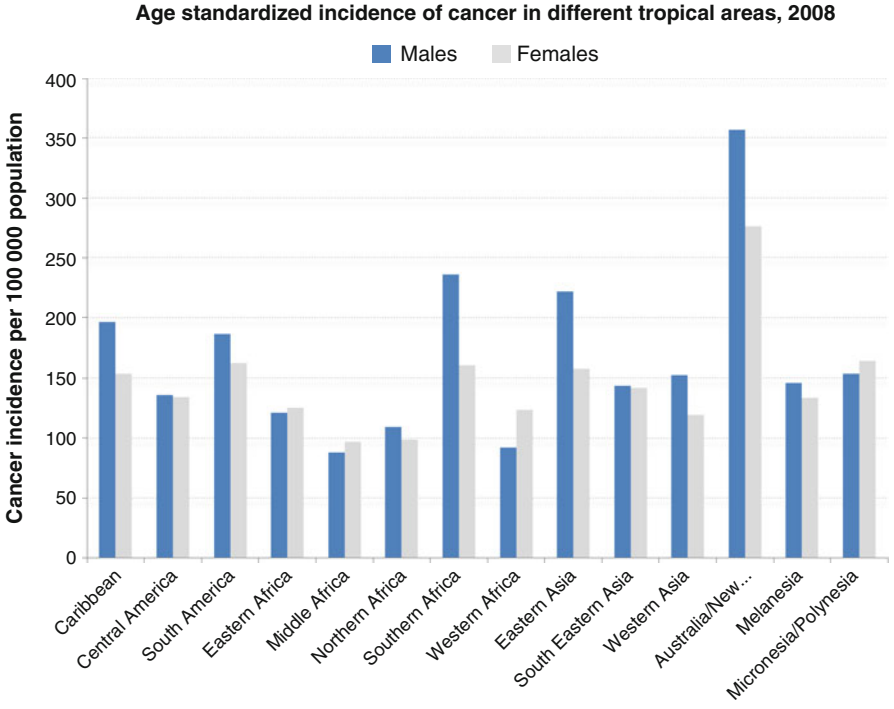

Fig. 1 Age-standardized incidence of cancer (all sites) in different tropical areas in 2008

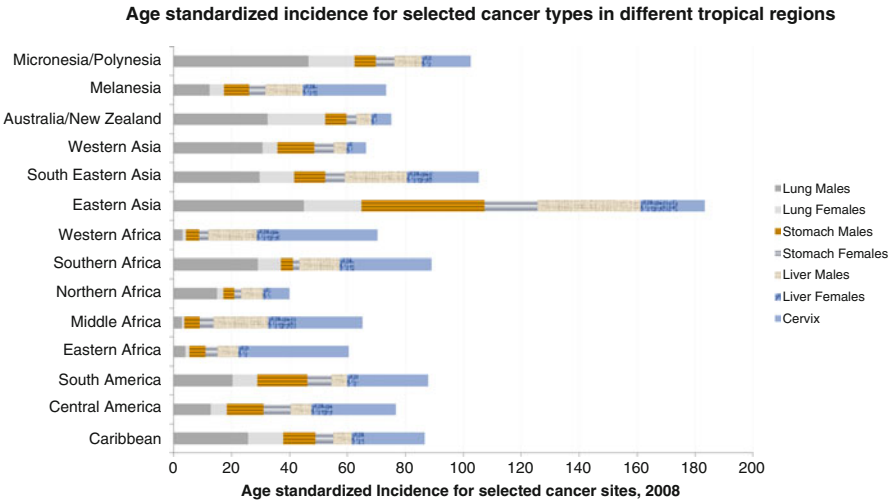

Fig. 2 Age-standardized incidence of selected types of cancer in different tropical areas in 2008

trend situations of cancer in the tropics. Figures 1 and 2 shows the incidence of the top cancers per subregion.

For countries with low or medium human development index, the highest incidences reported for cancer are by decreasing order lung, gastric, liver, female breast, colorectal, cervical, and esophageal. The standardized incidence for stomach, liver, cervical, and esophageal cancer is significantly higher in the low- and medium-human development index countries than in the high- or very high-human development index countries. For mortality, the main cancers for low and medium development index are lung, liver, gastric, esophageal, colorectal, breast, and cervical cancer. There again, as for incidence the standardized mortality for stomach, liver, cervical, and esophageal cancer is significantly higher in the low- and medium-human development index countries than in the high- or very high-human development index countries [2]. Recent trends extracted from the registries show a transition in low and medium human development index with prostate, breast, and colorectal cancers increasing since 1988, whereas cervical and gastric cancers tended to decrease. These trends however rely on the very rare registries in these countries.

In 2008, about 47 % of all cancer cases were from less developed areas (45 % in medium-human development index and +2 % in the low-development index areas which represented 6 % of the world population). However, GLOBOCAN projections suggest that at the 2030 horizon, assuming constant incidence rates and UN population growth estimates, the total number of cancer cases should increase 75 % mostly in the areas of lower human development index, where the number of cases should increase 93 %. Colorectal, breast, and prostate cancer should increase, whereas gastric and cervical cancer are expected to decrease [2].

Given these figures and projections, prevention and screening are of paramount importance to alleviate the burden of cancer in the tropics.

1 Primary Prevention

1.1 Infectious Causes of Cancer

When all infective causes of cancer are pooled, they represent the second most important cause of cancer, after tobacco [5]. In developing countries up to 25 % of cancers could be avoided by controlling these infections [1].

1.2 Viruses

The human papillomavirus is the infectious agent that contributes to the highest number of cancer cases [5, 6]. HPV viruses cause cervical cancer, cancers of the anus, penis, vulva, and vagina and cancers of the oropharynx. Primary prophylaxis through vaccination against HPV 16 and 18 subtypes before entering sexual life could avoid about two out of three cervical cancer cases. However, it is still too expensive and logistically complex to implement for many tropical countries. Nevertheless, a study has shown that one or two vaccine doses may lead to sufficient immunity in Costa Rica [7]. If confirmed, this would reduce the costs and facilitate implementation in the most isolated areas to achieve sufficient coverage. Delaying sexual activity and reducing the number of sex partners and unprotected intercourse could contribute to reduce cervical cancer incidence. This is part of measures to reduce the burden of sexually transmitted infections and early pregnancies and thus should be easily integrated in general health promotion. Cervical cancer is an AIDS-defining illness in HIV-infected persons. Given the huge burden of HIV throughout the tropics, HIV prevention, early testing for HIV, and access to antiretroviral treatments are likely to reduce the incidence of cancers associated with HPV.

Hepatitis B viruses are responsible for 60 % of all primary cancers of the liver [5]. The prevalence of hepatitis B chronic infection is still very high in Africa and South East Asia, with up to 10 % of the population being chronically infected. Transmission may occur at different ages, from mother to child, between children during childhood, by sexual relations, or through the parenteral route. Primary prophylaxis opportunities thus reflect transmission risks. However, the most cost-effective intervention in countries of high prevalence remains routine mass vaccination with an anti-HBV vaccine, as recommended since 1992, and early vaccination of newborns from chronically infected mothers. Although most countries adopted this recommendation, vaccine coverage is still suboptimal in highly endemic areas. Moreover, a substantial proportion of infants did not receive the first

dose within 24 h after birth to avoid transmission of hepatitis B from chronically infected mothers.

Hepatitis C viruses are responsible for about a quarter of all primary cancers of the liver worldwide. In Africa, it is estimated to cause up to 40 % of hepatocarcinoma, in Japan 36 %. Transmission is mostly parenteral and thus screening of blood donors and improvements in sterilization techniques for medical and nonmedical techniques (body adornments) can reduce the prevalence of chronic hepatitis C and hepatocarcinoma [5, 8]. There is no vaccine at the moment.

The human T-cell leukemia virus 1 infection is complicated with T-cell leukemia/lymphoma in 2–5 % of the cases, notably when the infection was acquired from mother to child [9]. The tropical areas with the highest prevalence are the Caribbean, South and Central America, Melanesia, and Central Africa [5]. Although in regions of higher development index, such as Japan, prevention of mother to child transmission through breast feeding avoidance has been successful, it is not applicable in parts of the world with low development index where the burden of diarrheal diseases and malnutrition may end up being far greater than that of T-cell leukemia/lymphoma. Screening of blood donors also may help reduce the prevalence of HTLV1 but most T-cell leukemia/lymphoma cases concern persons infected during infancy.

Other infections such as the Epstein-Barr virus, in conjunction with malaria, may result in Burkitt's lymphoma or nasopharyngeal carcinomas. However, most persons are infected by EBV during childhood and specific primary prophylaxis measures against these cancers do not exist. The HHV8 virus is related to Kaposi's disease and Castleman's disease, notably among HIV-infected patients. Apart from antiretroviral to avoid immunosuppression, no specific primary prophylaxis exists for these tumors. HIV is also associated with an increased incidence of various cancers, notably in the most severely immunocompromised patients. There again, antiretrovirals to maintain immunity may contribute in preventing cancer.

1.3 Bacteria

Helicobacter pylori infects up to 90 % of the populations in the tropical areas. Some will develop ulcers, chronic gastritis, and rarely gastric cancer. Although, once diagnosed, *H. pylori* may be eradicated by antibiotics, success is not constant and reinfection may occur. General socioeconomic development, improvement of hygiene levels, increased use of refrigeration, increased availability of fresh fruits and vegetables, decreased reliance on salted and preserved foods, and increased availability of antibiotics may decrease *H. pylori* colonization rates in the population and ultimately reduce the burden of gastric cancer.

1.4 Parasites

Chronic infection by *Schistosoma haematobium* is an important cause of squamous cell carcinoma of the bladder in Africa [10]. Infection by *Schistosoma mansoni* in Africa and *S. japonicum* may lead to liver and colorectal cancer. Primary prophylaxis of bilharziasis relies on the reduction of contacts with infested water.

Chronic infection by liver flukes, such as *Clonorchis sinensis* (Asia and Southeast Asia) or *Opisthorchis viverrini* (Southeast Asia), may lead to cholangiocarcinoma [10]. Primary prophylaxis relies on avoiding the consumption of raw fish in endemic areas and treating infected persons to avoid chronic infection of the bile duct and cancerous transformation.

1.5 Mycotoxins

While not an infection per se, *Aspergillus flavus* may contaminate foods such as nuts, oilseeds, cereals, and spices and produce aflatoxin, a potent carcinogenic that can lead to hepatocarcinoma. This contamination may occur during harvest or storage of the foods. Primary prevention is through crop selection, timely harvest, and dry and cool storage conditions. Insecticides and fungicides also avoid fungal contamination of food. Other fungal toxins, fumonisins, have been suspected in esophageal cancer in Africa [11].

1.6 The Tobacco Epidemic

Tobacco is a major risk factor for cancers such as lung (population attributable fraction 80–85 %), oropharyngeal and esophageal (population attributable fraction 55–70 %), laryngeal (population attributable fraction 80 %), gastric (population attributable fraction 15–26 %), liver (population attributable fraction 15–27 %), bladder (population attributable fraction 34–38 %), kidney and ureteral (population attributable fraction 15–29 %), pancreatic (population attributable fraction 26–31 %), colon (population attributable fraction 7–10 %), cervical (population attributable fraction 7 %), ovarian (population attributable fraction 3 %), and myeloid leukemia (population attributable fraction 6–19 %). Smoking cessation has a rapid impact on the risk of cancer. The population attributable fractions indicated were obtained from the UK. The application of these attributable fractions to the current incidence and mortality data in the tropics suggests that the highest impact will be for lung cancer.

Whereas in richer countries public health laws and programs are tackling this major health hazard, in most of the tropical world, little is done and the tobacco industry is actively promoting smoking with little resistance. Women who often

have less rights than men in tropical regions are targeted by the industry, associating smoking with emancipation, slimness, and sophistication. Rising incomes make cigarettes more affordable for a growing proportion of the population in the poorest countries. WHO identified six evidence-based tobacco control measures that are the most effective in reducing tobacco use [12]. Known as "MPOWER," these measures are monitor tobacco use and prevention policies; protect people from tobacco smoke; offer help to quit tobacco use; warn people about the dangers of tobacco; enforce bans on tobacco advertising, promotion, and sponsorship; and raise taxes on tobacco. Although there is progress, only a third of the world population is covered by at least one of these measures. The tobacco epidemic is just beginning in many parts of the tropical world. Knowledge of what to do and not to do is available and should be disseminated to decision-makers and the populations. There is therefore a great opportunity to avoid the fatality of having a large proportion of the tropical world addicted to cigarettes and a future surge in tobacco-related cancers [2, 4].

1.7 Cancers of Development

With socioeconomic development, diets and exercise patterns change, and women control their reproductive lives with access to contraception and delay their first pregnancy and have fewer children, leading to structural population changes as populations age. This transition has an impact on the incidence of a number of cancers [1]. Changes in the patterns of women's reproductive lives modify the overall exposure to estrogens and thus may increase breast cancer but also ovarian and endometrial cancer. The transition toward a high animal fat and protein diet and a low-fiber diet gradually raises the risk of colorectal cancer. This transition is often propelled by aggressive marketing of unhealthy processed foods. Decreased exercise, increased weight, and obesity that accompany this transition are associated with increased colorectal cancer, breast cancer after the menopause, endometrial cancer, but also gallbladder cancer, kidney cancer, and pancreatic and esophageal adenocarcinoma. Sustainable comprehensive national-, regional-, and/or community-level policies to improve dietary patterns and physical activity have been developed by WHO.

2 Screening

Screening is important for health problems that are severe, with a prolonged asymptomatic phase and possible early detection and treatment effectively improving the prognosis and for which a reliable and cost-effective test is available. Unfortunately, in much of the tropical world, access to care is difficult and health infrastructures cannot support facilities that are usually the foundation of early detection in the richest countries (mammography, cryptologic examination of smears, hemoccult

and colonoscopy, etc.). In addition, health inequalities are widespread. These factors explain why cancer patients often present very late with extended lesions. For the early detection of a number of cancers (breast, prostate, colon) in the poorest countries, it seems difficult to advocate for a specific priority, given the rudimentary state of a number of facilities in the tropical world. The general improvement of diagnostic facilities (imagery, laboratory facilities) is important and should gradually improve with development and will allow to make progress in the early detection of cancer. Increasing public awareness of early signs of breast, cervical, prostate, bladder, rectocolic, and oral cancers could help in detecting these cancers at earlier stages and improve prognosis. Ensuring patient treatment capacity is also important so that persons are convinced of the benefits of screening. For cervical cancer, the benefits of teen vaccination will be delayed as the cohort of unvaccinated women age. When the standard screening methods cannot be used, some tropical countries use visual inspection of the cervix with Lugol iodine or acetic acid to detect lesions. HPV DNA tests have also been used and have proven to be superior to the visual methods above to prevent late-stage disease and death. However, cost-effectiveness studies remain to be undertaken in the poorest regions in order to guide decision-makers with constrained budgets to choose screening strategies. Modeling studies have suggested that one or two low-cost/low-tech HPV DNA screening between 35 and 55 years of age would reduce the burden of cervical cancer by 30 %. In China rapid HPV DNA test coupled with visual inspection of lesions and cryotherapy in a single visit was possible and cost-effective. Strategies may still be further optimized to improve cost-effectiveness.

3 Conclusion

There is a growing burden of cancer in developing countries in the tropics. This burden is partly due to population growth and aging and to slow progress against infection-related cancers and the marketing-driven rise of smoking and obesity. The predicted demographic changes will probably increase the number of people with cancer to more than 20 million per year by 2030. However, the implementation of preventive measures targeting known risk factors in low- and middle-HDI countries could be highly effective and could avert much of the predicted rise of incidence and mortality. These interventions include smoking reduction, promotion of physical activity and healthy eating, and vaccinations against hepatitis B virus (HBV) and carcinogenic human papillomavirus (HPV) infections. Early detection of cervical cancer and, where possible, breast and colon cancer will also contribute to the reduction of cancer mortality.

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Pathology and Cancer Research

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In adequate pathology, data and infrastructure do not only negatively affect clinical case; they demotivate research. In the developing countries, there is inadequate attention put during training on the important role good pathology practices play in getting correct diagnosis. A case in point is improvement in sample acquisition process right from obtaining disease-representative samples to transmission to the lab. It is important to emphasize that sample acquisition cuts across disciplines although commonly tissues are obtained following surgical procedures such as excision biopsy. Fresh tissue should be obtained and examined by gross inspection, touch preparation, or frozen section examination especially when dealing with lymphoid malignancies. Ideally pathology service should perform frozen section diagnosis to guide surgical resections and track histopathologic and cytopathologic diagnoses. Examination of tissues by microscopy is a key step. First, the general algorithm starts with the low-power appearance of the tissue section. The cell size, the nuclear shape gross examination, tissue sampling, and histological slide preparation transportation, reporting, and archiving should be emphasized [1]. There is a need for diligence in obtaining representative tissue sample, a process informed by experience, training, and tutoring. Second is timeliness in moving samples from surgery to pathology departments for processing [1, 2]. Third is appropriate and

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timely processing and fixation of samples for routine and special procedures. Fourth, prompt reporting is important in raising interest in the services of pathologist to clinicians and patients. Fifth, at the end of the process, there must be a reliable system of archiving/storage of samples and results for continuing care and research. The archival system must ensure there is safety of materials, confidentiality, and at the same time ease of retrieval for review and reanalysis.

1 Basic Steps in Good Pathology Practices in Developing Countries [1, 2]

- Appropriate and timely fixation for routine and special procedures
- Efficient transfer of material to pathology
- Receipt and documentation of specimens
- Case tracking
- Reporting
- Archiving
- Basic working equipment for tissue evaluation and processing
- Uninterrupted supply chain of quality reagents, equipment procurement, and maintenance

Good pathology practices are the basis for meaningful cancer research that enhances strategies for prevention, diagnosis, treatment, and cure. Cancer research is of great importance because it improves our understanding of this diverse set of diseases which in turn brings us closer cancer control goals. We have outlined cancer research into different categories as an aid to understanding of specified areas for possible interventions.

1. Basic cancer research: Basic cancer research takes the form of in vivo and in vitro studies in the laboratory aimed at improving our understanding of the behavior of cancer cells and therefore how normal cells can become cancerous. In other experiments, cancers may be induced in lab animals in order to study carcinogens or how well a possible new treatment works including its side effects.
2. Translational research: Translational research takes the form of bedside cancer research that uses information gathered from basic cancer research. Knowledge accrued from this research in turn generates hypotheses that drive further basic cancer research.
3. Molecular research: This is a research that looks for new cancer genes. Developing cancer may be caused by the presence of certain gene(s) that may or not be inherited. Genetic testing may be performed in a cancer patient or in healthy individuals from families known to have a cancer gene (screening).

4. Clinical research: Clinical research involves testing of cancer treatment in individuals. This type of research is most useful in establishing the efficacy and safety of anticancer medicines/test devices prior to their approval for use in clinical practice. Generally, these studies involve large groups of people on the test drug/device who are carefully monitored.
5. Epidemiological research: Population-based research uses big databases that accrue information about people in defined geographic regions who develop cancer over a specified period of time. This research attempts to find the causes of cancer and the risks of specific cancers in different populations of people with cancer according to factors such as age, sex, race or ethnicity, family history of cancer or place of birth. Such information enables hypothesis generation about causes of cancer. Further, population-based research enables the study of changes in cancer risk over time and the quality of cancer care and access to it in different communities across the country so that disparities can be corrected.
6. Behavioral research: This investigates how our lifestyle (diet, physical activity, type of work, smoking or alcohol consumption, etc.) affects risk of cancer occurrence or recurrence. It also looks at what motivates people to have healthy behaviors and why they do not always choose them. Information so gathered informs the development of strategies to encourage adoption of healthy behaviors.

2 Ethical Issues

When research and clinical care coincide as much as in the oncology setting, several ethical problems arise including conflict between research and care goals, problems with informed consent, and promoting best practices in a research setting [3]. These challenges become even more complicated in the context of patients who have cancer in poorly resourced countries that have high illiteracy and poverty rates and a poor health care infrastructure [4]. The basic ethical principles in research involve human subjects' protection of vulnerable groups (pregnant women, human fetuses, and neonates; babies and children). Development of regulatory bodies, institutional review boards (IRB), national authorities, and involvement of community through community advisory boards in most countries in the developing world are a welcomed development. Training in good clinical and laboratory practices should be emphasized. Good science must be matched with high ethical standards.

In conclusion, the importance of pathology in cancer research cannot be overemphasized in the overarching goal of being able to control cancer across the spectrum of cancer care from prevention to palliation. Despite this, cancer research is fraught with challenges in the developing countries which need to be addressed in the national, regional, and international context and with strategies that are continuously evolving.

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Transcultural Mediation in the Management of Cancer Patients in the Tropical Area

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1 Introduction

Considering the fact that over 40 % of patients feel they were left out of treatment-related decisions,[1] the French Cancer Plan for 2014–2017 aims at allowing patients to become actors of their own treatment.[2]

This change results from the epidemiological transition and the growing frequency of chronic diseases. In that context, there is growing pressure so that individuals may play a role in the management of their disease, bring their contribution to treatment, and share responsibility. This new paradigm was also influenced by new theoretical trends supporting vulnerable individuals' capacity to participate and play a role, such as the empowerment theory [31].

While in the context of infectious diseases patients tend to remain passive, in the case of chronic diseases, they are bound to take on a more active role. This change has impacted the traditionally paternalistic patient-doctor relationship in favor of a more equal partnership.

[1] 2010 data, VICAN2 study 2012.

[2] See French National Cancer Plan- objective 7– ensure global and personalized treatment: "Quality care implies providing the cancer patient with all means necessary to encourage his/her participation to treatment options."

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Obviously, allowing patients to take on a more active role could not be limited to a personalized treatment program and the provision of information resources relating to his/her pathology and associated treatment.[3]

Rather it implies that, together with the treatment plan, the patient is able to grasp doctors' understanding of his/her disease. In reverse, medical professionals should be able to access the patient's representations of his/her disease and the ways it transformed his/her life. This mutual understanding rests upon the articulation between lay knowledge and expert knowledge, which is at the basis of transcultural care [16].

How can cross-cultural mediation promote this articulation?

How could it apply to the treatment of cancer in tropical regions?

How to implement it using local human resources?

Before answering these questions, it is necessary to outline the bases of medical anthropology and its contributions to understanding the illness experience. We then discuss the Centre Babel's fifteen-year long experience implementing cross-cultural mediation in hospital settings.

2 Disease from an Anthropological Perspective

Anthropologists have shown that the illness experience is above all a social and a cultural event [1]. Disease is a shared social construction between society, the ill individuals, and healthcare professionals. In that respect, expert and lay representations of the disease and of therapeutic responses both confront and inform one another.

In the case of life-threatening diseases, two discourses are produced that often never dialogue with one another. One is the professional physician's discourse, shaped by a technical knowledge of the body, and elaborated from the patient's symptoms. Its goals are to establish a diagnosis and to propose a treatment. It is based on scientific evidence. Then there is the patient's discourse, shaped by existential queries, and seeking to provide meaning to a life-threatening situation. Why me? Why now? This quest for meaning in the face of a serious illness is shared by all universally. It goes beyond the search for causes, which the physician focuses on. It is a quest which narrative is based both on individual and collective experiences and which is informed by shared representations of disease and misfortune, varying from one community to another, as medical anthropology studies have shown [1].

This narrative may lead patients to seek their own therapeutic responses, such as the so-called alternative therapies. Several studies have pointed to the frequency of resort to such therapies [38].

[3] See French National Cancer Plan 2014–2017.

Diseases are thus not merely defined by medicine: They are multidimensional, as they are the expression of different points of view. In that perspective, cultures do not merely provide disease representations. They are essential to their construction as a human reality.

3 The Cultural Representations of Cancer and Their Impact on Communication and Care

Today, while the scientific and therapeutic achievements in the field of oncology allow us to perceive treatment as efficient and as offering hope for recovery, cancer remains symbolically associated with death, and cancer patients – together with their close kin – have to face their own finitude [5]. This ordeal triggers among individuals – cancer patients but also relatives and healthcare professionals – the production of myths and symbols to help make sense of the disease [43]. Such representations must be considered as "acts of communication" [39], underlying how much the illness experience is shaped by culture and its context, the hospital included [41, 47].

Cancer is a significant focus for anthropological analysis because of its symbolic and social meanings across global contexts [34]. For several decades, anthropologists have explored such issues as representations and experiences of cancer and the display and production of authoritative knowledge about cancer treatment and healthcare access. This literature focuses predominantly on cancer patients and biomedical treatment in Europe and North America [11, 13, 19, 24, 37]. A smaller body of research explores patient narratives and meanings associated with cancer in other regions, in such countries as Mexico [23], Botswana [32], and South Africa [48]. These anthropological studies explore a range of themes, including the stigma that cancer patients commonly face, inequalities of care, and the significance of support groups for survivorship.

A substantial literature focuses on cancer as metaphor [14, 19, 22, 43]. McMullin and Weiner [34] observe that "cancer" is a global word – "one that can be a metaphor for lack of control and degeneration" [13, 33]. Despite these studies on discourses surrounding cancer in the USA and Europe, we know little about how non-western populations conceptualize the term "cancer" and whether they categorize cancer as having particular consequences for one's identity or social relations [21].

In her book entitled "Femmes et cancer" (or *Women and Cancer* [20]), Hélène Hamon-Valanchon identifies the "cancer trajectory" of women suffering from a reproductive cancer as an initiation ritual involving different stages and implying deep identity transformations. In the case of reproductive cancers, anthropologists have indeed shown how gender norms come to be challenged in the course of the disease [12, 48]. By drawing the relation between the disease and the social identity of the individual, anthropologists show the weight of social representations [44] and

underline the need for information support so as to develop appropriate coping strategies. In their study on gynecological cancers among women in Australia, Wray et al. [48] conclude that the main obstacle to communication about cancer comes from the absence of a vernacular discourse devoid of sexual connotations, which prevent women from being able to share their experience with others. For example, stigma may derive from "external" social representations linked to reproductive cancers as resulting from bad hygiene and promiscuity [9, 49].

Once a diagnosis is established, although cancer treatment is accessible through the public hospital system, the complexities of interactions and communications involving clinicians, patients, and their families may complicate an already uncertain illness trajectory. A hospital-based ethnography [29] suggests that contested biomedical and nonspecialist representations of cancer shape strategies of immigrants and family members in response to a cancer diagnosis. In that respect, in the context of immigration and cultural diversity, interpreters and cultural mediators have become indispensable figures for communication with public health institutions [17]. Little research has focused on how interpreters and cultural mediators actually translate complex diagnoses and communicate negative prognoses to patients and/or families. The very question of vocabulary requires interrogation of, for example, what terms are used for "cancer" or "tumors," chemotherapy, or radiation. Preliminary research [29] suggests that interpreters may deviate from direct translations of biomedical practitioners, to conform to cultural conventions concerning discussions of illness and death. Interpreters tasked with conveying terminal diagnoses thus play a central role in reframing such messages with reference to potential returns to the "home country," for example. They thus have a central role in negotiating reasons for and the terms of that return.

Altogether, anthropological studies on cancer – its cross-cultural meaning and experience – underline how pivotal the communication between healthcare professional and patients is and demonstrate its clinical impact in the context of oncology [36]. The confrontation between lay and expert explanatory models on the disease – each one relying on a different set of myths and symbols to relate to the body and the functioning of organs – is a challenge for clear communication. It is all the more complex in a multicultural setting, and this complexity increases the likelihood of miscommunication [15, 28]. Recent public health efforts at better informing and communicating with patients remain out-of-reach for foreign-speaking, culturally diverse patients. A study on communication campaigns for breast and cervical cancer showed that they are "little adapted to cultural representations of the disease and to screening access for women living in poor social conditions" [10].

Despite the policies sustaining "healthcare democracy" and defending patients' rights to access information, the quality of communication between patients and healthcare professionals remains problematic [4, 18]. While the dynamics of the clinical encounter have drastically evolved around the treatment of chronic diseases, the power of the doctor in selecting the information and holding the truth remains relatively unchanged [18].

4 Cultural Mediation: A Tool for Improving Healthcare Communication and Clinical Outcomes

For psychiatrist and anthropologist Arthur Kleinman [25, 26], patients and doctors each bring in a specific model that establishes the meaning and reality of the disease. As a result, he portrays the healthcare relationship as a confrontation of two explanatory models of the disease. On the basis of this assertion, we may consider that communication problems most likely arise from situations in which the negotiation between healthcare professionals' and patients' explanatory models of the disease failed.

While such miscommunication may occur when both doctor and patient share the same cultural identity, its challenge has been particularly stressed in transcultural situations, which – as we described above with cultural representations of cancer – bring in additional linguistic and cultural complexities. It is within such context that countries like Europe, the USA, Australia, and Canada developed cultural mediation and culturally competent health approaches, to better respond to the healthcare issues of immigrant populations or members of minority groups. There now exists a vast literature on the topic and its stakes in different health settings or with different immigrant or minority groups (see among others: [3, 35, 45]).

Cultural mediation involves more than linguistic translation. In fact, the use of mediation for translation needs only may be detrimental to the quality of care, and it does not take into consideration all relational dimensions and nonverbal aspects of communication [30]. As most reports point out, its function is to bridge between two worlds, two sets of representations. Culture is located on both ends of the communication, not simply on the immigrants' or the ethnic minority members' side. It also has to be in an anthropological perspective, giving consideration to such dimensions as religion, tradition, and individual experience. All aspects of language are of primary importance, including body language. Cultural mediators enable the confrontation of cultural "explanatory models" on both ends of the communication, by explaining and relating the values and norms associated with such models. The ultimate goal is for interlocutors to be able to identify with one another's model by way of understanding it.

The cultural mediator is neither only a translator nor a "cultural expert": with her or his active and critical presence, the cultural mediator introduces a "difference" in the setting, representing the possibility to reformulate the meaning of stories, experiences, and symptoms in a new productive form. Identity is not a fixed and stereotyped attribute of the person, but a representation of oneself and the other constantly enacted and reformulated according to the situation. Cultural mediation is thus properly "productive" of a new "possible common identity," allowing communication, mutual reformulation, and efficacy. In no case should the presence of a cultural mediator be imposed in health settings, but always negotiated as a specific moment of the therapeutic process. It is not simply a strategic tool to obtain compliance and acquiescence, but a critical device introduced into the therapeutic system for questioning its premises, its organization, and its practice.

Developing a culturally competent intervention also implies the acknowledgement of the role that social and political factors have as compelling aspects in the production of illness and in the construction of therapeutic initiatives [6, 40]. Clinical settings are to be considered as places of conflict and change, where social actors with different positions and belongings interact. This is a process that conveys the recognition of the patients' (and their groups') voice, listening to histories and narratives and integrating local interpretations and explanations in the process. To do this is to acknowledge the dignity of the patient and the effectiveness of his/her "local" knowledge.

Definitions of cultural mediation and conditions for its practice vary quite significantly from one society to another. In multicultural settings like the USA or Canada, cultural mediation is an institutionalized and policy-sponsored practice, while in more "assimilationists" societies such as France, Italy, and Spain, cultural mediation raises issues of legitimacy and professional identity [46]. In those contexts where it is confined to the informal level and to the sole responsibility of nonprofessional volunteers, cultural mediation often lacks the minimum professional standards necessary for an appropriate and efficient treatment of a patient. It may generate partly or generally incorrect information (i.e., due to the lack of understanding of specific terminology), with potentially serious consequences on treatment decisions. Also, when formal mediation is not perceived and exercised as a systemic basic right, it tends to reproduce existing relations of power, not only between doctor and patient, but husband and wife, parents and children, or citizens and migrants.

5 An Original Way of Practicing Mediation in Healthcare: A Presentation of Centre Babel's Experience in Paris

Regardless of variations between national and ideological contexts, cultural mediation in healthcare settings raises common issues: the legitimacy of the mediator as a nonmedical professional and his/her capacity to access the medical jargon and make it intelligible to the patient.

In response, a Paris-based research team experimented an original mediation unit, composed of an interpreter/cultural mediator and of a doctor trained in transcultural care and leading the mediation session. The goal of this team unit is to resume the negotiation process and to allow the patient to have access to the medical model while asserting the validity of his/her own model. We thus managed, at the hospital, to have expert and lay discourses[4] dialogue without disqualifying one another [7].

When it was first established in 1998, the transcultural consultation offered a response to hospital professionals who face dead-end situations with immigrant patients suffering from chronic pain [8][4]. Progressively, the unit responded for all chronic conditions.

[4] This first consultation was initially set up by the IPAOS Health and Culture Association.

Relying on patients' own resources proved to be a powerful way to enhance healthcare provision. By substituting model sharing to prescription in the medical encounter, the mediation highlighted the fruitful complementarity between the physician's expertise and the patient's experience-based knowledge of his/her condition.

How this methodology be implemented in the treatment of cancer in tropical areas?

Let us take the example of French Guiana, where the linguistic and cultural diversity of the population is extremely rich: from Guiana creoles to Indian Natives, Bushinengués, people from the Caribbean, China, Laos, Lebanon, Brazil, Haiti, etc. Such diversity is often considered an obstacle in hospitals, as it creates cultural distance between patients and healthcare professionals.

In response to this difficulty, cross-cultural mediation experiences were established, often in the context of delivering a diagnosis or during treatment periods for long-term patients suffering from chronic conditions [2]. These cross-cultural mediators – who often share the same cultural origins as the patient's – work towards enhancing mutual understanding between patients and professionals. Considering this method has proven so useful, how could it be reinforced in the context of cancer specifically, in the interest of cancer patients and healthcare professionals?

First, it is crucial to be mindful of the limits of such interventions. Those were highlighted in a research conducted in Belgium on the impact of cultural mediators in hospitals [17]. The limits relate to mediators' legitimacy for intervening in a specific professional domain, to their lack of competence, and to the limits of their neutrality in case of a conflict.

Besides, if the cultural mediator is designated as a cultural expert, inevitably he/she becomes responsible for all patients coming from the same cultural community, with the risk of healthcare professionals disengaging from their own responsibilities towards specific categories of the population.

In order to avoid this, it is important to develop the cultural competences of all healthcare professionals – in parallel with the implementation of cultural mediation. As we stated earlier, the notion of cultural competence refers to a set of attitudes, knowledge, and professional experience that allow medical teams to provide quality care to patients from diverse social and cultural backgrounds. It consists in one's ability to interact with someone in the context of cultural diversity and to both identify and understand what is at stake in the confrontation of explanatory models as analyzed by anthropologists [27].

In that perspective, there should be a specific focus on healthcare professionals coming from the different communities residing in French Guiana. An ongoing research in the Paris area[5] seems to show that the cultural identity of healthcare professionals can be an asset to promote such competence in the interest of patients coming from the same community. In Guyana, those healthcare professionals may have cultural competences that incorporate knowledge of cultural representations

[5] Ongoing participatory action research project entitled "Developing transcultural competences for immigrant background healthcare practitioners" – leading investigators: Centre Babel and INSERM 669 – University Paris Descartes- sponsored by the Regional Health Agency (ARS-IDF).

and language skills and could strengthen mediation strategies. They could then be considered competent at two levels: at the technical level – as healthcare professionals – and at the cultural level – proving specific support to patients and their colleagues. Once again, it is important to underline that such competence is not innate, but must be acquired through training and must be supervised.

For such a project to be successful, it must not only be sponsored by the professional interested in acquiring new training, but also from the team he/she works with. This implies that chief administrators actively support the project. Finally, it implies recruitment policies that, beyond recognizing the technical competences of their employees, also strive to promote the same diversity as the one present in their patient population [42].

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Cancer Clinical Trials in the Tropical Area

Ian F. Tannock and Zeba Aziz

1 Introduction

New treatments for cancer are adopted ideally following the demonstration of their effectiveness to improve either duration or quality of survival in well-designed clinical trials. In tropical countries with limited resources, several factors limit the generation and application of evidence-based cancer treatment: (1) Most clinical research is carried out in developed countries (especially North America and Europe), and even for cancers that are common worldwide, the presence of genetic, environmental and socioeconomic differences may limit application of treatments to tropical countries. (2) The incidence and prevalence of cancers are different in tropical countries and in the developed countries of Europe and North America [3, 5], and there are proportionately fewer trials investigating treatments for cancers that are more common in tropical countries. (3) There are major logistic and financial limitations to both conducting clinical trials and applying their results to the populations of tropical countries. These factors are discussed in more detail below.

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2 Geographical Distribution of Clinical Trials for Cancer

We examined previously registries of clinical trials (most were listed in clinicaltrials.gov) to obtain a cross-sectional snapshot of the distribution of new cancer clinical trials that were registered between January and June 2008. We determined the type of cancer studied and the geographic location(s) of recruitment [6]. We sought correlations between the number of clinical trials and the incidence, prevalence and mortality of the cancers studied in different regions of the world (obtained from GLOBOCAN 2002, [5]). Among 399 newly registered trials, the most common types of cancer studied were breast (18 %), lung (14 %), prostate (11 %) and colorectal (7 %), all of which have high incidence and prevalence, especially in western countries. More than 80 % of trials recruited only from developed countries. Lethal cancers that are common in less developed regions, including stomach, liver and esophageal cancers, were underrepresented in clinical trials. We concluded that, with the exception of lung cancer, which is a global problem, drug development for cancer is focused predominantly on prevalent cancers of the developed world, which are the most important cause of cancer death there but not in tropical countries [6].

The above findings are consistent with those of Tas [8], who determined the geographical origins of clinical cancer research published in the meeting abstracts of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) and their journals, Journal of Clinical Oncology and Annals of Oncology, from 2000 to 2006. Overall, 96 % of published articles were from developed countries (North America, Europe, Australasia and Japan), with ~3 % from the rest of Asia, <0.5 % from South America and <0.1 % from Africa (with a slightly higher percentage of meeting abstracts from these regions). Thus, the sites of clinical cancer research are grossly out of proportion to the populations and cancer burden of less developed tropical countries.

Since the development of new cancer treatments is usually undertaken to generate a profit for commercial companies, rather than as a response to a public health problem, the above results are not surprising. More than 80 % of phase 3 clinical trials are now sponsored by pharmaceutical companies (henceforth ‘Pharma’), and such trials tend to be weighted towards treatment of cancers that are common in wealthy countries [6]. The trials are aimed at developing (and ultimately marketing) new drugs, and since new drugs are invariably given a price tag of the order of US$5,000 per month, they are irrelevant to the majority of the population of tropical countries; very few trials evaluate new uses for inexpensive older drugs or other non-patentable treatments that could be applied to a large proportion of people in a poor country.

3 Participation in Clinical Trials Designed for Developed Countries

The cost of developing a new drug for cancer has been estimated at close to US$1 billion; this huge cost is due to increasing bureaucracy and regulation, with diversion of funds to contract research organisations (CROs), and also because advances

in cancer treatment occur in small steps, so that very large randomised phase 3 trials (typically recruiting ~1,000 patients) are required to detect or rule out improvements in outcome that might be expected to occur. Understandably, Pharma wishes to reduce the costs associated with drug development and also to complete trials as quickly as possible, since they then have a longer time from approval to patent expiry to reap profits from marketing an active drug. Both of these factors can make it attractive for Pharma to recruit patients to large phase 3 trials from tropical countries: Investigators and institutions are paid less, and there is a large population of patients for whom participation in trials is a route to obtaining treatment (including control treatment) that would otherwise be unobtainable because of cost. This can therefore be a win-win-win situation for Pharma, doctors in tropical countries (who receive some funding) and their patients. However, regulatory authorities require that all drug registration trials meet requirements of so-called good clinical practice (GCP), and only a small proportion of institutions that treat cancer in tropical countries are able to develop the infrastructure to meet GCP requirements, including government approval to administer experimental therapy, a properly constituted Research Ethics Board and resources such as clinical trial assistants to ensure reliable collection of high-quality data. Breast, lung, colorectal and prostate cancers are common in the tropics as well as in developed countries and are becoming more common with increasing longevity. To give one example, recent papers published in New England Journal of Medicine describing practice-changing trials evaluating therapy for HER2-positive breast cancer have included sites from Central and South America and Asia, including countries with limited resources such as India and the Philippines; it is likely that some patients from these countries included in such trials would not have received anti-HER2 therapy without such participation.

Despite the advantages to the patients in poorer countries that benefit from inclusion in such Pharma-sponsored trials, they do not intellectually stimulate oncologists to develop their own indigent trials and data and may even discourage clinical research that is more relevant to tropical countries.

4 Clinical Trials in Tropical Regions

Given the limited resources in tropical regions, it is not surprising that few trials have been undertaken to address specific problems related to cancer, but there are notable exceptions. The most relevant studies, which might lead to change in practice, are large simple trials that do not require large amounts of data to be collected, and which use inexpensive drugs or other resources to answer locally relevant questions. An excellent example is the cluster randomised trial of screening for cervical cancer with acetic acid (vinegar) that was undertaken in ~150,000 women living in primitive conditions in Mumbai and which led to a 31 % reduction in mortality from this disease [7]; it is to the credit of the ASCO meeting that this study was selected for presentation at their plenary session in 2013.

Although less common than trials for cancers that are common in Western developed countries, a few large phase 3 trials have been performed largely in tropical countries to evaluate treatments for diseases that are common there, including

hepatocellular, esophageal, stomach and nasopharyngeal cancers. Many of these trials were organised in wealthier Asian countries such as China, Hong Kong, Japan, Korea and Taiwan, with some recruitment in less developed countries. There is substantial potential to increase recruitment to these trials by enlarging the number of participating Asian sites. A small number of phase 3 cancer trials have been led from South America, mainly from Brazil, but we were unable to identify cancer-specific trials from tropical parts of Africa.

5 Clinical Trial Organisations in Tropical Countries

Practice-changing phase 3 trials can only be performed by recruitment from institutions working in collaboration. Such cooperation can occur when institutions are invited by Pharma to participate in their trials, but that is only likely to happen in tropical countries if there is already infrastructure in place to ensure high-quality treatment and record keeping. Alternatively, institutions can become members of clinical trial groups, which can have multiple functions to stimulate clinical trials in their region, much as they do in developed countries: these functions include education (how to write a protocol and do trials), quality control (including site visits and central checks on data) and the ability to negotiate with companies (and potentially national health systems) to bring trials to a region.

Some cancer organisations that are active in tropical countries are listed in Table 1. Only the International Network for Cancer Treatment and Research (INCTR) and the Cancer Therapeutics Research group (CTRG) are involved in organising and running clinical trials, but the International Agency for Research on Cancer (IARC) undertakes epidemiological and prevention studies, and several organisations support courses to enable oncologists in developing countries to learn about clinical research. For example, the International Affairs Committee of ASCO runs International Clinical Trials Workshops (ICTW) in various countries and has a free web-based program on clinical research through ASCO University (http://university.asco.org/fundamentals-clinical-trials); together with other organisations, it also supports the Australia and Asia Pacific Clinical Research Development (ACORD) workshops, which provide training in clinical research methods to oncologists from the Asia-Pacific region. The authors of this chapter are contributors to these programs.

6 How to Stimulate Clinical Trials in Tropical Countries

There is a pressing need for clinical trials to address cancer prevention, diagnosis and treatment in tropical countries with limited resources. While Pharma might be attracted to recruiting patients from tropical countries to trials that address new treatments for common cancers, they are likely to profit from marketing new drugs

Table 1 Cancer organisations active in tropical countries

Organisation	Geographic location	Areas of interest	Website
International Network for Cancer Treatment and Research (INCTR)	HQ in Brussels Offices worldwide	Build capacity for cancer research and treatment in developing countries	www.inctr.org
Cancer Therapeutics Research Group (CTRG)	Singapore, Australia, Korea, Hong Kong, Taiwan	Drug development	www.ctrg.org
African Organisation for Research and Training in Cancer (AORTIC)	Africa	Promotion of cancer control in Africa	www.aortic-africa.org
American Society of Clinical Oncology (ASCO) International	Based in Virginia, USA	Wide range of initiatives to promote new research and cancer awareness	www.asco.org
International Agency for Research on Cancer (IARC)	Based in Lyon, France (part of the World Health Organisation)	To conduct research on causes of human cancer and mechanisms of carcinogenesis and to develop scientific strategies for cancer prevention and control	www.iarc.fr
Union for International Cancer Control (UICC)	Based in Geneva	To reduce the global cancer burden, to promote greater equity and to integrate cancer control into the world health and development agenda	www.uicc.org

only in wealthy developed countries and have, in general, refused to make any concessions in drug pricing to allow patients in poor countries to receive them, even in the face of strong evidence that they enhance survival, and regardless of whether some of that evidence came from participation of patients in tropical countries. That is unlikely to change, and governments of such countries are either unable or unwilling to support cancer clinical trials. So how can oncologists in tropical countries engage in clinical research to support the well-being of their patients?

There are no simple answers to the above questions, but some strategies are suggested below.

1. Education about the nature and requirements for clinical research is now easier to disseminate, both because of ready access to the internet and the educational outreach of organisations such as those listed in Table 1. Funding is available (although competitive) to allow young oncologists to participate in courses such as ACORD and other clinical trials workshops. This type of education should be encouraged.

2. Cancers that are common in tropical regions are common in some wealthier countries: for example, cancers that are common in poor countries throughout South-East Asia are also common in China (including Hong Kong) Japan, Singapore and Korea. There are resources in these countries to lead cancer clinical trials, and they should be encouraged to expand efforts to organise and provide base funding to allow recruitment from larger centres in neighbouring poorer countries and to form regional trial organisations. If such organisations can recruit from large populations and show good quality control, they will be attractive to Pharma. They might also raise sufficient resources to fund trials in the region that are relevant to local needs and are not profit-driven.
3. There is a substantial number of oncologists, originally from tropical countries, who trained in developed countries and then remain to pursue an academic career there. Some of them retain strong links with their country of origin and work in institutions that would like to develop links with poorer countries. These oncologists should be encouraged to stimulate pragmatic clinical research relevant to their home country and to mentor colleagues there in writing protocols and in conducting research. There might be advantages to oncologists that have emigrated to a developed country as well as to colleagues and cancer patients in their country of origin: they have access to peer-reviewed grants and could advance their academic profile by undertaking research that is unlikely to be performed by other oncologists without experience of cancer in tropical countries.
4. International organisations like ASCO and ESMO have increased international membership and initiatives as they seek to expand their spheres of influence. This should be encouraged, and these and other organisations with political clout (IARC, UICC, WHO) should lobby governments and Pharma to support organisations like ICTR, which undertake clinical trials in developing countries, and to support the establishment of new clinical trial centres.

7 Uptake of New Treatments

A final and major problem for tropical countries, which is discussed widely in this book, is that treatments shown to be of substantial benefit in pivotal clinical trials are not available to the vast majority of patients in poorer countries, because they are priced at a level that can only be met (and even there with difficulty) in wealthy developed countries. There needs to be concerted lobbying by cancer organisations for Pharma to price its drugs differentially, ideally in proportion to the average wage in each country. While one can understand the concern that cheaper drugs in poor countries will make their way to wealthy countries and undercut profits, there are ways of preventing or minimising such effects. There are a few examples of partnerships between Pharma and charitable foundations to assist patients in receiving important drugs, such as the Novartis Max Foundation International Patient Assistance Program to provide imatinib free of charge to eligible patients in developing countries (http://www.themaxfoundation.org/gipap/Default.aspx), but they

are quite rare. Making antiretroviral therapy available at an affordable price has done much to reduce the burden of HIV in tropical countries [1, 2, 4], and a similar approach is needed for drugs to treat cancer.

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Part II
Basic Science Background

The Spectrum of Infectious Disease-Related Cancers

Mathieu Nacher and Tristan Roué

Despite the epidemiologic transition shifting the burden from infectious diseases to chronic noncommunicable diseases, infections still remain a huge cause of morbidity and mortality in much of the tropical world. In addition to their acute and subacute complications, a number of infectious agents causing chronic infections also lead to a great burden in terms of cancer incidence, morbidity, and mortality. When considering all infectious causes of cancer together, they amount to the second most frequent cause of cancer, after tobacco. In sub-Saharan Africa, infections cause one third of all cancers [1, 2]. In developing countries, up to 25 % of cancers could be avoided by controlling these infections [3, 4].

The infectious agents most involved are viruses which cause the majority of infection-related cancer [5]. However, bacteria and, to a lesser extent, parasites also cause a significant number of cancers every year [1]. Finally, although this is not an infection per se, some fungal pathogens may secrete mycotoxins that may cause cancer [6].

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1 Viral Infections: A Major Cause of Cancer

Seven oncoviruses cause 10–15 % of human cancers worldwide, predominantly in tropical areas.

1.1 Human Papillomaviruses

The transmission of human papillomaviruses is mostly sexual but may entail hands or shared objects; perinatal transmission is also possible. Human papillomaviruses (HPV) cause 5.2 % of the cancer burden worldwide and 7.7 % in developing countries. HPV viruses mostly cause cervical cancer. HPV 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, and 66 can cause cervical cancer [7, 8]. HPV 16, mostly, and HPV 18 can also cause squamous cancers of the anus, penis, vulva, and vagina and cancers of the oropharynx. HPV in general causes all cervical cancer cases in the world (492,800 worldwide, 409,400 in developing countries), 3 % of oral cavity and 12 % of oropharyngeal cancer cases (8,800 in developing countries), 90 % of anal cancer cases (14,300 in developing countries), and 40 % of penile cancer cases (8,400 in developing countries) [2, 9].Vaccination against HPV 16 and 18 subtypes before entering sexual life could avoid about two third of all cases of cervical cancer. Unfortunately, it is still too expensive and logistically complex to implement for many tropical countries [4].

1.2 Hepatitis B

Transmission of hepatitis B (HBV) may occur through sexual contact, blood transfusions, contaminated needles and syringes, vertical transmission from mother to child during childbirth, and breast-feeding. HBV can also be transmitted between family members, possibly by contact of nonintact skin or mucous membrane with secretions or saliva containing HBV.

Hepatitis B viruses are globally responsible for 340,000 cases of hepatocarcinoma, 303,000 of which occur in developing countries, which represents nearly 60 % of all primary cancers of the liver [3, 10]. In developing countries, the prevalence of hepatitis B chronic infection is still very high in Africa and South East Asia, with up to 10 % of the population being chronically infected, which favors the transformation into hepatocarcinoma [3]. Routine mass vaccination with an anti HBV vaccine has been recommended since 1992. Early vaccination of newborns from chronically infected mothers could also have a great impact on preventing hepatitis B and 60 % of primary hepatocarcinoma notably in Africa and South East Asia.

1.3 Hepatitis C

The primary routes of transmission in the developing world are blood transfusions and unsafe medical procedures. Intravenous drug use is also an important source of infections. Infected mothers may transmit the virus during delivery in 3–10 % of cases and transmission is highest if the mother is coinfected with HIV.

Hepatitis C viruses are responsible for 25 % of hepatocarcinomas worldwide, reaching 40 % in Africa. In developing countries, hepatitis C causes an estimated 172,000 cases of hepatocarcinoma [3, 10]. Progress in the sterility of invasive medical procedures known to have been a source of HCV transmission in the past will lead to a decline in future age cohorts.

1.4 HIV and HHV8, EBV, HBV, HCV, and HPV

There are over 30 million of persons living with HIV throughout the world, most of whom are in sub-Saharan Africa. HIV is associated with an increased incidence of various cancers, notably in the most advanced stages of immunosuppression [1, 11]. Cervical cancer, non-Hodgkin lymphoma, and Kaposi's disease are AIDS-defining conditions. HHV8 virus is related to Kaposi's disease and Castleman's disease, notably among HIV-infected patients. The cancerous transformation involves increased replication of HHV8 as the immune suppression deepens. In 2002, the estimated incidence for developing countries was 62,500 cases, two third of which concerned males. Anal cancer due to HPV infection is greatly increased in HIV-infected men that have sex with men; notably after 15 years, it does not yet constitute an AIDS-defining infection [12].

In HIV-infected patients, lymphoma of the central nervous system and immunoblastic lymphoma are mostly also associated with EBV. A significant proportion of HIV-infected patients are also infected with HBV or HCV which also leads to an increased risk of liver cancer. HIV infection is also associated with several other cancers, such as squamous cell carcinoma in Africa, myeloma, anal cancer, and seminoma. The scaling up of the use of highly active antiretroviral therapy has dramatically decreased the incidence of AIDS-defining cancers, but the incidence of non-AIDS-defining cancers on the contrary increases [11].

1.5 HTLV1

Human T-cell leukemia virus 1 (HTLV1) is transmitted sexually, via breast-feeding and through blood transfusion. In 2–5 % of HTLV1 infections, the chronic infection is complicated with T-cell leukemia/lymphoma, notably when the infection was

acquired early from mother to child. The Caribbean, South and Central America, Melanesia, and Central Africa have the highest prevalence rates of HTLV1 infection. Overall, in tropical countries, there are close to 2,500 cases of HTLV1-related T-cell leukemia/lymphoma cases.

1.6 Epstein-Barr Virus

For Hodgkin lymphoma, in developing countries, an estimated 17,000 cases are attributed to EBV, with age variations in the cases attributable to EBV (80 % before 14 years of age, 20 % between 15 and 54, and 70 % after 54 years of age). The Epstein-Barr virus also causes non-Hodgkin lymphoma. In Africa, Burkitt lymphoma is strongly associated with EBV infection. Overall, around 6,000 yearly cases of Burkitt lymphoma are attributed to EBV [1].

Finally, EBV infection is also associated with most cases of nasopharyngeal cancers (78,100 estimated annual cases) which occur in Southern China, Southeast Asia, India, and North Africa.

1.7 Polyoma Virus

Recently, it was discovered that most Merkel cell carcinoma were due to the infection by a Merkel cell polyoma virus [13]. Merkel cell carcinoma mostly affects Caucasians 60 years of age, and ultraviolet radiation is a risk factor.

2 Bacterial Infections

Helicobacter pylori colonizes the stomach early in life, notably in countries where refrigeration and food hygiene are lacking. *H. pylori* has been classified as carcinogenic in 1994. It is causally related to gastric carcinoma and gastric lymphoma. The improvement of hygiene levels, the spread of refrigeration, the increased availability of fresh produce, a decreased reliance on salted and preserved foods, and increased availability of antibiotics that come with socioeconomic development have decreased *H. pylori* infections and ultimately reduced the burden of gastric cancer in countries with midlevel Human Development Index. However, *Helicobacter pylori* infection often concerns over 75 % of the persons living in the tropical areas. It is mostly causative of ulcers and chronic gastritis and when untreated may evolve toward gastric cancer. The risk of cancer that is attributable to *H. pylori* mostly affects the *antrum* or the *pylorus*, but not the *cardia*. The relative risk of developing gastric cancer for those having been infected for at least 10 years is increased by a factor 5.9 (95 % CI = 3.4–10.3). The attributable fraction for noncardia gastric cancers was 78 %

in developing countries and 74 % in developed countries. Overall, *H. pylori* causes 592,000 cases of gastric cancer, 63.4 % of all gastric cancers, and 5.5 % of all cancers, worldwide. In less developed countries, this amounts to 400,000 unusual cases [1, 9].

For gastric lymphoma, the relative risk increase is 6.3 (95 % CI = 2–19.9) in those infected by *H. pylori*. It is estimated that 79 % of cases are attributable to *H. pylori* in the developing world (a total of 5,900 cases) and 74 % in developed countries (for a total of 5,600 cases).

2.1 Tuberculosis or Pneumonia

Persons with a history of tuberculosis or pneumonia have an increased risk for lung cancer (relative risk 1.9 (95 % CI = 1.45–2.5) or 1.36 (95 % CI = 1.1–1.65), respectively) [14].

3 Parasitic Infections

3.1 Schistosomes

The most common way of getting schistosomiasis in developing countries is by wading or swimming in water where infested snails are present. *Schistosoma haematobium* causes a chronic bladder infection which is an important cause of squamous cell carcinoma of the bladder in Africa. *Schistosoma mansoni* in Africa and *S. japonicum* may lead to liver and colorectal cancer; the evidence is, however, more limited than for *S. haematobium*. Overall, *Schistosoma haematobium* infection increases the risk of bladder cancer fivefold, which amounts to a total annual number of cancer cases of 10600, or 3 % of all bladder cancers worldwide [1].

3.2 Liver Flukes

Opisthorchiasis is caused by the consumption of raw or undercooked fish infected by the metacercaria of liver flukes. Chronic infections by the liver flukes *Clonorchis sinensis* (Asia and Southeast Asia) and *Opisthorchis viverrini* (Southeast Asia), may lead to cholangiocarcinoma, a cancer of the bile ducts. Overall, an annual total of about 2,000 cases are attributable to liver flukes in tropical areas [1].

Although the bacteria *H. pylori* cause a very large number of cancers (27 % of all infection-related cancers), viruses are the main causes of infection-related cancers (72 %). Given the numerical importance of these cancers and their preventability, efforts must be sustained to roll back the burden of infection-related cancers (Fig. 1).

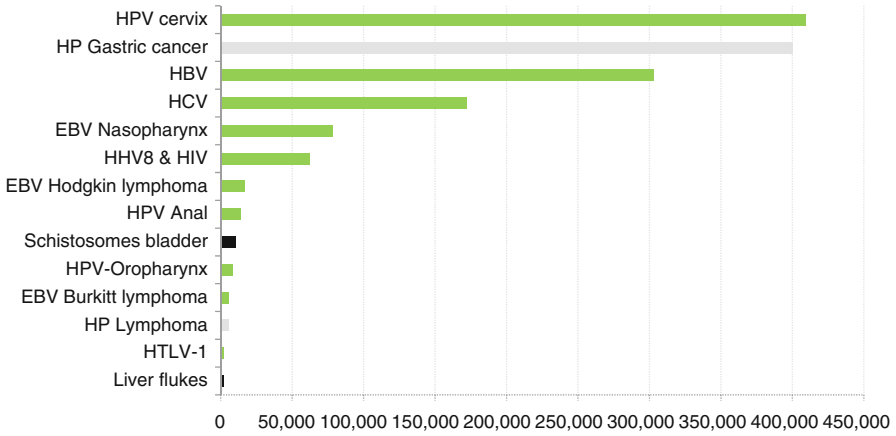

Fig. 1 Estimated number of cancer cases attributable to different infectious agent for the developing world in 2002

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Epidemiology and Mechanism of Carcinogenesis of the Retrovirus HIV

James J. Goedert and D. Cristina Stefan

1 Introduction

Human immunodeficiency virus (HIV) causes the acquired immunodeficiency syndrome (AIDS) by infecting and destroying, through both direct and indirect mechanisms, CD4+ T cells that orchestrate the body's immune response to particular viral, bacterial, fungal, and protozoan pathogens. Cancer risk is greatly increased for people who have advanced, HIV-related, immune deficiency. This risk increase primarily reflects failure to adequately control Kaposi sarcoma-associated herpes virus (KSHV, also known as human herpesvirus 8), Epstein-Barr virus (EBV), hepatitis C virus (HCV), and oncogenic types of human papillomavirus (HPV).

The mechanisms by which viruses may trigger cancers are not entirely elucidated, but either directly or indirectly, they alter the structure of cellular DNA or the expression of genes involved in the control of cell division. Viral oncogenes may be added to the cellular DNA, leading to excessive expression of the respective encoded proteins and consequent disturbance of cell multiplication. Other viruses may activate cellular oncogenes or inactivate tumor suppressor genes.

Cancer risk is also increased because of cigarette smoking and the diverse perturbations of immunity and inflammation that are commonly noted in people with HIV. This chapter reviews the basic epidemiology and pathogenesis of HIV infection and the major HIV-associated cancers that occur in adults.

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2 HIV Epidemiology and Pathogenesis

Most HIV transmission events occur during vaginal or anal intercourse. The virus also is readily transmitted from mother to infant during labor and delivery and less efficiently across the placenta during gestation and by breast feeding. Before blood and plasma donors were screened for HIV, transfusion accounted for many HIV infections. Parenteral drug users and health care workers continue to be at risk for injection-related HIV. HIV is not transmitted through intermediate vectors, such as insects, or through household or other casual contacts.

A simplified version of HIV's lifecycle is illustrated in Fig. 1. To achieve infection, HIV's envelope glycoproteins (gp120–gp41) must bind to both the CD4 molecule and to a coreceptor, most often CCR5, both of which are expressed on the surface of macrophage cells in the tissue. In the cytoplasm of the infected cell, HIV's RNA genome is reverse transcribed to make a DNA copy that is transported into the nucleus and integrated into the host genome. From this "provirus" genome, HIV uses host mechanisms to make viral proteins and an RNA copy of the viral genome that are exported to the cytoplasm, assembled at the cytoplasmic membrane, and budded out of the cell as virions to propagate new infections of other

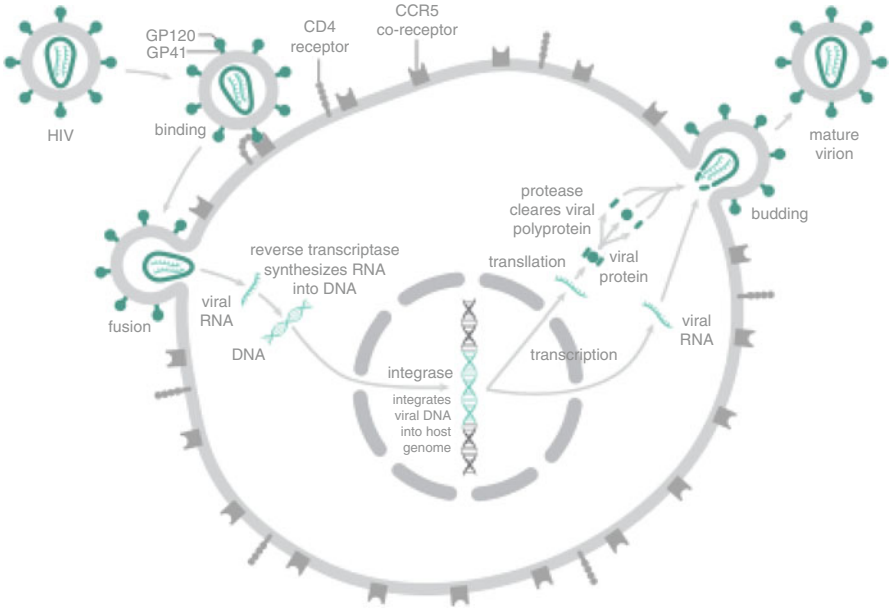

Fig. 1 Simplified life cycle of HIV. The viral envelope, gp120-gp41, attaches to CD4 and a chemokine coreceptor, usually CCR5, and then fuses with the cell membrane. The HIV RNA genome is released in the cytoplasm, where it is reverse transcribed to a DNA copy that is transported into the nucleus where it is integrated into the host genome as the HIV provirus. Expression of HIV genes yields copies of the viral proteins and RNA genome that are exported to the cytoplasm, assembled into virions at the cell membrane, and budded into daughter virions

cells or people. The infected cells die via several mechanisms and are replaced too slowly to avoid progressive immune deficiency.

Some of HIV's life cycle stages have been effectively targeted by the 2 dozen antiretroviral therapy (ART) drugs that are currently approved for the treatment of HIV, leading to partial recovery and markedly improved survival. However, because cells with integrated HIV proviral genome cannot yet be eradicated, treatment must be continuous and potentially lifelong.

It has been established that HIV is not able to induce malignant transformation, but promotes the effects of oncogenic viruses. This is achieved through compromising immune surveillance against infectious agents as well as against the cells displaying malignant characteristics. Another contribution is brought by the chronic hyperactivity of the immune system seen in the earlier stages of HIV infection. The excessive proliferation of the immune cells is coupled with an increased replication of the oncogenic viruses within those cells. Ineffective immune response could be the reason why other cancers, not related to infections, are encountered more often in people living with HIV [1].

3 Overview of Cancers in People with HIV

In most populations with HIV, cancer risk is dominated by Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL). Effective ART reduces the risk for KS and NHL and increases longevity, such that other malignancies emerge. The risk factors and mechanisms for the most important malignancies among adults with HIV are summarized below. Malignancies in children are covered in Chap. 53.

4 Kaposi Sarcoma (KS)

KS is a malignancy of poorly differentiated, reprogrammed lymphatic endothelial cells particularly in the dermis [2]. KS typically appears as one or more red or violaceous skin lesions. Progression can include skin lesions that are widely disseminated and occasionally massive, lymphatic lesions that can cause lymphedema, mucosal lesions particularly on the hard palate and conjunctivae, gastrointestinal lesions that may bleed, and hepatic and lung lesions that result in death.

KSHV infection is necessary, but not sufficient, for the development of KS. KSHV primarily infects B lymphocytes and also T lymphocytes, macrophages, and the endothelial cells that may emerge as KS. Like EBV, the other human gammaherpesvirus, KSHV is primarily transmitted by saliva, in which infected individuals have a high concentration of virions. Susceptible individuals have readily accessible B lymphocytes in crypts of the tonsils and Waldeyer's ring. In the latent phase of its life cycle, KSHV DNA persists as a circular episome in the nucleus, where it is copied and transmitted to daughter cells during mitosis. When

triggered into its lytic phase, the circular episome splits open and dozens of viral genes are transcribed resulting in multiple copies of the KSHV genome and proteins that are assembled into virions that kill the cell when they are released to propagate the infection. A simplified life cycle of the gammaherpesviruses, KSHV and EBV, is presented in Fig. 2.

A number of viral genes were identified, which may be responsible for the malignant transformation of the lymphatic endothelium induced by KSHV. Some of these have no correspondent in the target cells: K1, kaposin, and viral G protein-coupled receptor. Other viral genes generate proteins similar to those of human origin, thus deregulating the processes of cell multiplication and apoptosis. These viral genes include interleukins IL-6 and IL-10, CC-class chemokines, and the FLICE-inhibitory protein that blocks apoptosis. Two additional genes, latency-associated nuclear antigen (LANA) and K15, are involved in maintaining the persistence of the virus through the process of cell mitosis [3].

The prevalence of KSHV differs greatly between populations, being common in much of sub-Saharan Africa and in homosexual men in developed countries, rare in most of Asia, and intermediate in the Mediterranean region. The incidence of HIV-associated KS reflects these differences in KSHV prevalence.

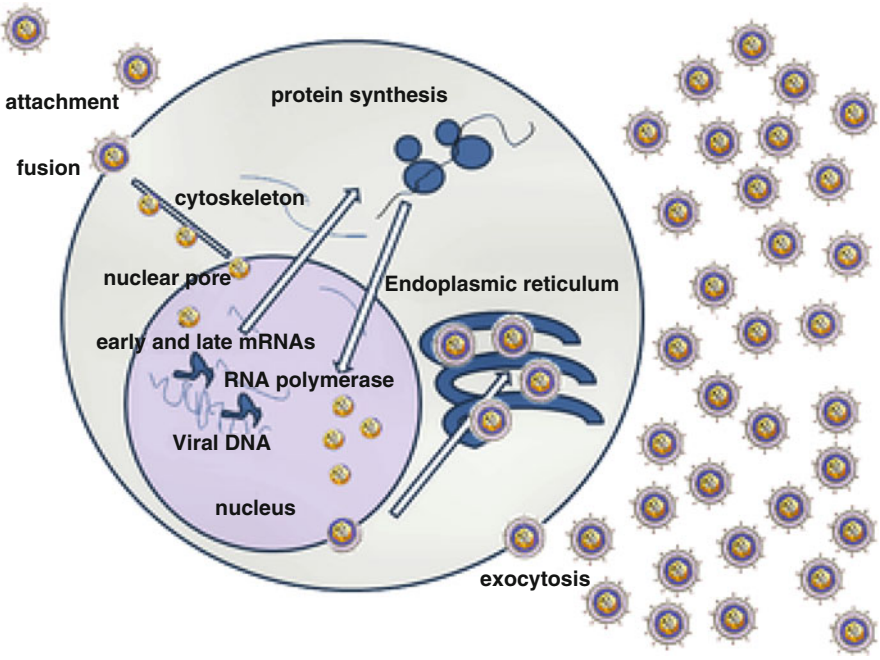

Fig. 2 Simplified life cycle of the gammaherpesviruses, KSHV and EBV. Virions are transmitted in saliva and primarily infect B lymphocytes in the tonsil. Following transit to germinal centers, viral DNA resides in the nucleus as an episome. During latency, few viral genes are expressed, but the viral genome is copied into daughter cells during mitosis. During the lytic phase, as illustrated, a cascade of viral genes is expressed resulting in release of daughter virions that kill the cell

Importantly, the risk for KS and its progression also are directly related to the severity of the immune deficiency, typically measured as the CD4 cell count in peripheral blood. Effective ART greatly reduces, but does not eliminate, the risk for developing KS. Effective ART also may be curative for early stage HIV-associated KS and improves the likelihood of response to chemotherapy for more advanced stages. Antiherpesvirus drugs have not been proven effective in preventing or treating KS.

5 Non-Hodgkin Lymphoma (NHL)

High-grade, aggressive NHL, especially diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), and Burkitt/Burkitt-like lymphoma are considered AIDS-defining among people with HIV. After KS, they have been the most common malignancies among people with AIDS.

Differences among these subtypes of AIDS-related NHL are noteworthy. PCNSL predominantly occurs with extreme immune deficiency (e.g., CD4 lymphocyte count <50/μL), is associated with very high mortality, and nearly always contains EBV in the malignant cells. Burkitt lymphoma can occur across the immune deficiency spectrum, even with CD4 lymphocyte count >500/μL and in people on effective ART [4]. Thirty to forty percent of AIDS-associated Burkitt lymphomas contain EBV. DLBCL is predominantly seen in people with a CD4 lymphocyte count <200/μL and may contain EBV in 30–80 % of cases [5].

Another, much less encountered NHL is the primary effusion lymphoma, characterized by a body serous cavity (pleura mostly) effusion as its main clinical sign. This malignancy appears in advanced AIDS and always contains KSHV, but EBV is also present in 80 % of cases. The mechanism of cooperation of the two viruses in the oncogenesis of the primary effusion lymphoma is not yet established [5].

The role of EBV in the pathogenesis of AIDS-related NHL is highlighted by a number of significant findings. EBV is one of the most widely spread viruses in humans, as it infects around 95 % of adults worldwide. As illustrated in Fig. 2, the lytic portion of the EBV life cycle can be triggered, leading to generation of daughter virions and infection of other susceptible cells or people. In contrast to the lytic cycle, for most of the time, EBV is present in latent form, mainly as a circular episome of DNA in the nucleus of B lymphocytes that replicates during cellular mitosis. Only a few viral genes are expressed during the latency phase, producing proteins that facilitate replication during mitosis but that also have the potential to support malignant transformation. EBV DNA also can be integrated into the host genome of malignant cells. The genetic lesions identified in EBV-infected malignant cells include c-myc gene rearrangement, bcl-6 gene rearrangement, ras gene mutations, and p53 mutations/deletions [3]. Three distinct patterns of viral gene expression have been identified during latency, each of them associated with different types of B-cell malignancies.

Perhaps the best understood oncogenetic process is the one which engenders the Burkitt lymphoma. The same genetic anomaly is present in all Burkitt tumors,

namely, a translocation that brings the c-myc oncogene from chromosome 8 to either chromosome 2, 14, or 22, next to genes participating in the synthesis of immunoglobulins (Ig). In its new locus, c-myc is copied without restrictions whenever the synthesis of Ig is triggered. It important to note that this event is random and, in fact, that the cells containing this defect would undergo apoptosis sooner than the normal ones. However, EBV-infected mutated cells live longer, and those containing a particular mutation in the EBV genome, even much longer. Since not all Burkitt lymphomas contain EBV genomes, other mechanisms to ensure the protection from apoptosis of the mutated B lymphocytes may exist. This sequence of events is thought to constitute the first step in the development of Burkitt lymphoma [5]. As discussed above (see HIV epidemiology and pathogenesis), the role played by HIV in this process is to indirectly increase the chance of a spontaneous c-myc gene move to a new locus. This is achieved by inducing a massive B-cell proliferation in the early stages of the infection.

6 Hodgkin Lymphoma

HIV-associated Hodgkin lymphoma behaves like an AIDS-related condition, although it does not meet surveillance criteria for AIDS. Differences between HIV-associated and general population Hodgkin lymphoma are noteworthy. HIV-associated Hodgkin lymphoma is usually widely disseminated at diagnosis, and the tumors almost always contain EBV. The histologic subtype is predominantly mixed cellularity or lymphocyte depleted, whereas nodular sclerosis subtype is distinctly uncommon with HIV. The highest risk for HIV-associated Hodgkin lymphoma, especially mixed cellularity, is with moderately severe immune deficiency, with CD4 lymphocyte count 100–200/μL [6, 7]. It is possible that some cases of severe lymphocyte-depleted Hodgkin lymphoma are mistakenly diagnosed as NHL.

While the mutations in the B lymphocyte leading ultimately to the development of Hodgkin lymphoma are different from those in Burkitt lymphoma, the roles played by HIV and EBV are thought to be similar in both malignancies [5].

7 Squamous Cervical and Anal Cancers

Persistent infection with oncogenic types of HPV is the underlying cause of these malignancies, but accumulating evidence points to an important contributory role for HIV. In the general population, HPV is a very frequent sexually transmitted infection. The prevalence of HPV in the US female population aged 14–59 years was 42.5 % for the period 2003–2006 [8]. A review of the literature on HPV prevalence among men in Europe found a lower figure, 12.4 %, but in high-risk men, it was around 2.5 times higher, at 30.9 % [9]. Prevalence rates as high as 92 % have been found in HIV-positive men having sex with men (MSM) in San Francisco [10].

HPV, a DNA virus, has over 120 genotypes identified so far, but most of these are not oncogenic and HPV genotypes 16 and 18 account for around 70 % of cervical cancers and a higher fraction of anal cancers. Oncogenesis requires insertion of the HPV genome into the host cell's DNA. A number of viral oncogenes have been identified; their mechanism of action is not entirely known. More specifically, three oncoproteins of viral origin, E5, E6, and E7, are responsible for interfering with cell multiplication controls. One such interference may be the inhibition of p53 protein with resulting suppression of apoptosis in the cells involved [11].

People with HIV are more likely to have prevalent anogenital HPV infection and, at least those with severe immune deficiency (CD4 lymphocyte count <200/μL), are less likely to clear an anogenital HPV infection compared to people without HPV [12, 13]. In the presence of HIV infection, the longer persistence of HPV increases the risk for squamous intraepithelial lesions of the uterine cervix. Incident HPV-related abnormal cervical cytology is less likely to occur and, if it does occur, more likely to resolve with the use of ART [14]. Compared to the general population, the incidence of invasive cervical cancer was nearly sixfold higher in women with AIDS [15], a portion of this excess related to the higher prevalence of HPV in women with HIV/AIDS. Likewise, compared to HIV-infected women with a CD4 count above 500 cells/μL, invasive cervical cancer was two- to threefold higher with a CD4 count of 200–499 cells/μL and 7.7-fold higher with a CD4 count <200 cells/μL [16].

Anal cancer is likewise an important morbidity for people with HIV, especially MSM. The incidence of anal cancer has been increasing in the general population, doubling over the past 30 years in the USA in both men and women [17]. On top of this increase, anal cancer incidence has been approximately 30-fold higher for people with AIDS [15]. The roles played by HPV and HIV in the pathogenesis of anal cancer are thought to be similar with their involvement in the cervical carcinoma.

The primary prevention of cervical carcinoma, and presumably of anal cancer too, is at present possible by means of HPV vaccination. Bivalent vaccines (against HPV 16 and 18) and quadrivalent ones (against HPV 16 and 18 and also HPV 6 and 11, known to produce genital warts) have been shown to prevent almost entirely the squamous intraepithelial lesions that precede invasive carcinoma [18, 19]. The population target of these vaccines, ideally, would be prepubertal and adolescent girls and boys. The immunization is safe and immunogenic in HIV-infected people too, as long as they still have the capability of producing a durable immune response [20].

The vast majority of the world's population is not vaccinated, though. The Papanicolaou (pap) smear, combined or not with detection of HPV DNA in samples of cervical cells, remains useful in revealing the intraepithelial squamous lesions, precursors of invasive cervical cancers which are present for years before invasion begins. Such precursors, once localized by colposcopy, can be resected or destroyed. Where pap smears or colposcopy cannot be performed due to lack of resources, a simple visual inspection of the cervix after application of 5 % acetic acid can reveal areas of intraepithelial neoplasia and guide their treatment as above. Due to the faster progression of intraepithelial neoplasia to invasion in women with HIV, pap smears should be repeated yearly, as opposed to 3 years for the general population.

With limited resources, this frequency may not be sustainable, but even offering three smears over a lifetime has the potential to halve the number of invasive cancers in the general population. Pap smears have not been evaluated for anal cancers. Here, as the disease is rare in the general population, only individuals at risk would require screening, which, at this time is possible only by anoscopy.

Lastly, it is noteworthy that the incidence of invasive cervical cancer with HIV, although it remains much higher than in the general population, decreased between 1996 and 2010 in the USA [21]. Whether this improvement reflects use of ART or improved cervical screening of women with HIV is unknown. No equivalent decline in anal cancer was observed [21].

8 Hepatocellular Carcinoma (HCC)

The current status of HCC with HIV was well reviewed by Sulkowski [22]. Irrespective of HIV, most cases of HCC are the result of chronic infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV). HBV infection affects about one-third of the planet's population, but only 6 % ultimately become chronic carriers, which nevertheless adds up to 350 million people. HCV infection is less widespread, involving about 3 % of the world's population, but the ratio of chronic infection is higher than for HBV, estimated at between 55 and 85 % of those contaminated. Chronic hepatitis C is gaining more importance in the etiology of HCC as hepatitis B is preventable by vaccination. Moreover, HCV is usually acquired, at least in the USA and Europe, in the same way as HIV, by transfusion of blood from unscreened donors or by needle-sharing among drug users. In these populations, about 16 % of HIV-positive people also carry HCV [23].

The mechanisms by which HBV and HCV produce cancer in the liver are not elucidated, but they may be different. HBV is a DNA virus and integrates its genome in that of the hepatocyte. In contrast, HCV is an RNA virus, but not a retrovirus and thus without a nuclear intermediate. Factors identified to contribute to oncogenesis by HCV are deregulation of cell cycle proteins, interference with p53 activity, and chronic inflammation.

HCV infection is more likely to persist indefinitely, with high levels of replication and viremia, in people who have also been infected with HIV. Such chronic HCV infection increases the risk for HCC. The contribution of HIV consists, on the one hand, in degrading the innate immunity of the host, which normally would play an important role in clearing HCV infection, by means of increased production of interferon-gamma. On the other hand, depletion of CD4+ T-cells by HIV reduces the antibody response to HCV and thus additionally facilitates the persistence of the latter. Further, a variant in the interferon λ-4 gene, while facilitating clearance of HCV infection, may paradoxically shorten the survival of HIV-infected individuals who receive ART [24–26]. HCC morbidity and especially mortality with dual HCV-HIV infection is very high [27, 28]. Newly developed direct-acting antiviral agents offer the hope that HCV can be effectively treated prior to progression to HCC, even with HIV coinfection [29–31].

9 Lung Cancer

After KS and NHL, lung cancer is the leading cause of cancer mortality for people with HIV [32, 33]. The risk of lung cancer is three times higher in HIV-positive people than in those who are HIV-negative [27, 34]. In both HIV-positive and HIV-negative individuals, the most important risk factor for lung cancer is smoking. Surprisingly, because HIV infection is often associated with high-risk behaviors, smoking prevalence and intensity did not differ by HIV status among injection drug users in the USA [35]. Thus, other HIV-associated factors probably contribute to oncogenesis, to the overrepresentation of non-small-cell lung cancer histology with HIV, and to the apparent acceleration of this malignancy with HIV [34, 36, 37].

Fundamentally, lung cancer arises from interactions of smoke-derived carcinogens and bronchopulmonary inflammation [32], and HIV may heighten these interactions. As noted above for liver and HPV-associated cancers, the incidence of lung cancer is higher with low CD4 count [38]. However, the use of ART does not appear to attenuate this risk [38]. Pulmonary infections, which occur frequently in people with HIV, may contribute to their excess of lung cancers [39, 40]. HIV has been associated with higher genomic instability in malignant tumor tissue [41], and higher rates of oncogene methylation with HIV have been postulated [42]. It also is possible that some individuals have an increased susceptibility to lung cancer due to genetic abnormalities, such as the identified mutations in the epidermal growth factor receptor gene or the fusion of EML4-ALK genes. This latter event results in a protein that facilitates the malignant behavior of cancer cells [43].

Screening heavy smokers in the general population with low-dose computed tomography can reduce lung cancer mortality by 20 % [44], but there are as yet no data to indicate the benefit of such surveillance for HIV-positive people. Smoking cessation is the only immediately available intervention, and interesting favorable trends have been noted in the USA [21].

10 Summary and Future Perspectives

Malignancies are and will continue to be major causes of morbidity and mortality for people with HIV and AIDS. This chapter has focused on the malignancies that currently impose the greatest burden. However, with increasing use and effectiveness of ART, other cancers are increasing in frequency as the HIV population grows and ages [21, 27]. This diversity presents challenges to the clinician caring for the patient with HIV.

Suppressing HIV replication with ART is paramount, because this reduces the risk of most of the malignancies discussed above and especially because AIDS continues to be the leading cause of death. For all HIV patients, and particularly those on effective ART, screening for early detection of breast cancer and cervical neoplasia can be lifesaving, as it is in the general population. For the patient who presents with symptoms or signs of possible malignancy, prompt evaluation can lead

to earlier diagnosis and better chance for cure. Guidelines are starting to emerge for combining ART with effective chemotherapy for NHL and Hodgkin lymphoma [45–48]. Care of the HIV patient who has other types of cancer requires substantial clinical acumen and judgment.

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Human T-Cell Leukemia Virus Type 1: Epidemiological Aspects

Antoine Gessain and Olivier Cassar

In 1980, R. Gallo's laboratory (National Institutes of Health, USA) reported the isolation of the human T-cell leukemia virus type 1 (HTLV-1). This was the first oncoretrovirus to be discovered in humans. HTLV-1 was present in the peripheral blood cells of an Afro-American patient suffering from a T lymphoproliferative disease, originally considered as a cutaneous T-cell lymphoma, with a leukemic phase [1]. The virus was thus named human T-cell leukemia/lymphoma virus (HTLV) (Fig. 1). Later, it was recognized that this cutaneous lymphoma was, in fact, an adult T-cell leukemia/lymphoma (ATL) case, a severe T-cell lymphoproliferation, originally described in Japan in 1977 by Takatsuki et al. [2]. The epidemiological characteristics of ATL in Japan strongly suggested an environmental factor, which prompted researchers to search for an oncogenic virus in the tumor cells. In 1981, a virus was isolated in Japan and termed adult T-cell leukemia/lymphoma virus (ATLV). Japanese and American scientists rapidly demonstrated that both isolates referred to the same virus and agreed to name it HTLV-1. In parallel, the causal association between ATL and HTLV-1 was established [3]. HTLV-1 infection was in 1985 also associated with a chronic neuromyelopathy, named tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM) [4], and later on with other clinical conditions including mainly uveitis, infective dermatitis, and myositis (Table 1) [5].

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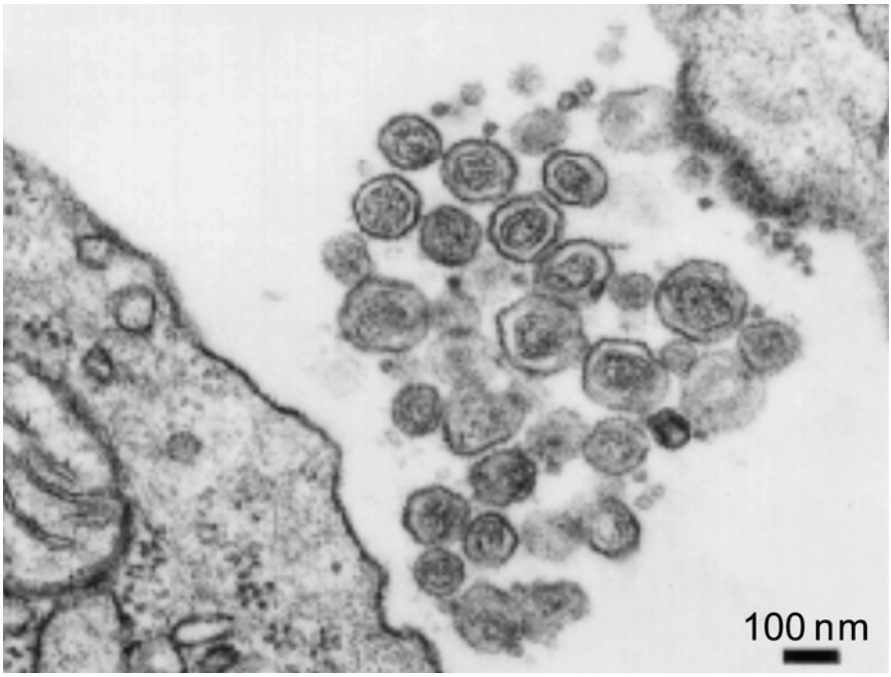

Fig. 1 Type C retroviral particles in the extracellular spaces of a CD4 + lymphoid cell line infected by HTLV-1. The cell line has been established from a long-term culture in presence of IL-2 of the peripheral blood lymphocytes obtained from a patient with a TSP/HAM. HTLV-1 is a deltaretrovirus. An HTLV-1 virion contains two copies of single-stranded genomic RNA. After viral entry into a host cell, the viral RNA is reverse transcribed, and the viral genome becomes integrated into the host cellular DNA as a provirus. This viral genome encodes the structural, enzymatic, and nonstructural regulatory (including Tax) and accessory proteins (including HBZ). Tax and HBZ proteins play a major role in the ATL development

1 Epidemiological Aspects of HTLV-1 Infection

HTLV-1, which is not a ubiquitous virus, is present throughout the world, with clusters of high endemicity located often nearby areas where the virus is nearly absent (Fig. 2). In these regions, the HTLV-1 seroprevalence in adults is estimated to be at least 1–2 %, but it can also reach 20–40 % in persons older than 50 years in some foci. The main very highly endemic areas are the southwestern part of the Japanese archipelago; parts of the Caribbean area and its surroundings regions; foci in South America including parts of Colombia, French Guiana, and Brazil; some areas of intertropical Africa (such as South Gabon); and of the Middle East (such as the Mashhad region in Iran) and isolated clusters in Australo-Melanesia. In Europe, only Romania seems to represent an endemic region for HTLV-1 [5–8]. The origin of this puzzling geographical or rather ethnic repartition is not well understood but is probably linked to a founder effect in some groups, followed by the persistence of a high viral transmission rate due to favorable environmental and cultural local

Table 1 Main diseases associated with HTLV-1 infection

Diseases	Association
Adulthood	
Adult T-cell leukemia/lymphoma (ATL)	++++
Tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM)	++++
Intermediate uveitis (Japan/Caribbean)	+++
Myositis (polymyositis and SIBM)	+++
Infective dermatitis (very rare)	+++
HTLV-1-associated arthritis (Japan)	++
Bronchiectasis – (Central Australia)	++
Childhood	
Infective dermatitis (Jamaica/Brazil/Africa)	++++
TSP/HAM (very rare)	++++
ATL (very rare)	++++

The strength of association is based on epidemiological studies as well as molecular data, animal models, and intervention trials. ++++ proven association, +++ probable association, ++ likely association, + possible association. *SIBM* sporadic inclusion body myositis

Fig. 2 Map of the geographical distribution of HTLV-1 based on recent estimates of the number of HTLV-1 infected carriers among approximately 1.5 billion of individuals from known endemic areas and reliable epidemiological data obtained from studies including pregnant women and/or blood donors and/or different adult populations. Correct estimates in other highly populated regions, such as China, India, the Maghreb, and East Africa, are currently not possible. Thus, the current number of 5–10 million HTLV-1 carriers is very probably much higher

situations [9]. Interestingly and despite different socioeconomic and cultural environments, HTLV-1 seroprevalence increases gradually with age, especially among women in all the highly endemic areas. This might either be due to an accumulation of sexual exposures with age or to a cohort effect [5–8].

Three modes of transmission have been demonstrated for HTLV-1: (1) mother-to-child transmission, which is mainly linked to a prolonged breast-feeding after 6 months of age. Ten to 25 % of the breast-fed children born from HTLV-1 infected mothers will become infected. High level of HTLV-1 proviral load in milk and in blood cells as well as high HTLV-1 antibody titers in the serum and long duration of breast-feeding (at least >6 months) represent major risk factors for HTLV-1 transmission from mother to child [10, 11]; (2) sexual transmission, which mainly, but not exclusively, occurs from male to female and is thought to be responsible for the increased seroprevalence with age in women [12]; and (3) transmission with contaminated blood products (containing HTLV-1 infected lymphocytes), which is responsible for an acquired HTLV-1 infection among 15–60 % of the blood recipients [13].

It is difficult to precisely appreciate the number of HTLV-1-infected persons throughout the world (Fig. 2). However, in Japan, the number of healthy carriers reaches probably more than one million and Africa is considered to be the largest endemic area with few millions of infected persons. Our best recent world estimates range from 5 to 10 million HTLV-1-infected individuals [6]. Importantly, these results are based on only approximately 1.5 billion of individuals originating from known HTLV-1 endemic areas. Correct estimates in other highly populated regions such as China, India, the Maghreb, and East Africa are currently very difficult; thus, the number of HTLV-1 carriers is very probably higher (for review of HTLV-1 epidemiology, see [5–8]).

2 Epidemiological Aspects of Adult T-Cell Leukemia/Lymphoma

Large series of ATL patients have now been reported in several HTLV-1 endemic areas including Japan [14, 15], several of the Caribbean islands (especially Jamaica, Trinidad, Martinique) [16], numerous countries of South and Central America (Brazil, Peru, Colombia, French Guiana) [17–19], and Iran as well as in immigrants originating from high HTLV-1 endemic areas living in Europe (mainly in France and UK) [20, 21] and in the USA. Sporadic cases of ATL have also been described in Australo-Melanesia [22, 23]; North, West, and South African countries [24]; and Romania [25]. Studies performed especially in Brazil, some African countries, and French Guiana concluded that ATL prevalence is usually underestimated until a specific disease research is performed. This is due to several factors including, among others, the difficulty of diagnosis in some chronic and smoldering cases and the very rapid evolution in some acute leukemia and lymphoma cases [18]. In addition, laboratory tests, such as HTLV-1 Western blot, and molecular investigations as polymerase chain reaction (PCR), clonality, and also cellular immunophenotyping and histological markers are not easily available in some tropical areas, especially in African countries.

ATL occurs mostly in adults at least 20/30 years after the HTLV-1 infection. The age at onset differs according to geographical areas, with an average age in Central and South America and the Caribbean area being around 40 years, while it is around

60 years in Japan [14, 26]. ATL occurs mostly in persons infected in childhood by prolonged breast-feeding. HTLV-1 infected male carriers have about three- to fivefold higher risk of developing ATL than female. To give an example, in Japan, where the situation is the best known, nearly 1,000 new cases of ATL are diagnosed and nearly 1,000 patients die of ATL each year over a period of 20 years. The annual incidence among HTLV-1 carriers is approximately 60/100,000 with an estimated lifetime risk of 6–7 % for men and 2–3 % for female. Prevalence and incidence of ATL are less known in the other high HTLV-1 endemic areas (for review see [14]). For TSP/HAM, the lifetime risk among HTLV-1 carriers is estimated to be around 0.25–3 %, (i.e., lower than ATL). TSP/HAM mainly occurs in adults, with a mean age at onset of 40–50 years [27]. In contrast to ATL (male/female ratio = 1.4), TSP/HAM is more common in women than in men, with a sex ratio of 0.4. Blood transfusion is a major risk factor for TSP/HAM development. The coincidence of ATL and TSP/HAM has been rarely reported. Two to 10 % of the infected persons will develop an HTLV-1-associated disease (ATL, TSP/HAM, uveitis, infective dermatitis) during their life (Table 1).

3 Molecular Epidemiology of HTLV-1: Existence of Geographical Subtypes

On a molecular point of view, HTLV-1 possesses a remarkable genetic stability, an unusual feature for a retrovirus. Viral amplification via clonal expansion of infected cells, rather than by reverse transcription, is probably the main reason for this striking genetic stability. The low sequence variation of HTLV-1 can be used as a molecular tool to follow the migrations of infected populations in the recent or distant past and thus to gain new insights into the origin, evolution, and modes of dissemination of such retroviruses and of their hosts [28]. The few nucleotide substitutions observed among virus strains are indeed specific to the geographic origin of the patients rather than the pathology. Four major geographic subtypes (genotypes) have been reported. They include the cosmopolitan subtype A, the Central African subtype B, the Central African/Pygmies subtype D, and the Australo-Melanesian subtype C. A limited number of strains found in Central Africa belong to other rare subtypes (E, F, G) [6–8]. The cosmopolitan subtype A, which comprised several geographical subgroups (Japanese, West African, North African, etc.), is the most widespread, being endemic in Japan, the Caribbean area, Central and South America, North and West Africa, as well as part of the Middle East. The sequence variability within subtype A is very low. This is very likely to reflect a recent dissemination (some centuries) of this genotype from a common ancestor. The Australo-Melanesian subtype C is the most divergent when compared to the reference strain (ATK). This result reflects a long period of evolution in isolated populations living in different islands of the Pacific area [29]. The appearance of these HTLV-1 subtypes in humans was demonstrated to be linked to interspecies transmission between STLV-1 infected monkeys and humans, followed by variable period of evolution in the human host. Indeed, STLV-1, the simian counterpart of

HTLV-1, infects several species of nonhuman primates (NHPs) of the Old World, ranging from chimpanzees and gorillas to mandrills, as well as several African small monkey species and a wide range of macaques. Such interspecies transmission is still ongoing at least in Central African hunters [30, 31]. Interestingly, STLV-1 infection was also associated to the development of ATL in some NHPs [32]. There is so far no strong evidence that either a particular specific mutation or a genotype is associated with the development of a TSP/HAM or an ATL in an asymptomatic carrier.

4 Diagnosis Methods for HTLV-1 Infection

On a practical point of view, the diagnosis of HTLV-1 infection is based on the demonstration of a HTLV-1 positive serology. The screening test is mainly an ELISA and several commercial assays are available. Particle agglutination (PA) or immunofluorescence (IF) can also be used. The confirmation assay is mainly a Western blot (WB), but Innogenetics line immunoassay (INNO-LIA) is also used. The results can be negative, indeterminate (frequent in tropical area – for review see [33]), or positive. Strict diagnosis criteria (complete pattern) should be applied for positive results. A positive serology by WB or INNO-LIA demonstrates the presence of antibodies directed against the major HTLV-1 (gag and env) proteins in the sera/plasma of the tested person. Serial dilution by PA or IF allows the determination of the HTLV-1 antibody titers. PCR can be used to demonstrate the presence of HTLV-1 provirus in the peripheral blood cell DNA. Using different primer sets, PCR is also useful to differentiate HTLV-1 from HTLV-2 infection. Determination of the proviral load can be done by quantitative PCR. Amplified products can be sequenced allowing genotyping. Several methods (Southern blotting, inverse PCR, deep sequencing) can be used in specialized laboratory to demonstrate the clonality of HTLV-1 integration in ATL tumor cell DNA, either in leukemic cells (in a case of acute leukemia form) or in the lymph node (in a lymphoma form) but also in cutaneous tumor lesions.

5 Infective Dermatitis

HTLV-1 associated infective dermatitis (IDH) is a unique clinical entity mainly characterized by a chronic and severe exudative dermatitis involving mainly the scalp, external ear and retro-auricular areas, eyelid margins, paranasal skin, neck, axillae, and groin. A generalized fine papular rash is common in most of the severe cases. In infective dermatitis, positive cultures for *Staphylococcus aureus* and/or B-hemolytic streptococci are frequent from the anterior nares and skin samples. The evolution is typically chronic with relapse and several flares of superinfected lesions. Infective dermatitis responds well to antibiotic treatment, especially co-trimoxazole. However, relapse is very common if antibiotics are withdrawn. Infective

dermatitis occurs mainly in young children (range 1–12 years). Pathological examination revealed a mild inflammatory lymphocytic infiltration in the dermis and epidermis. Epidemiological studies with long-term follow-up of IDH patients have indicated that such disease may be associated with the latter development of ATL or TSP/HAM. In the great majority of cases, IDH has been reported in children from low socioeconomic backgrounds in West Indies, Brazil, and Africa.

6 Prevention of HTLV-1 Infection and ATL

Reduction of HTLV-1 transmission from mother to child is crucial to prevent the occurrence of ATL and IDH. Such preventive programs, currently performed in several areas of high HTLV-1 endemicity (as Japan, countries of the West Indies, and Brazil, etc.), are based on HTLV-1 screening programs during pregnancy followed by an adequate counseling that is adapted to the socioeconomic situation of each infected mother. Furthermore, prevention of HTLV-1 infection transmission through blood donor screening is necessary in high-HTLV-1 endemic areas [34].

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Epidemiology and Mechanism of Carcinogenesis of the Virus HBV

Natali Abeywickrama Samarakoon and Paul Dény

1 Epidemiology

Hepatocellular carcinoma (HCC) is the leading form of primary tumors of the liver (90 %). According to Globocan 2012 from the International Agency Research on Cancer (http://globocan.iarc.fr/Default.aspx), liver cancer is the fifth most common cancer in men (554,000 cases) and the ninth in women (228,000 cases) corresponding to 7.5 and 3.4 % of total of human cancers (excluding nonmelanoma skin cancer). Liver cancer is a high problem in the developing regions where 83 % of the estimated new liver cancer cases occurred in 2012 with a high incidence from China (50 %). Associated with a poor prognosis, liver cancer is the second most common cause of death from cancer on earth, responsible for approximately 750,000 deaths in 2012 (9.1 % of total death due to cancer). Indeed, the overall ratio of mortality to incidence is 0.95. HCC rates are very high in Eastern/South-Eastern Asia and sub-Saharan Africa where the endemic of hepatitis B virus (HBV) is the highest (Fig. 1a).

Indeed, HBV endemic has been linked to HCC, and it is well known from the prospective work of Beasley from 22,707 Taiwanese patients followed for 11.25 years [1] that there is an excess risk of dying of liver cancer among hepatitis B surface antigen (HBsAg) carriers compared to non-carrier (relative risk = 217). Furthermore, it has been very well sustained that the risk of chronic HBV carriage

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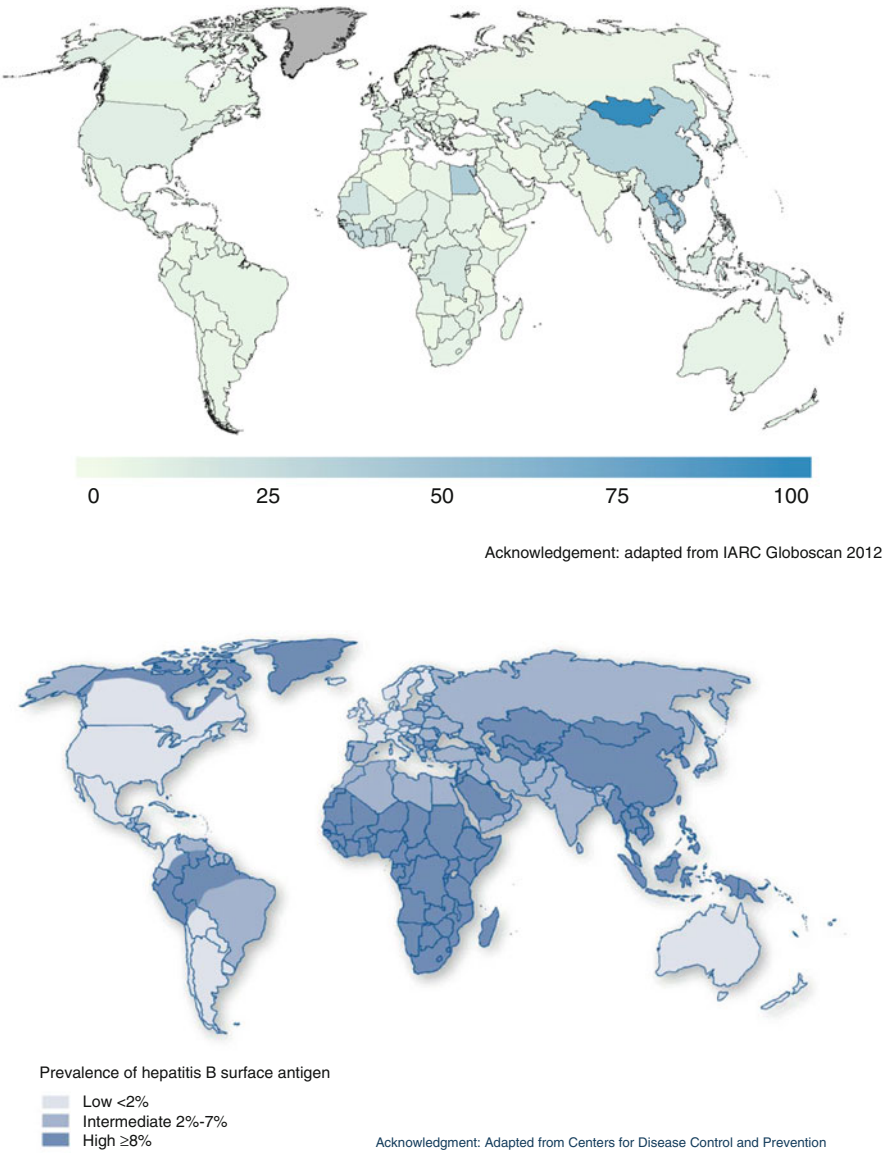

Fig. 1 Comparison of liver cancer incidence in 2012 (Acknowledgment: adapted from IARC Globocan 2012) (**a**) and HBV chronic carriage prevalence in 2006 (Acknowledgment: adapted from Center for Disease Control and Prevention 2012) (**b**). Note that with the exception of Egypt due to a very high rate of HCV infection, liver cancer incidence in 2012 is higher in regions where HBV prevalence was high in 2006. See text for details in Mongolia and Laos

is the highest (up to 90 %) when the patient is infected at birth or during early childhood, whereas this risk is more in the range of 5–10 % when infected during adult life. Therefore, offspring when infected at birth from an HBV-infected mother are more susceptible to developing HCC in the future. Of particular interest in Taiwan is the fact that when a mass vaccination program against HBV to immunize

newborn infants was implemented in 1984, the hepatitis B carrier rate in children covered by the program decreased from 15 to <1 % 20 years after. Most importantly, hepatocellular carcinoma in the vaccinees was also found to decrease in parallel. This is the first example that a human cancer might be prevented by a vaccination against its virally associated etiology.

This HBV transmission prevention by vaccination will profit to young new generation. Today, considering the still high number of chronic HBV carriers ($n = 240{,}000{,}000$), and due to the poor prognosis of HCC, deciphering the mechanism of HBV-associated cancer liver development is mandatory. If HBV infection by itself is an important risk factor, complex interactions between HBV viral elements and multiple host and environmental factors influence HCC. For example, hepatitis C virus (HCV) (see chapter "Hepatitis virus scientific background: Epidemiology and mechanism of carcinogenesis of hepatitis C virus (HCV)") or hepatitis delta virus (HDV) [2] coinfections; exposure to aflatoxin B1 (AFB1) [3, 4]; alcohol and tobacco consumption; and metabolic diseases, such as nonalcoholic steatosis hepatitis (NASH) [5] and diabetes [6], might also be taken into consideration for cofactors or comorbidities implicated in liver carcinogenesis.

2 The HBV Natural History May Induce Chronic Inflammatory Infection

Hepatitis B virus primary infection may be asymptomatic or may cause an acute illness with symptoms including jaundice, dark urine, fatigue, and digestive-associated complaints. Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia (≥8 %, see Fig. 1b), where transmission from generation to generation occurs. High rates of chronic infections are also found in the Amazon and the southern parts of Eastern and Central Europe. In the Middle East and the Indian subcontinent, an estimated 2–5 % of the general population is chronically infected, whereas <1 % of the population in Western Europe and North America is chronically infected (Fig. 1b). What had been noted for a long time is that the liver cancer incidence is higher in areas with high HBV prevalence (see Fig. 1).

In individuals chronically infected by HBV, the need for efficient antiviral therapy remains clear when a viral replication is observed to control the risk of progression and delay liver transplantation, which represents the only end-stage treatment. Indeed, patients having advanced chronic hepatitis B (CHB) can now be successfully treated using nucleos(t)ide analogs (NA) or pegylated interferon (PEG-IFN). Therefore, beside vaccination, prevention of the progression of the disease to cirrhosis and liver decompensation, leading to end-stage liver disease and/or to hepatocellular carcinoma, by inhibiting viral replication, represents a logical approach to improve survival.

During chronic infection, liver regeneration (renewal of the pool of cell) and architecture reconstruction (due to stimulation of stellate cells) will lead to activation of cell cycle and fibrogenesis, respectively (Fig. 2). Collagen scar tissue, in response to liver injury, may lead to nodular reconstruction pattern of fibrosis, progressively interrupting the normal communication between portal space and subhepatic venous

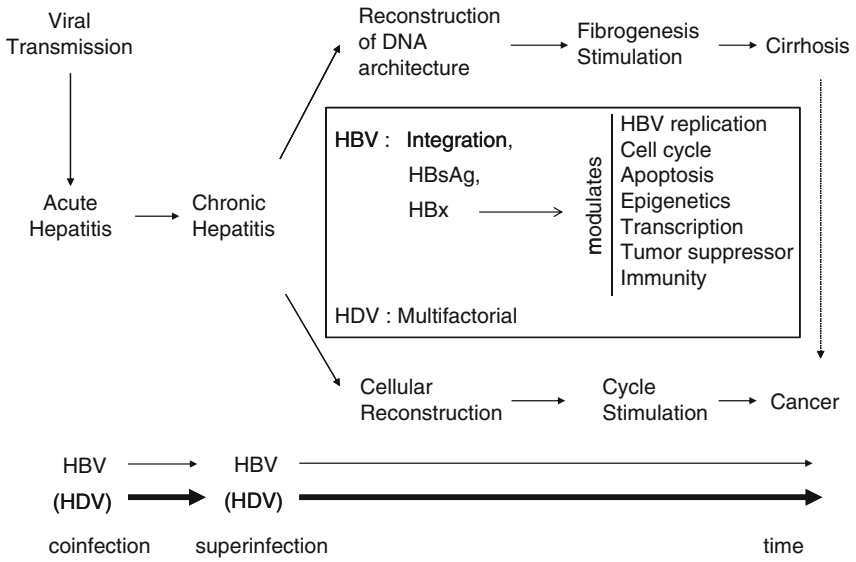

Fig. 2 After HBV transmission, infection leads to chronicity especially in neonates (90 %) and in adults (5–10 %). Due to liver inflammation, both liver fibrosis and cell regeneration are stimulated leading to cirrhosis and cell proliferation. Cirrhosis is by itself a precancerous state. In the square are simplified possible viral-induced mechanisms of hepatocarcinogenesis

circulation leading to liver cirrhosis. This advanced state of nodular fibrosis is often present in the West countries before the emergence of HCC and corresponds to a risk factor by itself. In a Western series of 30 patients without cirrhosis, all patients had some non-tumorous pathological changes such as iron overload and large cell dysplasia in their liver [7]. In contrast, in developing countries, cirrhosis is typically overshadowed by the signs of the tumor, unfortunately when it has reached an advanced stage. Indeed, analyzing 14 trials (six Asian and eight non-Asian) [8], Hsu and coworkers found that median survival rate of HCC reflecting natural history was 3.57 ± 1.88 month in Asian trials versus 5.96 ± 1.46 in non-Asian trials.

3 The Hepatitis B Virus

Both HBV and hepatitis delta virus (HDV) use heparan sulfate membrane-anchored molecules and the Na taurocholate cotransporting polypeptide (NTCP) receptor to infect hepatocytes [9, 10]; L-HBsAg protein, coded by HBV PreS1/PreS2/S gene, is required for infection. The replication of the two viral genomes is fully independent in the nucleus of the cell. HBV DNA genome replicates through an RNA intermediate depending on its own viral polymerase having a reverse transcriptase activity, which is the step that will be inhibited by nucleoside/nucleotide analogs. Even under this therapy, the HBV DNA genome will persist as an episome in the nucleus of the infected cell. HBV genome can also integrate into the cellular genome (*see below*).

During viral replication, the intracytoplasmic reverse transcription step of the viral polymerase introduces errors that are not corrected due to the lack of a 3′→5′ exonuclease activity leading to mutations. In a chronically infected patient, more than 10E11 viral particles are produced per day, and viral polymerase introduces non-corrected errors every 10E4 to 10E5 nucleotides. Viral load and punctual mutations might also be involved in HCC. For example, the REVEAL study indicated clearly that the serum HBV DNA level is significantly and independently associated with incidence of HCC. In addition, viral genetic features such as core promotor mutations A1762T/G1764A mutant or precore G1896A were documented as predictor of HCC risk [11].

Eight different genotypes, A to H, have been described. Recently, a ninth "genotype" evidenced in North-West China, India, Laos, and Vietnam and tentatively termed "I" was suggested, although it is still subject to debate, as being a recombinant strain having a genotype C backbone. Finally, a tenth genotype provisionally assigned to genotype "J" was proposed for a Japanese patient's HBV isolate.

Genotype-specific HBV genomes have sizes ranging from 3,182 nt (HBV/D) to 3,248 nt (HBV/G). This has consequences on the size of the viral proteins. Genotypes and subgenotypes might also be associated to specific geographic distributions reflecting ancient evolution. However, associated to human migrations, this picture may evolve. Furthermore, in some specific area, the recombinant strain represents the dominant variant such as the HBV/CD recombinant in Tibet [12]. Indeed, high endemy and coexistence of different genotypes in borders will favor a recombination process such as the recently described HBV/DE recombinant in Niger and India [13, 14].

Whether or not a specific viral genotype/subgenotype is linked to a specific pathogenic power or treatment sensitivity is a field of active research. However, there are still conflicting results. In addition, emerging strains might take benefit of the possibility of recombination to acquire resistance to the only available antiviral class of drugs or to escape from vaccine. Another important point relies on the fact that 78 % of chronic carriers live in Asia. This high percentage might by itself contribute to a high number of severe cases in this part of the world where genotype B and C are predominant. In the countries where genotypes A and D coexist, it has been suggested that patients infected by genotype A might evolve more rapidly during chronic infection than those infected with genotype D. Furthermore, different studies seem to sustain that patients infected with genotype C would progress to cirrhosis and liver cancer earlier than those infected by genotype B at the age of 30; however, at the age of 45 years, the same proportion of patients had been evolving to cirrhosis and liver cancer whatever the genotype was [15]. Other studies in the Amazonian basin indicated that the F genotype was frequently associated to severe acute hepatitis. In such cases, most of hospitalized patients were co- or superinfected by the hepatitis delta virus genotype 3 (HDV-3).

In contrast, several authors have found no link between HBV genotypes and the severity of hepatitis. For example, a study conducted in Uzbekistan didn't demonstrate any difference of the severity of the liver histology between infections by HBV genotype D and A. Another recent study considering all case of liver damage (asymptomatic HBsAg carriers, acute or chronic hepatitis, cirrhosis, and hepatocellular carcinoma) also found no concrete link between genotype A or D and the

severity of the hepatitis or response to treatment [38]. In summary, if there is not yet enough clear data to attribute to a specific genotype a clear predictive severity value, there is increasing evidence that in Asia, genotype C might be more frequently associated to HCC than genotype B. It is also important to evaluate these genotypes in function of the therapeutic response as this could represent predictive criteria. In a trial of PEG-IFN, patients infected with genotypes A and B had a higher rate of HBeAg loss (about 45 %) as compared to patients infected with genotype C or D (about 26 %).

4 Role of the HBx Protein

HBV encodes a small regulatory protein known as the HBx protein that stimulates HBV viral transcription and replication. HBx is a small polypeptide of 154 amino acids (16.5 kDa) encoded by the X gene which is highly conserved among mammalian hepadnaviruses. Designed as a probable "viral oncoprotein," HBx favors HBV virus replication by exerting pleiotropic activities, such as destabilization of orderly cellular functions of cell cycle regulation, deregulation of different signaling pathways and DNA repair. Accumulation of such dysfunctions and alterations in cells may lead to viral persistence and hepatocarcinogenesis. In fact, during natural HBV infection, HBx is essential to initiate and maintain HBV [16]. In spite of HBx low expression levels both in acute and chronic infections, HBx induces humoral and cellular immune responses [17].

4.1 Epigenetic Modifications of Cellular Genes Due to HBx Protein

Many etiological forms of HCC focus on alterations that may take place at an epigenetic level [18]. Changes such as DNA methylation, histone modifications, and RNA-mediated gene silencing are largely responsible for HCC which lead to inactivation of tumor suppressor genes or chromosomal instability [19].

4.1.1 Modification of Gene Methylation

HBx acts as transactivator to activate its own promoter. Although considered as a weak transactivator, HBx is capable of activating a large number of cellular promoters. HBx is known to significantly increase the expression of genes by hypomethylating gene promoters of tumor-promoting genes. Such genes are retinal dehydrogenase 1, plasma retinol-binding protein precursor, and cellular retinol-binding protein I [20].

As demonstrated by chromatin immunoprecipitation analysis, HBx cannot bind directly to promoters of target genes.

However, the ability of HBx to transactivate a large number of cellular promoters can be explained by the direct interaction of HBx with DNMT3A (DNA methyltransferase 3A). In 2009, it was put into evidence that the expression of CDH6 and IGFBP3 was upregulated by the removal of DNMT3A from these promoters via the HBx-DNMT3A interaction [21]. Moreover, in the presence of HBx, the expression of DNMT1 and DNMT3A was also revealed to be upregulated. DNMT1 and DNMT3A are both responsible for the hypermethylation of gene promoters, implied in tumor suppression followed by gene silencing. The p16INK4A gene that regulates the cell cycle negatively undergoes such aberrant hypermethylation of CpG islands in the presence of HBx [22].

Contrary to the potential of HBx to transactivate genes, HBx is also capable of silencing the transcription of interleukin-4 receptor and metallothionein-1 F by recruiting DNMT3A to their regulatory promoters. This recruitment was shown to be responsible for de novo DNA methylation of these promoters that results in gene silencing [21].

These subtle mechanisms could portray a key role in HBx-induced HCC via cellular epigenetic modulations.

4.1.2 Histone Remodeling in the Context of HBx Protein

Aberrant histone acetylation can disturb cellular gene expression profiles. Such disturbances caused by abnormal histone acetylations via histone acetyl transferases or histone deacetylases are usually correlated with HCC. HBx is largely involved in HBV-induced HCC pathogenesis by promoting histone acetylation of tumor-associated genes. HBx was shown to interact directly with CBP/p300 in vitro and in vivo, thus synergistically enhancing C-AMP response element-binding protein (CREB) activity. It was also shown that HBx physically invades the CREB-binding domain of CREB responsive promoters of genes such as interleukin-8 (IL-8) and proliferating cell nuclear antigen (PCNA). Hence, an increased recruitment of CBP/p300 to the promoters of these genes was observed in the presence of HBx. The deregulation of these components can explain the neoplastic transformation of liver cells. For instance, IL-8 is a leukocyte chemotactic molecule that is upregulated in many human cancers, notably in liver cancer by its maintenance of an inflammatory state during the HBV infection. PCNA is involved in DNA replication and DNA repair, implying the potential contribution to cellular transformation when unbalanced [23].

Gene expression can also be modulated through induction of histone deacetylation. From recent findings, it was shown that HBx binds with histone deacetylase 1, thus involving itself in the repression of insulin growth-like factor binding protein 3 (IGFBP-3) [24]. The histone deacetylation of E-cadherin gene (CDH1) followed by hypermethylation by HBx silences the expression of CDH1. The mechanism involved in the loss of CDH1 is associated with various tumors and is present in numerous cancer cell lines. With reference to HBV, HBx was shown to form a complex together with mSin3A; thus, HBx downregulates E-cadherin expression by

recruiting the mSin3A/histone deacetylase complex. Moreover, it was shown that HBx downregulated the expression of mir-373 known as a positive regulator of E-cadherin expression [25].

Aberrant histone methylations are also important modifications that occur in HBV-induced HCC pathogenesis. HBx upregulates the expression of SET and MYND domain containing 3 (SMYD3), which is a histone H3-H4-specific methyltransferase that is involved in the transcriptional activation of genes in relation to different cancers and, notably, HCC. The upregulation of SMYD3 during the HBV infection was shown to switch on the transactivation of the C-MYC oncogene. The latter is a famous oncogene, whose overexpression leads to the activation of various other genes promoting cellular proliferation and/or halting cellular differentiation. The HBx-related upregulation of C-MYC oncogene expression may occupy an important role in HCC development [26].

4.1.3 HBx and MicroRNA (miRNA)

HBx has also been shown to induce alterations on other epigenetic regulators such as miRNA. Such alterations of host miRNA profiles could be held responsible for the development of HCC. HBx was shown to upregulate miRNA 602 which inhibits the expression of the tumor suppressive gene RASSF1A [27]. Likewise, HBx was shown to increase strikingly the levels of miRNA-143 in HCC patients. This overexpression is mediated by the nuclear factor kappa B (NF-KappaB) repressing FNDC3B expression. The upregulation of miRNA-143 is in favor of the development of invasive tumors with metastatic properties [28].

Besides overexpressing certain miRNAs, HBx is involved in the downregulation of certain miRNAs. The let-7 family of miRNA which is generally highly expressed was shown to be downregulated in the presence of HBx. The downregulation of the let-7 family of miRNA by HBx was followed by a decreased expression of signal transducer and activator of transcription 3 (STAT3). The downregulated expression of STAT3 triggered cellular proliferation giving an additional indication of HBx deregulating cellular proliferation [29].

HBx was also shown to downregulate microRNA-101. The same downregulation was also put into evidence in HBV-related HCC tissues. DNA methyltransferase 3A which is a direct target of miR-101 is upregulated in the absence of miR-101; this upregulation in HBx-expressing cells increased the DNA methylation of tumor suppressor genes. Similarly, HBx was shown to downregulate the expression of microRNA-152 (miR152) in HBV-related HCC tissues. This downregulation leads to a heightened expression of DNA methyltransferase 1 (DNMT1) followed by a DNA hypermethylation of tumor suppressor genes such as glutathione S-transferase pi 1 (GSTP1) and E-cadherin (CDH1) [30].

Hence, HBx may regulate the cell epigenetic regulation through miRNA-related mechanisms. More studies are needed to explain the exact role of HBx together with different miRNAs. Whether HBx acts via a complex and consequent series of different cofactor recruitments to modify gene expression is a highly probable phenomenon.

4.2 HBx Gene DNA Integration

In a large number of HCC, HBV DNA integration into or near to cellular genes has often been detected. It was demonstrated by a modified Alu-polymerase chain reaction assay that among 68 HCC examined, nearly 89 % had HBV DNA integrated into cellular genes that are actively transcribed [31]. The integration of the viral host sequences results in the production of chimeric HBV cellular transcripts that consequently produce hybrid viral/cellular proteins. This was demonstrated in a liver tumor where the viral HBV X gene promoter was shown to cis-activate two chimeric HBV X/SERCA1 transcripts. These transcripts were translated to give chimeric proteins with a C-terminal-truncated SERCA1 and its N-terminal end replaced by the C-terminal-truncated X protein. SERCA proteins are known to play a crucial role in the regulation of cellular calcium that is also involved in basic intracellular messenger activities such as cellular proliferation. When compared to the wild-type SERCA1 protein, the chimeric protein altered the control of cell death showing the significance of HBV-related insertional mutagenesis in HCC [32].

The HBx/MLL4 fusion protein was also detected in HCC patients due to the integration of HBV DNA into intron 3 of MLL4 gene. cDNA microarray experiments indicated that HBx/MLL4 fusion protein suppressed the expression of specific genes relevant to liver oncogenesis [33].

The X gene of HBV is generally partly deleted during the HBV integration into the host genome. This integration creates a truncated HBx protein in its COOH-terminal. Both in vivo and in vitro studies have shown that the COOH-terminal truncation of HBx could adequately transform immortalized human liver cell lines such as MIHA cells and increase their tumorigenicity [34].

4.3 HBx Deregulates Different Cellular Pathways

Furthermore, HBx has been put into evidence to promote liver progenitor cell proliferation in vitro by increasing cyclin D1 expression. The upregulation of cyclin D1 by HBx relied upon the activation of the MEK/ERK and PI3K/Akt signaling pathways [35]. HBx was also shown to activate the Yes-associated protein (YAP) promoter through CREB pathway. The expression of YAP was significantly elevated in HCC samples in addition to being overexpressed in the presence of HBx. YAP is an oncogene that operates as a downstream effector of the Hippo-signaling pathways [36].

Another significant pro-carcinogenic activity of HBx is how it targets the mitotic cell cycle by its interaction with BubR1, a factor of the mitotic checkpoint complex. HBx binds BubR1 and co-localizes with BubR1 at the kinetochores leading to a decreased association between BubR1 and CDC20, an activator required for full ubiquitin ligase activity of the anaphase-promoting complex/cyclosome (APC/C). This co-localization of HBx and BubR1 causes the skipping of mitotic arrest in the presence of microtubule poisons as well as the accumulation of lagging chromosomes and chromosome bridges [37].

4.4 HBV DNA Integration

HBV-related HCC development may take place by the integration of the viral genome into the host genome. Such HBV DNA integrations into host chromosomes are known to take place during the early stages in natural acute infection [38, 39]. While multiple integrations have been detected in chronic hepatitis tissues, around 80 % of HBV-related HCC patients have HBV-integrated sequences. Childhood HCC is often associated with single HBV insertion; however, multiple integrations may accumulate in a single cell during long-lasting HBV infections [40].

Although incomplete HBV insertions into the host genome cannot serve as a template for viral replication, HBV insertions have been linked to radical genetic alterations within the cell genome. Consequences of such insertions are genomic instability, gene-chromosomal deletions, translocations, and creation of fusion viral/host transcripts. These changes in the host genome may contribute to the overexpression of oncogenes and the suspended expression of tumor suppressor genes, preparing the ground for the development of HCC. In HBV-related HCC, HBV DNA integration has been mapped on numerous regions, implying that HBV DNA integration is probably dispersed randomly all over the host genome [41]. These incidents are developed to give multiple consequences such as large-scale chromosome changes or cis-acting effects on the expression or function of neighboring genes.

It was shown that HBV was inserted targeting the retinoic acid receptor-ß(RARß) gene producing a fusion gene including 29 amino-terminal residues of the HBV pre-S1 gene to the DNA-binding and hormone-binding domains of RARß. The expression of this chimeric protein was demonstrated to carry cell-transforming capabilities [42]. HBV DNA integration was also shown to integrate the intron of the human cyclin A gene, a crucial gene for cell cycle evolution. This integration delivered hybrid HBV/cyclin transcripts which were translated into stabilized cyclin A fusion proteins. The overexpression of hybrid cyclin A was demonstrated to be linked to liver carcinogenesis. Hence, HBV insertion locations are not trivial as their insertions provoke disruption of cellular proliferation and differentiation [43].

5 HBV Surface Protein (HBsAg)

HBsAg accumulation in the endoplasmic reticulum (ER) during the HBV replicative cycle can induce ER stress. This accumulation is followed by cellular oxidative stress causing DNA impairment and inducing changes of various signaling pathway related to cell proliferation and cell apoptosis. It has also been shown that pre-S2 mutant accumulations in the endoplasmic reticulum can induce ER stress. Pre-S2 mutant-induced ER stress activates the calcium-dependent protease calpain that produces N-terminal-truncated cyclin A. The N-terminal-truncated cyclin A is translocated to the cytoplasm and causes centrosome over duplication.

Truncated cyclin A was also predominantly detected in the cytoplasm of HBV HCC tissues [44].

Pre-S2 mutant of HBsAg has also been shown to interact directly with the c-Jun activation domain-binding protein 1 (JAB1), thus causing hyperphosphorylation of tumor suppressor retinoblastoma resulting in a disrupted cell cycle [45]. HBV protein pre-S2 also functions as a transactivator and induces human telomerase reverse transcriptase hTERT upregulation. Telomerase activation is known to be a key step in the development of most fatal tumors. Pre-S1-mediated hTERT upregulation also enhanced the malignity of hepatocarcinoma cells both in vitro and in vivo [46]. To add more evidence to HBV mediation on telomerase activity, it was also shown that HBV DNA integration at the proximity of the hTERT promoter and the ability of HBx to promote SP1 binding to hTERT upregulated hTERT transcription [47].

HBsAg was shown to bind both exogenous and endogenous ECHS1 proteins. HBsAg-bound ECHS1 proteins are co-localized to the cytoplasm and were shown to enhance HepG2 cell apoptosis by delocalizing ECHS1 from the mitochondria [48]. Moreover, HBsAg was shown to silence the expression of JTB (jumping translocation breakpoint) by inhibiting JTB translocation to the mitochondria. The silencing of JTB expression stimulates cancer cell mobility and has antiapoptotic functions. HBsAg could thus exhibit an ability to promote tumor progression [49].

6 Mongolia and Laos: Two Examples of High HCC Incidence

When analyzing the Globocan liver cancer incidence estimation (Fig. 1a), it is noteworthy that Mongolia and Laos represent the highest incidence of liver cancer. If we try to compare the two situations, some features can be pointed out.

In Mongolia, both HBV and HCV have a very high prevalence of 11.8 and 15 %, respectively [50]. Among patients with cirrhosis, 40 and 39 % are positive for HBsAg and anti-HCV antibodies, respectively, and 20 % are positive for both. Furthermore, approximately 60 % of HBsAg-positive carriers are co-infected with HDV, which by itself might accelerate the progression to liver cirrhosis and HCC. Analysis of HDV-relaxed phylogeny cannot exclude that HDV might have been introduced recently (<50 years) in the HBs-positive Mongol patients.

The situation is quite different in Laos, which is also a country with a high estimated liver cancer incidence. There, we looked for HDV prevalence in almost 150 Lao HBsAg-positive patients and did not find any anti-HDV antibodies (Phimpha Paboriboune, Vannary Mom, and Paul Dény, unpublished). However, it must be underlined that this country was part of a North to South Vietnam logistic trail, during the Vietnam War in the second part of the last century, and that chemical compound had been used to destroy crops. If the "orange agent," besides exercising birth defect, might have some effect on liver cancer as depicted in Vietnamese patients and Korean veterans [51, 52], it is also highly probable that arsenic compound present in the "blue agent" would increase the liver cancer risk [53].

7 Conclusion

In conclusion, during HBV infection, both HBV and HDV may be implicated in the advanced progression of liver injury and HCC. The reason for advanced liver disease may be due to the synergistic activities that both viruses exert. Much attention has been focused on how HBV-encoded proteins and viral integration interfere with and disturb intracellular signal pathways. HBx, HBsAg, and HDV proteins seem to have a regulatory effect on cellular promoters and also interact with a large number of cellular proteins.

The answer to the question "Does HBV play a role in liver injury and hepatocellular carcinogenesis?" may be related to the predicament that persistent liver damage, deregulated signal pathways, and deregulated liver regeneration may potentially lead to cirrhosis and/or development of HCC. However, the underlying mechanism responsible for enhanced malignant transformation of infected cells remains to be placed in a specific genetic, infectious, behavioral, and environmental background for each individual patient and to better clarify the interplay between HBV and HDV.

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Hepatitis Virus Scientific Background: Epidemiology and Mechanism of Carcinogenesis of Hepatitis C Virus (HCV)

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1 Hepatitis C Virus (HCV)

1.1 Epidemiology

Hepatitis C is considered a silent epidemic of global impact. The World Health Organization estimates that 170 million people in the world are chronically infected with HCV at risk of developing cirrhosis and hepatocellular carcinoma [35]. The prevalence of hepatitis C is categorized as high (>3.5 %), moderate (1.5–3.5 %), and low (<1.5 %). There is great variation in this prevalence according with the study area; in some countries, such as Egypt, the prevalence is so high that can reach 15 % [22]. As most acute cases are not clinically diagnosed, it is hard to determine the

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actual number of new infections [33]. Studies show that in Europe and the United States, an acute hepatitis C epidemic is especially common among injecting drug users (IDUs) and men who have sex with men (MSM) [34].

1.2 Transmission

Parenteral exposure is the most frequent risk situation for HCV transmission (blood transfusions from untested donors for anti-HCV, injection drug use, organ transplantation, and hemodialysis), followed by occupational exposure and vertical and sexual routes [4]. Procedures performed with contaminated equipments (such as tattooing, piercing, barber services, circumcision, acupuncture, or dental care) and personal hygiene equipment sharing (razor blades and nail pliers) are also considered risk situations [27].

1.3 Acute Hepatitis

Acute hepatitis C usually occurs 6–12 weeks after exposure to the virus and is rarely diagnosed since most cases are asymptomatic or with only nonspecific symptoms. It is accompanied by jaundice in less than 25 % of cases and lasts 2–12 weeks [4]. The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented, since there is no serological marker that proves that HCV infection is in the de novo acquired acute phase [9].

1.4 Chronic Hepatitis

Most infected individuals (80–100 %) remain with detectable HCV RNA after 6 months of infection, and liver enzymes generally may remain elevated [3]. Most patients with chronic infection are asymptomatic or have only mild and nonspecific symptoms, such as fatigue. Less common symptoms are nausea, weakness, myalgia, arthralgia, and weight loss. All these symptoms are nonspecific and do not reflect the activity and severity of the infection. Transaminase levels can vary considerably along the natural history of chronic hepatitis C [20].

1.5 Natural History

After acute infection, there are basically two possible paths for the infection: spontaneous resolution (25–50 %) or persistent infection (50–75 %), both determined by

a complex set of virus-host interactions [13]. In patients with chronic HCV infection, the risk of developing cirrhosis after 20 years is 10–50 % [28]. Some of them will also develop hepatocellular carcinoma. The factors associated with the different evolutions of HCV infection are not fully understood [6].

1.6 HCV

1.6.1 Taxonomy and Genotypes

HCV belongs to the genus *Hepacivirus*, family *Flaviviridae*. Seven genotypes currently described are all classified as a single species. Intragenotypic diversity is also observed and phylogenetic analyses of these variants are grouped into subgroups that are designated subtypes. HCV variants identified most frequently in Western countries are 1a, 1b, 2a, 2b, and 3a. Genotype 4 is common in the Middle East and genotype 6 in Southeast Asia [30].

1.6.2 Viral Genome

HCV is an enveloped virus with a single-stranded RNA genome with positive polarity with approximately 9.6 Kb. It presents a single open reading frame (ORF) comprising almost the entire genome and encodes a polyprotein with more than 3,000 amino acids that is cleaved by cellular and viral proteases in structural (core, E1, and E2) and nonstructural (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins as shown in Fig. 1 [26].

The single ORF is surrounded by 5′ and 3′ untranslated regions. Viral proteins have specific functions as shown in Table 1.

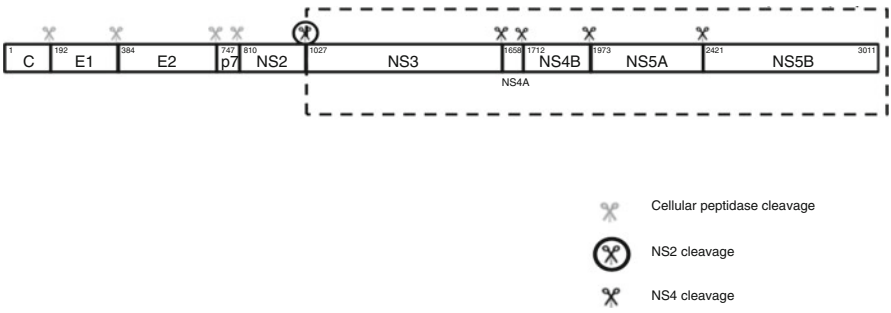

Fig. 1 HCV genome

Table 1 Key functions of structural and nonstructural HCV proteins

Viral protein	Function
Core	Regulation of translation, replication and viral assembly
E1	Viral envelope transmembrane proteins. Viral particle adsorption and endocytosis mediated through membrane receptors
E2	
p7	Ionic channel in the endoplasmic reticulum needed for infectious viral particle assembly
NS2	Protease (NS2–3 cleavage in the precursor polyprotein)
NS3	Protease (precursor polyprotein cleavage downstream of NS3 – NS3/NS4A/NS4B/NS5A/NS5B), ATPase, helicase
NS4A	NS3 protease cofactor
NS4B	Essential for viral replication. Induces a membranous web within the rough endoplasmic reticulum during replication
NS5A	Multifunctional phosphoprotein. Harbors the IFN-α sensitivity determining region (ISDR)
NS5B	RNA polymerase RNA dependent

1.7 Diagnosis

Serological and molecular tests are available for the diagnosis of hepatitis C [29]. Positive serological results require quantification of HCV RNA in order to differentiate between chronic hepatitis C and resolved past infection. In cases of acute hepatitis C, serological screening by itself is insufficient because the anti-HCV antibodies appear approximately 8 weeks after infection. However, HCV RNA is detectable in at most 2 weeks and therefore molecular testing is critical to the diagnosis of acute hepatitis C, also essential for the indication and duration of treatment success [31].

1.7.1 Serological Assays

The third generation of enzyme immunoassays (ELISA), which includes an NS5 antigen and/or the substitution of a highly immunogenic epitope of NS3 region, allows the detection of anti-HCV antibodies approximately 4–6 weeks after infection with sensitivity higher than 99 %. The newest generation of immunoassays available ("fourth generation") simultaneously detects HCV capsid antigen as well as antibodies to the core, NS3, NS4, and NS5 regions of the virus. These assays have further reduced the window period of HCV detection to 17 days [11].

False-positive results are more frequent in patients with rheumatic factors and in populations with low prevalence of hepatitis C, for example, blood and organ donors. False-negative results may occur in patients on hemodialysis or in severely immunocompromised patients or those with hematologic malignancies. Immunoblot assays can be used as supplemental assays to confirm serological reactivity by ELISA, but are now more and more replaced by molecular tests [36]. Recent studies have also suggested that the higher the anti-HCV antibody titer in patient's serum, the more chances of it being true positive than false positive and that repeating this samples with another ELISA test would be enough to confirm its serological status [11].

1.7.2 Molecular Assays

There are various assays from different commercial suppliers for the detection of HCV RNA. Currently, all these assays are carried out using real-time PCR with a very low limit of sensibility and a broad range of quantitation (10–100,000,000 mUI/mL). These assays are particularly useful for diagnosis, particularly for the indication and follow-up of HCV patients under treatment. Similar assays are also available for HCV detection in blood donors [19].

HCV genotypes must be determined, since most of the treatment regimens are differentiated according to the viral genotype. The determination of genotype and subtype of virus can be made based on direct sequencing of genomic regions of HCV (e.g., the 5′ UTR, core, and/or NS5B), reverse hybridization assay, and real-time PCR or sequencing [19].

There are other assays to determine the polymorphisms on the interleukin 28B (or interferon lambda 3) gene or resistance to new drugs utilized for the treatment that have been developed but are not routinely utilized even in most developed countries [5].

1.7.3 Treatment

New therapeutic regimens for hepatitis C utilizing direct-acting antiviral (DAA) drugs that can specifically inhibit viral proteins such as protease (NS3), NS5A, and RNA polymerase (NS5B) have been recently approved, some of them without the use of pegylated interferon or even ribavirin [5]. These treatments are highly effective with more than 90 % of response rates in almost all population groups, even in the presence of HIV coinfection and/or liver cirrhosis. Decisions to shorten, extend, or stop treatment with these regimens may require frequent and accurate quantification of serum HCV RNA levels [19]. This area is constantly changing and should be updated on the websites from international or national liver disease societies, such as AASLD/IDSA (http://www.hcvguidelines.org/) or EASL (http://www.easl.eu/).

2 Hepatocelular Carcinoma

2.1 Epidemiology

Primary malignant liver tumors correspond to the 6th leading cause of cancer and 3rd leading cause of cancer death worldwide. Hepatocellular carcinoma (HCC) corresponds to 85–90 % of primary liver cancers. The estimated global incidence of HCC is 500 thousand to 1 million new cases/year, leading to >500,000 deaths per year worldwide. Today HCC is the most common complication and the leading cause of death in patients with compensated liver cirrhosis. The vast majority of the cases of HCC are associated with liver cirrhosis. It is estimated that chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) are associated to more than 80 % of HCC cases worldwide [15].

HCC is found throughout the world with a very heterogeneous distribution, which is probably related to its etiological factors, such as HBV, HCV, and exposure to aflatoxin B1. Sub-Saharan Africa and East Asia comprise the majority of cases (>80 %) and are considered high-incidence areas. China accounts for approximately 50 % of all cases of HCC worldwide. Japan also has a high incidence of HCC with a case index of approximately 40 per 100,000 people. HCC in Africa is likely underestimated, because of lack of screening and access to medical care in rural areas, and is a major cause of death in the black African population [17].

Conversely, North and South America, as well as Europe, have a comparatively low incidence of HCC. Although the overall incidence of HCC in the United States is lower than in other parts of the world, the age-adjusted incidence rate tripled from 1975 to 2005 from 1.6/100,000 to 4.9/100,000. This increase is likely a result of the increasing prevalence of HCV from unscreened blood transfusions and IV drug use in the 1960s and 1970s, although there are other likely contributing factors. Europe has a slightly higher incidence (2–4 times) of HCC than the United States. The Mediterranean countries (Italy, Spain, and Greece) have incidence rates ranging from 10 to 20 per 100,000 individuals. These countries also attribute approximately two-thirds of their cases to chronic HCV infection [17]. In Latin America, hepatitis C was shown to be the leading risk factor for HCC, found in 38 % of 240 cases [21].

2.2 HCV and HCC

The increased risk of HCC development in HCV-infected patients comes from the development of liver fibrosis and cirrhosis as a result of chronic inflammation. This inflammation leads to the distortion of hepatic architecture and impairment of cellular functions as well as the microcirculation of the liver. The annual risk of developing HCC in patients with cirrhosis is in the range from 1 to 4 %, and about 1 to 3 % of patients chronically infected with HCV develop HCC after 30 years [32]. Unlike HBV, HCV is unable to integrate into the host genome. Instead, in HCV, viral proteins such as HCV core protein and their evoked host response have been implicated in apoptosis, signal transduction, reactive oxygen species (ROS) formation, transcriptional activation, and immune modulation through upregulation of interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α), contributing to malignant transformation [24].

There is an increased incidence of HCC observed in the Western population, most of which are related to this virus and for its increasing frequency in an aging population. The association between HCV and HCC is probably resulting from the combination of the independent effect of HCV in hepatocarcinogenesis and immunological indirect effects and the development of cirrhosis. HCV does not have a reverse transcriptase activity and its replication cycle does not lead to integration into the host genome. HCV is a virus that replicates only in the cytoplasm and the main hypothesis for carcinogenesis associated with HCV is through indirect ways, especially by the effects of chronic inflammation and hepatocyte injury.

This hypothesis is supported by the fact that the presence of cirrhosis is almost a prerequisite for the development of HCC [10].

On the other hand, for many proteins of HCV, a role in the development of HCC in experimental studies involving cell culture systems and animal models was described. The core protein of HCV is involved in the assembly of the viral particle and generation of complete virions. However, this protein is also involved in cell signaling, transcriptional activation, apoptosis, lipid metabolism, and cell transformation. Indeed, it affects the modulation of cellular gene products and several regulatory pathways involved in cell proliferation, cell cycle control, and tumor formation [18]. In models of transgenic mice, the core protein can induce HCC, although the exact mechanism by this occurs has not yet been fully clarified [23].

In addition to the core protein, other viral proteins have also been with hepatic carcinogenesis. E2 protein interacts with the CD81 receptor and inhibits NK and T cells promoting cell survival and proliferation. NS3 protein is a multifunctional protein with RNA helicase, protease, and NTPase activities and may promote the interaction with certain cellular proteins as p21 and p53 [16]. NS5A protein is a membrane-associated protein and is involved in the replication cycle of HCV that may also interact with the cellular components and signaling regulatory protein kinases, leading to suppression of the host immune response and inhibition of apoptosis [14].

2.3 HCC Risk Factors Associated to HCV

Alcohol intake in patients with chronic hepatitis C increases the risk of developing HCC [12], as well as diabetes, obesity, and steatosis [25]. Coinfection with HBV also synergistically increases the risk of developing HCC. A meta-analysis showed that HBV/HCV coinfection is associated with a 135-fold increased risk of developing HCC in relation to the monoinfection, even more evident in patients with established cirrhosis [7].

The role of the HCV genotype is less clear, but several studies have shown an increased risk of HCC in patients infected with the subtype 1b. In a previous work in Brazil, genotype 3 frequency was higher in HCC cases than that found in cases of hepatitis C without HCC [2].

Previous studies have shown that mutations in positions 70 (arginine) and 91 (leucine) in the coding region of the HCV core protein subtype 1b are predictors of poor response to treatment with PEG-IFN plus ribavirin [1]. A study of patients infected by genotype 1 significantly determined that the risk of HCC was increased by these mutations in combination with host factors, such as age, sex, and hepatic fibrosis [8].

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Epidemiology of Epstein-Barr Virus and Mechanisms of Carcinogenesis

Maria Raffaella Ambrosio and Lorenzo Leoncini

1 Discovery

The discovery of EBV was a direct consequence of the description of Burkitt lymphoma (BL) in 1958 by Denis Burkitt [6]. The typical geographical distribution of BL led to the idea that environmental factors like *Plasmodium falciparum* and maybe a virus could have a role in the pathogenesis of the disease. In 1964, Antony Epstein and Yvonne Barr started looking for virus particles in BL biopsies, and their efforts drove to the detection of a herpes virus, which later was called Epstein-Barr virus [19].

2 Structure and Genome of EBV

Like other members of the herpes virus family, EBV is an enveloped virus, which contains a core DNA surrounded by an icosahedral nucleocapsid composed of 162 capsomeres [77]. There are three major capsid proteins. The nucleocapsid is in turn enclosed by a protein tegument, which is surrounded by the viral envelope that consists of multiple viral glycoproteins and a tegument [23]. The genome of EBV consists of a 184 kbp double-strand DNA with terminal direct and internal repeats. Upon infection, the virus DNA becomes circular for replication and is maintained as multicopy episome inside the host cell's nucleus [5]. The EBV genome encodes

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for a series of almost 100 products interacting with or exhibiting homology to a wide variety of antiapoptotic molecules, cytokines, and signal transducers, hence promoting EBV infection, immortalization, and transformation [14].

3 EBV-Encoded Products

The EBV life cycle includes a *lytic phase*, resulting in the production of new viral particles, and a *latent phase*, during which the virus remains silent for the lifetime of the host in memory B cells [61].

3.1 Lytic Proteins

There are more than 90 lytic proteins, which are expressed in a temporally regulated manner [37]. The immediate early proteins, like BZLF1 and BRLF1, are important for regulating the expression of EBV genes and the metabolism of neoplastic cells (i.e., BRLF1) [40]. The early proteins, like DNA polymerase (encoded by BALF5), are important for the replication of the virus' DNA [32]. Finally, the late proteins, like gp350 and gp110, are the components of the viral particle and are involved in immune evasion [61].

3.2 Latent Proteins

Totally, nine different proteins are expressed by EBV:

(a) *EBNA-1*
EBNA-1 is a homodimeric protein which is responsible for EBV DNA replication and persistence by binding to the origin of replication of the EBV genome (oriP). It also plays an important role in transcriptional regulation of the C promoter and contributes to the control of apoptosis, cellular genomic instability, and immune escape by T-cytotoxic response [8, 21, 68].

(b) *EBNA-2*
The EBNA-2 protein is localized in the nucleolus and is one of the first viral proteins expressed during EBV infection of primary B lymphocytes. In cooperation with EBNA-LP, EBNA-2 induces the transition of resting B cells from G0 to G1 phase. EBNA-2 is also a key regulator of viral gene and modulates the transcriptional activity of some cellular genes (c-*FGR*, c-*MYC*, CD21, CD23, EBI1/BLR2, TNF-α, p55α) [9, 31, 45, 64].

(c) *EBNA-3 family*
EBNA-3 family includes EBNA-3A, EBNA-3B, and EBNA-3C, also known as EBNA-3, EBNA-4, and EBNA-6, which are present in tandem in the viral

genome and are indispensable for B-cell transformation by the virus. A large number of target genes of EBNA-3 family have been identified, including BCL6, IRF-4, BLIMP-1 (involved in B-cell differentiation), NFATC2, BACH2, EBF1CD21, CD40, CHK2 (disrupting G2/M checkpoint of cell cycle), RAC1, LYN, TNF-α, JAK-STAT, and MAPK signaling pathway members [26, 47, 79, 88].

(d) *EBNA-LP*

EBNA-LP, also known as EBNA-5, is the first viral latent protein to be expressed after the infection of naive B cells along with EBNA-2. EBNA-LP has been shown to increase the transcription effect of EBNA-2 in activating the expression of LMP-1 and LMP-2 and in inducing cyclin D2, and thus causing the transition of G0/G1 checkpoint. EBNA-LP has been shown to bind to p53, Rb, heat shock protein 70, DNA protein kinase catalytic subunit, HA95 (a nuclear protein that is involved in mitosis), and α- and β-tubulin [35, 54].

(e) *LMP-1*

LMP-1 consists of a short cytoplasmic N-terminus, six transmembrane domains that are located in lipid rafts on the membrane of the cell, and a long cytoplasmic C-terminus. The protein is a functional analog of a constitutively activated form of CD40, a receptor which belongs to the TNF receptor family, with an important role in B-cell activation. By this means, LMP-1 can activate important signaling pathways (NF-κB, MAPK, interferon-regulatory factor 7 and PI3K). LMP-1 has also an antiapoptotic effect achieved by regulating the expression of different cellular proteins like MYC, BCL2A1, TNFAIP3, and CL2 [39, 41, 58, 73, 89].

(f) *LMP-2 family*

LMP-2 family includes two forms of LMP-2 proteins (LMP-2A and LMP-2B) which are necessary for B-cell transformation and B-cell receptor activation. LMP-2A has been described as a B-cell receptor (BCR) signaling mimic inducing downstream pathways that inhibit apoptosis and promote cell survival [86]. Moreover, LMP-2A cooperates in reprogramming normal B-lymphocyte functions and enhances MYC-driven lymphomagenesis [17, 20].

4 RNA Molecules

EBV expresses two small RNA known as EBV-encoded RNAs (EBER1 and EBER2) and several microRNAs (miRNAs) [61].

(a) *EBER family*

EBERs are the most abundant viral transcripts producing during latent infection by EBV. Both of them are almost 170 nucleotide long and are expressed in all EBV latencies and in all the EBV-infected cells in vivo. Their high level of expression (almost 106 per cell) rendered them as invaluable targets in diagnostics of EBV infection. The evolutionary conservation of EBERs and their ubiquitous expression suggest that they may play a key role in EBV biology. In fact,

they have been demonstrated to elicit a variety of effects on cell growth, apoptosis, protection from protein translation shutoff, induction of cytokines, and lymphomagenesis [78].

(b) *MicroRNAs*

The miRNAs are small noncoding single-strand RNA molecules (~22 nucleotide long) which can regulate the expression of their target genes at posttranslational level [13, 25, 42, 50]. EBV expresses 44 mature miRNAs from 25 precursors, which are mapped in two regions of the EBV genome: BHRF1 (Bam HI fragment H rightward open reading frame I) and BART (Bam HI-A region rightward transcript), from which three belong to the BHRF family and the rest to the BART family. Expression of EBV miRNAs is dependent on a variety of factors including the host cell type. Viral miRNAs regulate both cellular and viral genes and thus play important roles in maintaining the EBV latency. In addition, they provide a potent mechanism for the virus to modulate the cellular environment by regulating host cell growth, survival, apoptosis, and immune evasion. EBV is also able by itself to affect expression of cellular miRNAs, thereby regulating cellular gene expression to enhance EBV effects in the pathogenesis of viral-associated diseases [4, 7, 44, 51, 56, 65].

5 Persistent Infection, Latency, and Viral Reactivation

In the generally accepted model of EBV persistence, the virus initiates infection by crossing the epithelium of the oropharynx and infecting resting naive B cells in Waldeyer ring, the major receptor for the virus on B cells being CD21 [57]. Although B cells represent the principle targets of EBV, epithelial cells are important for lytic infection, producing viral progeny that amplifies cell-to-cell spreading and enables transmission to the host. After the infection, EBV establishes persistent infection characterized by the sequential employment of a series of latency transcription programs that allow the virus to drive the newly infected naive B cell into the memory B-cell compartment [38, 62, 75, 76]. In this setting, the virus maintains a latent state as an episome and expresses no viral genes as viral DNA becomes methylated over time. Specifically, upon infection, EBV delivers its linear genomic DNA that is epigenetically naive to the nucleus of infected cells where it forms a circular plasmid and initiates a phase in the viral life cycle termed “pre-latent” [34]. This phase is characterized by the co-expression of two distinct sets of viral genes, latent and lytic. The expression of EBNAs, LMPs, EBERs, and miRNAs activates the quiescent B lymphocytes, which become lymphoblasts and begin to proliferate. At this early stage, the concomitant expression of certain lytic genes, which encompass transcription factors and cytokines, protects the activated B lymphocytes from endogenous stress, immediate activation-induced apoptosis, and, presumably, DNA damage response signals. The pre-latent phase is transient and ceases within 1–2 weeks; during this phase, histones acquire substantial epigenetic modifications over time, and the viral DNA becomes extensively methylated at CpGs. The pre-latent

phase is replaced by a strictly latent phase, in which the virus establishes a stringent and stable virus-host relationship. Viral gene expression is entirely restricted to EBNAs, LMPs, EBERs, and BHRF1 miRNAs (*latency III*). This program (named growth transcription program) may be important for cancer development, because it is capable of initiating the activation of B cells in vitro into continuously proliferating lymphoblastoid cell lines (LCL). Since the activated naive B lymphoblasts in vivo are targeted by the immune system, EBV adopts a strategy to survive in the organism. In fact, infected B cells rapidly migrate to the follicle to participate in a germinal center (GC) reaction and continue to proliferate by switching to a more restricted latency program (*latency II*) where only EBNA-1, LMP-1, LMP-2 s, EBERs, and BART miRNAs are expressed. This leads to the removal of the differentiation block imposed by EBNA-2 protein (default transcription program). Ultimately, the cells leave the germinal center as resting memory B cells at the site of long-term latent persistent infection. In memory B cells, all viral protein expression is extinguished (*latency 0*) except when the cells divide and express EBNA1 (the protein required for replication of the viral genome), EBERs, and BART miRNAs (*latency I*). This mechanism is thought to allow EBV-infected cells to remain hidden from the immune system, enabling lifelong persistence. Upon receiving certain activation signals (BCR stimulation, hypoxia, TGF-β, DNA damage, and chemical agents), latency can be disrupted, and the virus reactivates, switching to a lytic phase, with subsequent lysis/death of infected cells and release of virions that infect more cells and enable virus transmission also from host to host [37]. Lytic phase is also able to enhance tumor growth through growth factors and immunosuppressive cytokines.

6 Epidemiology and EBV Infection

The International Agency for Research on Cancer has demonstrated that more than 90 % of adults worldwide are infected with EBV [27, 72]. The age at primary infection varies substantially worldwide, and exposure to EBV is likely to be due to socioeconomic factors. In developed countries, two peaks of infection are seen: the first in very young preschool children aging 1–6 years and the second in adolescents and young adults aging 14–20 years [12]. In developing countries, infection occurs at a much earlier age so that 90 % of children over the age of 2 are seropositive [27]. There is no consistent difference in EBV seroprevalence by sex. EBV transmission occurs through saliva; however, in developing countries, infection is acquired mainly for crowding and/or the practice of pre-chewing food for infants, whereas in developed world, transmission is more likely because of intimate oral exposure (the so-called kissing disease). Primary EBV infection takes place in the oral route to which the virus is conveyed by saliva droplets from infected individuals [66]. The nature of the target cells in the oral mucosa is still controversial, but there is agreement that B cells are infected at some stage of the process as they traffic in close proximity to oropharyngeal epithelium. If infection is delayed to adolescence or

adulthood, it can cause an infectious mononucleosis syndrome, characterized by the polyclonal expansion of infected B cells. The disease is self-resolving as it elicits a strong cellular immune response which brings the infection under control, and newly infected cells are efficiently removed by the cytotoxic T-cell response [15]. Following resolution of primary infection, the virus establishes a lifelong persistence in memory B cells that usually remains clinically silent. In this B-cell reservoir, viral expression is entirely repressed; this is how these infected cells can persist in the face of a competent immune system [16].

7 EBV-Associated Malignancies

The strategy of EBV is to persist in healthy chronic carriers, avoid killing the cell, and prevent the cell from becoming a target for destruction by the immune system [24]. Therefore, the virus initiates an ongoing, tightly orchestrated interplay between itself, the host B cell, and the immune system that allows EBV to persist and eventually activate cellular growth control pathways. To promote viral persistence, EBV has evolved a number of strategies to modulate the host-immune response, including inhibition of immune cell functions and of apoptosis and interfering with antigen processing and presentation pathways [74]. However, in this long-standing interaction, something wrong could occur, leading to dysregulation of cellular pathways or perturbation of host immunity, thus resulting in the development of EBV-associated malignancies. In immunodeficiency settings, for the absence of an effective T-cell surveillance, latently infected cells in the peripheral blood or persistently infected cells on the oropharynx increase in number and usually express all the viral genes (growth program—latency III), thus activating multiple intersecting cellular pathways and producing its own miRNAs that alter the host cell regulatory machinery [28]. However, in immunocompromised patients, lymphomas other than posttransplant lymphoproliferative disorders show more restricted forms of latent gene expression, reflecting a complex pathogenesis that may involve additional cofactors. These tumors might evolve from EBV-transformed LCL-like cells through the acquisition of additional cellular genetic changes that render certain viral functions redundant. In immunocompetent individuals, EBV-induced cancerogenesis is a multistep process where oncogenic effect of EBV products in association with additional genetic, environmental (i.e., viral infection by HHV8, CMV, arbovirus, and HIV) [60], and microenvironmental factors (i.e., *Euphorbia tirucalli*) [46] contributes. There is increasing evidence that the microenvironment of the EBV-infected B cell can regulate virus gene expression and modulate the function of individual virus proteins [84]. For example, the cytokines interleukin-21 (IL-21) and IL-2, along with intercellular interactions such as CD40 ligation, all present in the germinal center of the tonsil, have been shown to downregulate the expression of EBNA-2 and upregulate the expression of LMP-1, thus imposing a type II

expression profile similar to that observed in Hodgkin lymphoma [84]. Changes to the microenvironment of the infected B cell might also help to explain the double function of LMP-1 in asymptomatic host: drive the differentiation of EBV-infected GC B cells and elicit a potential oncogenic effect [84]. Moreover, as the healthy immune system tends to remove EBV-infected cells expressing multiple immunogenic viral proteins, there is a selective negative pressure for which EBV-induced tumors evolve in a way that is EBV-independent by switching off EBV genes and by acquiring compensating genetic alterations to survival and growth [82, 83]. In addition, the view that only the latent phase of viral gene expression is important during the development of EBV-associated malignancies has recently changed, suggesting a potential role also for viral gene products [3]. There are several potential mechanisms by which EBV lytic gene expression could contribute to the growth of EBV-associated tumors in vivo: by increasing the horizontal transmission of the virus from cell to cell, lytic infection may increase the total number of latently infected cells; moreover, viral lytic genes, or cellular genes induced by viral lytic proteins, could potentially encode paracrine factors and angiogenic factors that promote tumor growth and immune escape [29, 33].

EBV-associated malignancies include B- and T-/NK-cell lymphomas as well as non-hematological malignancies [59, 71, 74, 80]. In particular, EBV-positive B-cell lymphomas might be thought of as rare accidents of EBV colonization of B cells, and the pattern of virus latency observed in the different histotypes might be taken as evidence of the stage of B-cell differentiation from which the tumor is derived [85].

Lymphoma:

- *Hodgkin lymphoma* both in non-immunodeficient and in immunodeficient (congenital, HIV, posttransplant) patients
- *Non-Hodgkin B-cell lymphomas* (NHL) both in non-immunodeficient (BL, diffuse large B-cell lymphoma (DLBCL) of the elderly, pyothorax-associated lymphoma (PAL), and lymphomatoid granulomatosis (LYG)) and in immunodeficient patients (BL, primary central nervous system DLBCL, primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL), posttransplant lymphoproliferative disorders (PTLD))
- *Non-Hodgkin NK-cell or T-cell lymphomas*: peripheral T-cell lymphomas, angioimmunoblastic T-cell lymphoma, extranodal nasal-type NK-/T-cell lymphoma, T-cell lymphoproliferative disorders of the childhood, and EBV-associated cutaneous T-cell lymphoproliferative disorders

Carcinoma:

- Nasopharyngeal
- Gastric
- Lymphoepithelioma-like

Sarcoma: in immunodeficiency setting (leiomyosarcoma)

8 EBV-Associated Lymphomas

- *Hodgkin lymphoma* (HL) is a neoplasia composed of tumor cells designated Hodgkin cells or Reed-Sternberg cells residing in an abundant heterogenous admixture of nonneoplastic inflammatory cells. The tumor cells are usually ringed by T cells in a rosette-like manner. EBV positivity in lymphoma tissue is detected in 70 % of mixed cellularity, 95 % of lymphocyte depleted, and 10–40 % of nodular sclerosis; the lymphocyte-predominant subtype is almost always EBV negative. The role that EBV plays in HL is still not fully understood. EBV gene expression follows the latency II pattern with EBNA-1, LMP-1, LMP-2A, and LMP-2B and the EBERs being expressed. The role of EBNA-1 in carcinogenesis and the oncogenic capabilities of LMP-1, LMP-2A, and LMP-2B and the EBERs have been addressed above. In addition, EBV provides important antiapoptotic signals that prevent cell death in HL progenitors lacking a functional BCR. Loss of BCR and of other key components of the BCR signaling machinery could be important for the pathogenesis because they might protect HL progenitors from entry into the EBV-replicative cycle and subsequent cell death. In addition, chronic inflammation in the microenvironment might not only dictate the pattern of EBV gene expression but also modulate the oncogenic functions of individual EBV genes such as LMP-1 [48].
- *Burkitt lymphoma* (BL) is a highly aggressive B-cell non-Hodgkin lymphoma characterized by peculiar clinical, morphological, immunophenotypical, cytogenetic, and gene expression profile features. Differences in geographical distribution and association with EBV and HIV account for three epidemiologically distinct variants: the endemic BL (eBL), sporadic BL (sBL), and immunodeficiency-associated subtypes. EBV has been detected in virtually all cases of endemic variant, 15–20 % of the sporadic form and 30–40 % of the immunodeficiency-related BL. Most EBV-positive cases exhibit the latency I type; however, we have recently demonstrated a noncanonical latency program in BL characterized by the expression of either LMP-1 and LMP-2 along with some lytic gene products (Leoncini L et al., 2014, personal communication). EBV contributes to the pathogenesis of BL by providing the antiapoptotic signals necessary to override MYC-induced cell death, thanks to EBNA-1 expression. Since only one EBNA-1 is expressed in BL, a substantial role for EBV-encoded miRNAs in BL does exist in regulating apoptosis, gene expression, immune system, and other processes [22, 51, 53, 63].
- *Posttransplant lymphoproliferative disorders* (PTLD) is a clinicopathological entity encompassing a heterogeneous group of disorders that follow solid-organ transplant or bone marrow allograft as a consequence of immunosuppression and range from reactive hyperplasia to malignant monoclonal forms. According to the WHO classification, they are divided into early lesions (reactive plasmacytic hyperplasia and mononucleosis-like syndrome), polymorphic lesions, monomorphic lesions, and Hodgkin-like lesions. EBV has been linked to most PTLDs, with a near 100 % association in the early occurring cases (within a year) and in

PTLD-associated HL. The EBV-negative PTLDs constitute approximately 20 % of all cases, have a tendency to late occurrence (>5 years posttransplant), and have an unknown etiology. Type III latency is exhibited by the EBV-positive B cells in PTLD, although some studies have reported a more restricted latency pattern. The wide expression of the latent EBV-encoded proteins strongly suggests an important role that EBV may play in the oncogenic process. Because approximately 50 % of PTLD cases are derived from GC B cells lacking a functional BCR for crippling mutations and because these cells manage to escape apoptosis despite lacking antigen affinity, it is believed that EBV aids in rescuing these cells from an imminent programmed cell death. As in HL, LMP-1 and LMP-2A may replace survival signals induced by activated BCR and CD40 receptors and also activate the NF-κB signaling pathway, inducing proliferation of neoplastic cells. The decreased cytotoxic T-cell surveillance because of immunosuppression in PTLD patients is also believed to greatly facilitate the actions of EBV [43].

- *Lymphomatoid granulomatosis* (LYG) is a rare angiocentric and angiodestructive B-cell lymphoproliferative disorder that is composed predominantly of reactive T cells and fewer neoplastic EBV-positive B cells. The most common site of involvement is the lung, with less frequent involvement of other extranodal sites such as the skin, kidney, liver, and central nervous system. The latency pattern for EBV has not been extensively studied in lymphomatoid granulomatosis; but one group has reported the detection of LMP-1 and EBNA-2 by immunohistochemistry and the EBERs by in situ hybridization, which is indicative for type III latency. The near 100 % EBV association with lymphomatoid granulomatosis and the presumed wide expression of EBV latent-encoded proteins strongly infer that EBV is not just an innocent bystander but may play a crucial role in the pathogenesis of the disease [18].
- *Other B-cell lymphomas*: *PAL* is an NHL developing in the pleural cavity after a long-standing history of pyothorax; it is characterized by a type III latency [70]. *EBV-positive DLBCL of the elderly* is a clonal B-cell lymphoid proliferation that occurs in patients over the age of 50 years and without any known immunodeficiency or prior lymphoma, showing a type II–III latency [36]. *PEL*, a rare and distinct tumor that affects body cavities without a detectable tumor mass, is predominantly associated with HHV-8 infection. The expression of EBV-encoded proteins is consistent with type II latency [10]. *PBL* is characterized by a diffuse proliferation of large neoplastic cells, most of which resemble B immunoblasts, but in which all tumor cells have the immunophenotype of plasma cells. The exact role elicited by EBV in inducing lymphomagenesis still remains unknown as well as its latency type, although a type I latency has been suggested [49]. However, we have recently performed an miRNA's profiling and a complete study of EBV products, finding the expression of EBV-encoded miRNAs belonging to the BART locus and a noncanonical latency of the virus with an abortive lytic cycle [3]. Lastly, virtually 100 % of *primary central nervous system DLBCL* shows EBV association with a latency III type [69].

- In *NK-cell and T-cell lymphomas*, the exact role of EBV (which has a type I/II latency) in the oncogenesis is still hypothetical, although the increased IL-9 levels induced by the EBERs possess antiapoptotic effects and promote T-cell proliferation and transformation. Moreover, LMP-1 may mimic or act as a viral analog for members of the family of TNF receptors, thereby transmitting growth signals through cytoplasmic TNF receptor-associated factors [87].

9 Non-hematological Tumors

EBV is also associated to a number of tumors of non-hematological origin; however, all these diseases arguably arise from rare circumstances in which the virus gains entry into an unnatural host cell type as situation where the intracellular signals that normally govern virus behavior in its natural target cells may no longer operate. This category includes *nasopharyngeal carcinoma* (in which it has been demonstrated that EBV may elude immune system by encoding a series of viral microRNAs) [81], *lymphoepithelioma-like carcinoma* (in which EBV expresses EBNA-1 and LMP-2A rather than EBNA-2, LMP-1, and ZEBRA and thus a latency I type) [1, 11], *gastric carcinoma* (in which EBV exhibits a novel latency pattern that includes the production of BARF-1, a homologue to human colony-stimulating factor 1 receptor and intracellular adhesion molecule 1, and the absence of LMP-1; although any mechanism relating EBV to tumorigenesis in gastric malignancies remains highly speculative, it has been demonstrated that there are a delay in apoptosis in EBV-positive gastric carcinomas, associated with upregulation of BCL-2 and p53, and a decrease in cellular differentiation, associated with decreased E-cadherin expression) [52], and *smooth muscle tumors* (although normal smooth muscle cells do not usually express the EBV receptor CD21 and it is not clear how the virus enters the cells, in both congenital and acquired immunodeficiency patients, EBV may activate the PI3K/mTOR signaling as well as the dysregulation of cellular miRNAs machinery; in this setting, the virus shows a type I latency by encoding EBNA-1 and EBER but not LMP-1) [30].

10 Treatment Strategies for EBV-Positive Tumors

Several treatment strategies have been tried in the management of EBV-positive tumors [55]. Some of these treatment modalities include combination cytotoxic therapies, induction of lytic EBV infection, and immunotherapy using EBV-specific cytotoxic T cells. A large body of evidence suggests that a combination of such approaches will be helpful in the near future. In particular, in those patients in whom an activation of lytic cycle does exist, a therapeutic regimen point to reduce the reservoir of latently infected cells (i.e., rituximab also in CD20-negative lymphomas)

and inhibit lytic replication (i.e., acyclovir), in combination with routine chemotherapy, should appear to be a promising approach [67].

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HPV and Cancer: Epidemiology and Mechanism of Carcinogenesis of the Virus HPV

Silvia de Sanjosé and Laia Alemany

1 Human Papillomaviruses (HPV)

1.1 Viral Structure

HPV viruses belong to the *Papillomaviridae* family that includes 16 genera (Fig. 1). The alpha and beta viral genera have humans as the main host. The alpha genus contains those types that infect mucosal epithelial cells leading to an important proportion of anogenital cancer cases, while the types included in the beta genus, with a specific cutaneous tropism, are related to skin tumors [1, 2]. Papillomaviruses are small non-enveloped double-stranded DNA virus (Fig. 2). Their genome is organized in three regions: the long control region (LCR) that regulates the viral gene expression and replication; the early region (E) encoding proteins required for viral expression, replication, and survival (E1–E7); and the late (L) region, which encodes the viral structural proteins L1 and L2. Two oncogenes E6 and E7 are recognized to deploy a major role in carcinogenesis inducing cell proliferation of the basal cells of the epithelium. E6 targets the tumor suppressor protein p53 and E7 targets pRb. E6 and E7 are the only viral proteins that are consistently expressed in HPV-associated cancers. E6 and E7 have oncogenic activities, and their expression is necessary for the induction and maintenance of the transformed phenotype. The activity of these

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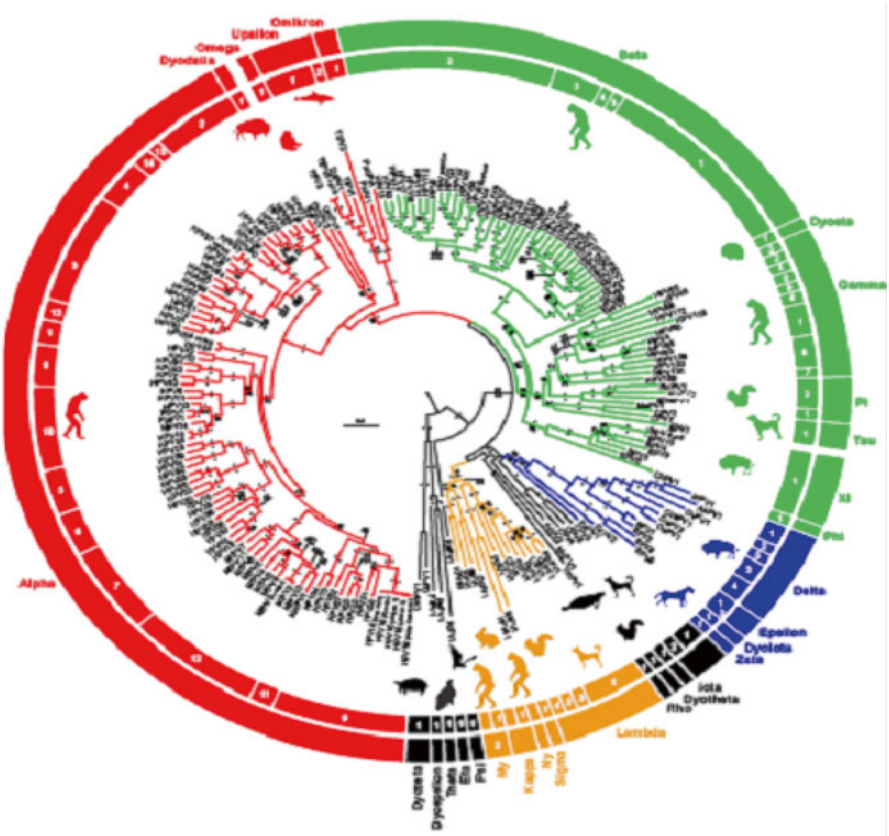

Fig. 16.1 HPV viruses belong to the Papillomaviridae family that includes 16 genera [2]

related proteins varies between different HPV types explaining part of the different oncogenic capacity of HPV types [3].

1.2 Genotypes

To date, more than 150 human papillomavirus (HPV) types have been completely sequenced. The HPV types linked to anogenital and oropharyngeal cancers are generally categorized as high-risk and low-risk types based on their association with human cancer on epidemiological studies or on their evolutionary profile [3, 4]. Among all potential high-risk types, 12 HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are classified by the International Agency for Research on Cancer (IARC) as *carcinogenic to humans* (category 1); HPV 68 is categorized as *probably* carcinogenic (Group 2A) and HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, and 97 as *possibly* carcinogenic (Group 2B) [5]. Among cervical cancer cases,

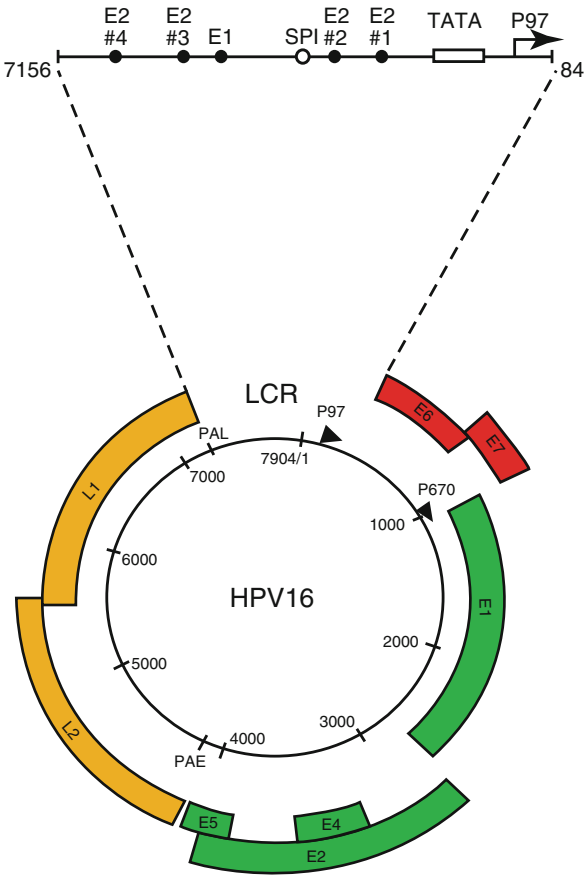

Fig. 16.2 Genetic structure of HPV 16 [3]

96.9 % will harbor types belonging to the IARC Group 1, and over 70 % of cervical cancers will be attributable to HPV 16 and/or 18 [6, 7]. In sites other than cervix, HPV 16 tends to play even a higher contribution (Table 1).

HPV 6 and 11 are considered low-risk types or *not classifiable as to their carcinogenicity to humans* (category 3) [5]. These later types are responsible of the large majority of genital warts and in very rare occasions have been linked to cervical, vulvar, anal, and penile cancer [8].

2 HPV Acquisition and Persistence in the Cervical Mucus

Mucosal HPV infection in the cervical mucus is very common and largely acquired through sexual activity. As such, HPV is highly prevalent in the years around sexual initiation decreasing thereafter as a consequence of acquired immune response and a decrease of sexual exposure of new partners with age [9, 10]. When data on women of all ages and with no disease are combined, the estimated point prevalence of HPV

Table 16.1 HPV types according to the level of evidence of carcinogenicity for human cancer

HPV broad risk categories	International Agency for Research on Cancer (Vol 100B)	HPV type	Relative contribution in cervical cancer (%)[d]
High risk	Group I Carcinogenic to humans	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59	96.9
	Group 2A Probably carcinogenic to humans	68	0.7
	Group 2B Possibly carcinogenic to humans	26, 53, 66, 73, 82	1.3
		30, 34, 69, 85, 97[a]	0.5
		5, 8[b]	0
Low risk	Group 3	6, 11[c]	0.1

[a]Based on phylogenetic similarity with other high-risk types
[b]Among patients with epidermodysplasia verruciformes
[c]Although very rare, HPV 6 and 11 were classified as Group 2B in IARC Monograph no. 90 due to their potential involvement in the larynx (squamous cell carcinoma) and in the vulva, penis, and anus (verrucous carcinomas of the latter three sites). Oncogenic role in anogenital sites is supported by additional data (Guimera et al. [8]) Ref. IARC 100B pp 295
[d]Based on the relative contribution among HPV DNA positive samples of invasive cervical cancer. =.5 % type unknown. Data from Ref. [10]

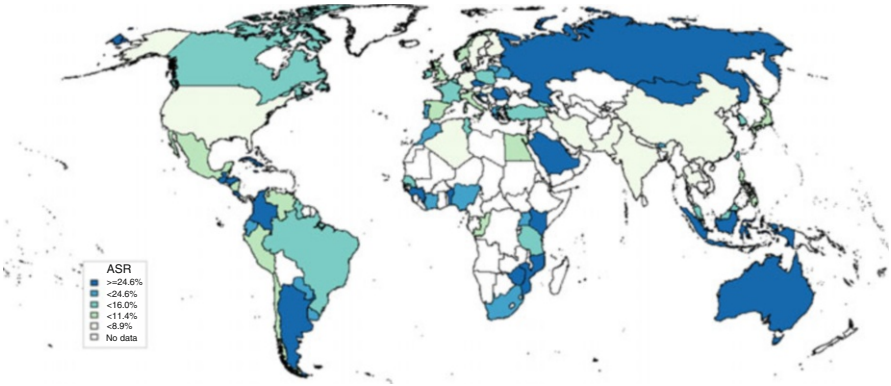

Fig. 16.3 Prevalence of HPV among women with normal cytology in the World Data updated at 15 Dec 2014 (data as of 31 Oct 2014). The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells. (Ref: http://www.hpvcentre.net)

infections worldwide is around 11–12 % (Fig. 3). The estimates are higher in sub-Saharan Africa (24 %), Eastern Europe (21 %), and Latin America (16 %). Lower estimates are seen in Northern Africa (9 %) and Western Asia (2 %). These geographical differences can largely be explained by variations of age at sexual initiation and the average number of sexual partners in the population. The study of HPV prevalence by age group is an excellent surrogate of the sexual behavior in the community which in turn can be useful when planning preventive strategies such as best age at vaccination

or screening strategies based on HPV DNA detection. As an example, one could compare the HPV DNA detection in vaginal samples in young girls in two contrasting countries in terms of cervical cancer incidence. In Tanzania, a country with very high incidence rate of cervical cancer, 36 % of girls aged ≤16 years were already HPV positive; the prevalence increased to 86 % in 19–20-year-olds and then declined to 64 % in those aged >23. In a similar period in Spain, a country with low incidence of cervical cancer, HPV picked at 29.9 % at age 19 [11–13]. After 12 months of follow-up of the young girls in Tanzania, only 27.2 % of those originally detected to harbor HPV infection remained positive, in agreement with other prospective studies [14].

Contrary, infections seen in women in the middle ages are more likely to be prevalent as new infection acquisition is less prominent at these ages [15]. The fraction of persistent carriers of HPV in this age group is estimated in a range of 4–10 %, and these women are the true high-risk group for cervical cancer.

Interestingly, HPV in postmenopausal women shows important variations in different geographies. While worldwide HPV reaches its lowest estimates after age 50, it is common to observe in some studies a second rebound of the prevalence. It is unclear what drives this second peak, but the lack of a universal pattern seems to indicate that it must relate to either behavioral aspects (i.e., acquisition of new partners or use of local estrogens) or to a cohort effect where the overall pattern reflects the sum of several cohorts with different background HPV prevalence.

In all these age-related scenarios of HPV infection, the time lag between the peak of HPV infection and the peak of cancer incidence is around two to four decades, making the initiating infections and precursor lesions of cervical cancer an appropriate target for screening and early detection.

Unfortunately, the mechanisms related to the process to clearance or persistent infection are still unknown. Host, virological, and behavioral factors may all play a role. Probably, the best recognized factor is the higher persistence associated to HPV 16 infection compared to other HPV types [14]. Some screening strategies now recommend to have a distinctive follow-up of women that screen positive for HPV 16/18 as compared to other types [16].

2.1 Non-viral

Several cofactors have long been proposed, such as smoking and parity that determine whether a woman develops CIN3 and eventual cervical cancer. Diet and coinfection with other STI (i.e., HIV, *Chlamydia trachomatis*) are also likely to play a role. Host immunity is an obviously important but difficult-to-study etiologic factor. Condom use is partially protective from initial infection; however, its role in clearance of persistent infections is less clear [14].

HIV infection is probably one of the most relevant cofactors for cervical carcinogenesis [17, 18]. Women infected with HIV had higher prevalence of HPV infection, persistent infection with HPV, infection with multiple types of HPV, and higher prevalence of cervical cancer precursors. In a study with South African women,

HIV seroconversion almost doubled the HPV prevalence after seroconversion and showed increased risk of low-grade cytological abnormalities compared with HIV-negative women [19]. However, data on 241 HIV-positive women with ICC, mainly from sub-Saharan Africa, suggest that the combined prevalence of HPV16 and/or 18 is 68 %, i.e., not different from the prevalence found in HIV-negative women with the same disease in the same region.

3 HPV and Cervical Cancer

Cancer of the cervix uteri is the fourth most common cancer among women worldwide, with an estimated 527,624 new cases and 265,653 deaths in 2012. This represents 4.1 % of the total cancers diagnosed in the world every year and 75 % of all HPV-related cancer sites. Worldwide, mortality rates of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 50.3 % [20]. The majority of cases are squamous cell carcinoma followed by adenocarcinomas [21, 22].

The first signs of an HPV infection are morphologically recognized as cervical intraepithelial lesions grade 1 or low-grade lesions (CIN1/LSIL). These have a high potential to regress, and no treatment is recommended. If the infection persists, the cellular changes become more generalized and pronounced leading to CIN 2/3 or high-grade lesions (HSIL). These lesions, generally asymptomatic, are detectable through screening and require treatment as their regression potential is very low [23]. In a very small proportion of women, the HPV infection can evolve ultimately inducing invasive cervical cancer. In this case, women show up with clinical symptoms such as abnormal bleeding, abdominal pain, or coital pain. The time from infection to invasive cervical cancer can be that of decades and is extremely rare to observe cancer cases before the age of 30. In screened populations, it is however common to detect CIN2–3 lesions in women younger than 30 years old which may favor overtreatment of regressing lesions.

Case-control studies exploring the risk to develop invasive cervical cancer associated to individual HPV types showed that the magnitude of the risk can be over 200 times higher for some high-risk types like HPV 16 and HPV 18 compared to uninfected women of same age [4]. As it can be seen in Fig. 4, only HPV 6 and HPV 11 showed a non-statistically significant increased risk. This is in agreement with the rare observation of these types as cause of human cancer.

HPV is recognized to be the necessary cause for cervical cancer development of epithelial origin, well accommodating the established causality rules [24, 25]. Over 90 % of the cervical cancer cases not only harbor viral HPV DNA but also show detection of transcripts encoding the viral E6 and E7 oncoproteins supporting the cell transformation step necessary for carcinogenesis [26, 27]. The HPV-type distribution in cervical cancer specimens has been extensively studied [4, 6, 28]. Worldwide, HPV 16 and 18 contribute over 70 % of ICC cases, and HPV 16, 18, and 45 can explain over 90 % of cervical adenocarcinomas. Globally, HPV 16, 18, or 45 ICC cases are reported to be diagnosed at younger ages than other HPV types [6, 29].

Few exceptions are documented in which cervical cancer tissue of epithelial origin is HPV negative after applying different HPV assays. In particular,

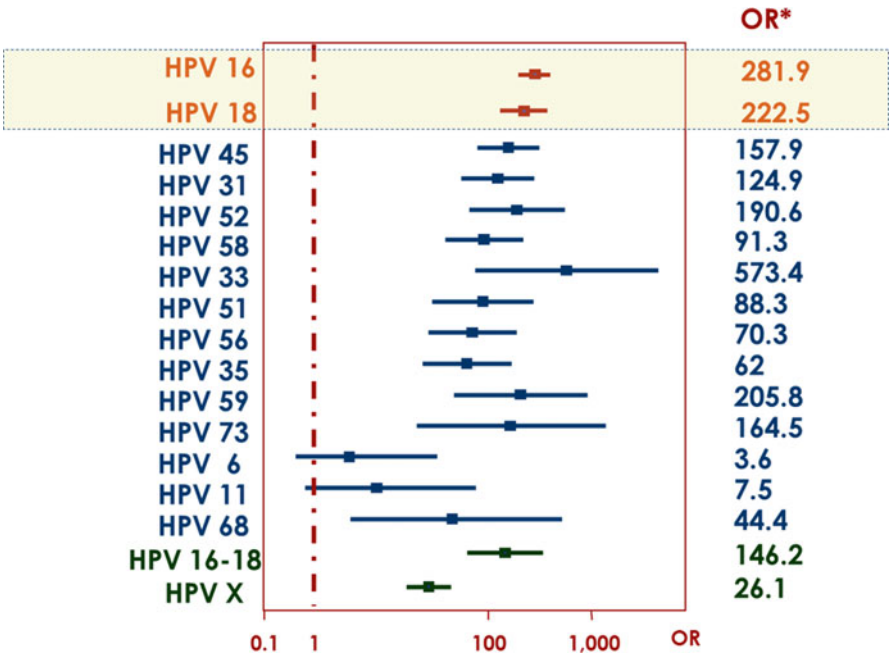

Fig. 16.4 Odds ratios and 95 % confidence intervals of invasive cervical cancer by individual genotypes [4]

HPV-negative cases are identified in some subtypes of the adenocarcinoma category [30, 31]. There are no large series of adenocarcinoma samples using fresh tissue where DNA is easily detected. However, a series of 682 paraffin-embedded tissue samples of adenocarcinomas has been recently evaluated in HPV detection after careful pathology review aiming to exclude misdiagnosis of endometrial tumors. In the series, cases classified as classic cervical adenocarcinoma type contributing 83 % of the total showed high HPV positivity (71.8 %), while the other less common subtypes had significantly lower HPV prevalence (endometrioid 27.3 %, serous 25 %, clear cell 20 %, not otherwise specified 13.9 %, and minimal deviation 8.3 %). Although a different etiological pathway cannot be dismissed for rare adenocarcinoma subtypes, negativity was related to region, advanced patient's age, and longer sample storage time. These cases can be considered anecdotal and do not suggest any major change of our understanding of cervical carcinogenesis.

3.1 Screening

Cervical cancer persistently shows a social inequality pattern by which the poorer have higher rates of disease [32]. This social gap between and within countries is largely attributable to poor screening uptake. Cervical cancer takes decades to develop, and early detection of preneoplastic lesions is a major asset for cancer

prevention. Regular exam of cervical exfoliates through cytology or HPV detection has been shown to decrease mortality of cervical cancer [33–35]. Unfortunately, few women in the world have a regular access to screening [36]. While in the Western Europe over 70 % are regular users of screening, in sub-Saharan Africa less than 5 % of the women have ever been screened. In developed countries, invasive cervical cancer mainly arises in non-screened women pointing to the relevance of reaching high population coverage to impact incidence and mortality of disease.

4 HPV and Vulvar, Vaginal, Anal, and Penile Cancers

Cancer incidence rates at anogenital anatomical sites other than cervical cancer are much lower than that observed for cervical cancer. Vulvar cancer is a rare entity with age-adjusted incidence rates ranging from 0 to 4.6 per 100,000 women-year, representing about 4 % of all gynecological malignancies. It is estimated that each year, about 27,000 new cases are being diagnosed worldwide [7, 21]. Lower rates are observed in Asia and Africa than in other parts of the world. Over the past few decades, the incidence rates of invasive vulvar cancer (IVC) and vulvar intraepithelial neoplasia (VIN) have both been reported to increase, particularly among younger women. However, in the United States, the increase is limited to preneoplastic lesions, and in the United Kingdom, trends are stable [37].

Squamous cell carcinoma (SCC) accounts for more than 90 % of the malignant tumors of the vulva. The basaloid and warty histological variants, representing about 1/3 of cases, are common in younger women and are often associated with HPV DNA detection. These tumors share many risk factors with cervical cancer. By contrast, keratinizing variants arise from chronic vulvar dermatosis, such as lichen sclerosus, are most commonly not associated with HPV and tend to occur in older women. A recent large-scale worldwide analysis using a homogeneous protocol for HPV testing reported HPV DNA positivity in 28.6 % of invasive vulvar tumors and 86.7 % in preneoplastic lesions. Positivity decreased to 25 % in vulvar carcinomas when in addition to viral DNA $p16^{INK4a}$ overexpression was also considered as a criterion for an HPV-induced cancer. HPV16 was the most common type identified representing over 75 % of all positive cases [38].

Vaginal cancer is also a rare malignancy, with an estimated of 13,000 new cases diagnosed worldwide in 2008 and accounting for about 2 % of all gynecologic cancers (Table 2) [7]. The age-adjusted incidence rates range from 0.5 to 1.7 per 100,000 women per year. Most vaginal invasive cancer cases occur in patients older than 60 years, except for adenocarcinomas, which occur in younger ages [37]. Like in vulvar cancers, the SCC is the most frequently diagnosed histological type (80–90 %), followed by adenocarcinomas. As for cervical cancer, squamous cell vaginal cancer is preceded by premalignant lesions or vaginal intraepithelial neoplasia (VAIN).

Several risk factors have been described for vaginal cancer and in particular for the SCC type which resemble those of cervical cancer like smoking, immunosuppression, high number of sexual partners, and also history of cervical precancerous

Table 16.2 Anogenital cancers associated with HPV infection and with HPV 16 and 18 types

	Contribution of HPV (%)		Number of cancers		
Site	Attributable to HPV (%)	Attributable to HPV 16/18 (%)	Total	Attributable to HPV	Attributable to HPV 16/18
Cervix	99	70	530,000	530,000	371,000
Vulva	43	37	27,000	12,000	10,000
Vagina	70	61	13,000	9000	8000
Anus (female)	88	79	15,000	13,000	12,000
Anus (male)			12,000	11,000	9000
Penis	50	35	22,000	11,000	8000

Based on Martel et al. [7]

and cancerous lesions. In contrast, the vaginal adenocarcinoma type, particularly the clear cell adenocarcinoma, has been largely related in the past to in utero exposure to diethylstilbestrol (DES), which was prescribed as an antiabortive until the early 1970s [37].

In the analyses of 189 VAIN 2/3 and 408 invasive vaginal cancer cases collected from 31 countries, HPV DNA was detected in 74 % of invasive cancers and in 96 % of VAIN 2/3. Among cancers, the highest detection rates were observed in warty-basaloid subtype of squamous cell carcinomas, and in younger ages, HPV16 was the most frequently type detected in both precancerous and cancerous lesions [39]. Although there is still a small proportion of adenocarcinomas that are related to DES which are expected to be HPV-negative tumors, the majority of the remaining cases are consistently HPV related.

4.1 Anal Cancer

Globally, there are about 27,000 new diagnosed cases every year with an average worldwide incidence rate of 1 per 100,000 (Table 2). Since the 1970s, the incidence of anal cancer has been increasing in developed countries by about 2 % per year in the general population. The median age of diagnosis of anal cancer is 57 years among men and 68 years among women. Anal cancer is more common in certain high-risk groups; these include MSM (men having sex with men), anyone with a history of anal warts or high-grade CIN/VIN/cervical or vulvovaginal cancer, and immunosuppressed populations, including those with human immunodeficiency virus (HIV) infection and graft recipients [7].

Anal cancer affects more women than men. In the United States, the average annual incidence of anal cancer in 2007 had risen to 1.4/100,000 among men and 1.8/100,000 among women. The incidence of anal cancer among MSM was estimated to be as high as 37/100,000 prior to the onset of the HIV epidemic [40] and is even higher among HIV-seropositive MSM [41]. The advent of antiretroviral

therapy has not led to a reduction in the incidence of anal cancer [42]. The incidence may continue to increase as this population lives longer with HIV disease.

Histologically, like in other HPV-related anogenital cancers, these cancers are predominantly squamous cell carcinoma. The study of 43 AIN 2/3 cases and 496 anal cancers diagnosed from 1986 to 2011 using a common protocol showed that HPV DNA was detected in 88.3 % of anal cancers and in 95.3 % of AIN 2/3. The highest prevalence was observed in warty-basaloid subtype of squamous cell carcinomas, in younger patients, and in North American geographical region, and there were no statistically significant differences in prevalence by gender. HPV16 was the most frequent HPV type detected in both cancers (80.7 %) and AIN 2/3 lesions (75.4 %). HPV18 was the second most common type in invasive cancers (3.6 %). p16 (INK4a) overexpression was found in 95 % of HPV DNA-positive anal cancers [43].

4.2 Penile Cancer

Globally, the annual burden for penile cancer has been estimated to be 22,000 cases with incidence rates strongly correlating with those of cervical cancer (Table 2) [7]. Invasive penile cancer is rare and most commonly affects men aged 50–70 years. Incidence of penile cancer is higher in less developed countries, where penile cancer accounts for up to 10 % of male cancers in some parts of Africa, South America, and Asia. Penile preneoplastic intraepithelial (PeIN) lesions are rare. Cancers of the penis are primarily SCC (95 %), and the most common penile SCC histologic subtypes are in decreasing order keratinizing, mixed warty-basaloid, verrucous, warty, and basaloid. HPV DNA is most commonly detected in basaloid and warty tumors but is less common in keratinizing and verrucous tumors.

HPV DNA is detected in approximately half of the penile cancers. Among HPV-related penile tumors, HPV16 is the most common type detected, followed by HPV18 and HPV types 6/11 [7, 44]. Recently, Hernandez et al. reported even a higher HPV DNA detection (63 %) in a series of 79 invasive penile cancers from the United States and observed that penile cases diagnosed in more recent years were more likely to be HPV DNA positive [45]. Preliminary data from the ICO surveys show however lower detection rate of HPV DNA when samples from many countries are being analyzed [46].

5 Head and Neck Cancers

Worldwide, an estimated 599,637 new cases of and 324,794 deaths from head and neck cancers (excluding nasopharyngeal cancer) occur annually [21]. The epidemiology of head and neck cancers presents gender and regional diversities with most of the cases occurring among males in Southeast Asia and Eastern Europe, typically attributed to a higher tobacco and alcohol consumption. Over the last decade, data have

accumulated showing that HPV plays an etiological role in head and neck cancers in addition to tobacco and alcohol. A recent review has estimated that HPV attributable fractions in cancers of the oral cavity, larynx, and hypopharynx is at least fivefold lower than that of oropharyngeal cancer [47, 48]. An increase in the incidence rates of oropharyngeal cancer has been observed in several high-income countries during the last two decades as well as in the proportion of HPV-related oropharyngeal cancer [49, 50]. Several studies have shown that HPV-related oropharyngeal cancer patients respond better to treatment and have higher survival rates. Moreover, preliminary results from an ongoing randomized clinical trial designed to evaluate the efficacy of the bivalent vaccine against cervical HPV infections and lesions have shown strong protection conferred by the vaccine against oral infection with HPV16 and 18 [48].

In a recent meta-analysis, 148 studies were included, contributing data for 12,163 HNSCC cases from 44 countries. HPV was identified in 46 % of oropharynx, 22 % in larynx (including hypopharynx), and in 24 % of oral cavity cancer cases. Among subsites, tonsils showed the highest prevalence, 53.9 %. HPV16 accounted for 82.2 % of all HPV-positive cases. Over 86 % of the HPV DNA-positive cases were also positive to $p16^{INK4a}$ overexpression and to E6/E7 mRNA detection. All these data resulted in an attributable fraction of HPV in the oropharyngeal cancer sites defined by expression of E6/E7 mRNA or $p16^{INK4a}$ of 39.8 % and 39.7 %, respectively [51].

In the coming years, it is expected that a better understanding of the natural history of the HPV-related tumors in head and neck sites will be available. The avenues for secondary prevention need to be further explored, and research is ongoing in this terms. HPV vaccines are likely to have an impact, but data will take several years to be fully available due to the limited availability of detection of precursor lesions in these sites.

6 Strategies for Prevention

The development of HPV-related vaccines has opened a new avenue in HPV-related cancer prevention. The three existing HPV vaccines are Gardasil® (Sanofi Pasteur MSD), a tetravalent vaccine that includes 4 types, HPVs 6, 11, 16, and 18; Gardasil 9® a nonavalent vaccine that includes nine types, HPVs 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Merck Sharp and Dome); and Cervarix® (GlaxoSmithKline Biologicals), a bivalent vaccine against HPVs 16 and 18. They have been licensed by several regulatory agencies such as the European Agency for the Evaluation of Medical Products (EMEA) or the US FDA. HPV vaccines have been approved in over 100 countries and have been introduced in some national immunization programs, mainly in developed countries. The results from randomized controlled trials have demonstrated high immunogenicity, safety, and efficacy against cervical preneoplastic lesions (CIN 2/3) and vaginal, vulvar, and anal-related lesions to the HPV types included in these vaccines. Moreover, the quadrivalent vaccine has shown high efficacy against genital warts related to HPV6 and 11. Some years will be needed to document the impact on invasive HPV related cancers [52, 53]. The predictions estimate that between 70 and 90 % of the cervical cancer cases could be prevented in vaccinated cohorts [54, 55].

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Human Herpesvirus-8 (HHV-8) and Cancers: Scientific Background, Epidemiology, and Carcinogenesis of the Virus

Antoine Gessain and Olivier Cassar

1 Kaposi's Sarcoma

Kaposi's sarcoma was first reported as a disease in 1872 by the Hungarian dermatologist Moritz Kaposi. This initial description corresponds to the classical (C-KS) form, which occurs mostly in elderly individuals of Mediterranean or Middle-Eastern origin. It usually remains as an indolent disease affecting the lower extremities. Then, in the 1920s, the endemic (E-KS) form was reported in patients from several African equatorial countries. These E-KS are usually more aggressive than the C-KS and can occur, albeit rarely, in children. In the 1970s, KS were observed among renal transplant patients and in other patients receiving immunosuppressive therapy. These iatrogenic or posttransplant KS represent, in some areas, the most common posttransplant tumor. Lastly, a rapid emergence of KS was observed, beginning in 1981, in young homosexual men (men who have sex with men – MSM) in the USA. These AIDS-KS are especially clinically aggressive with frequent lymph nodes and mucosal involvement (Table 1) (for review on the different KS forms, see [1, 2]). KS represents one of the most frequent tumors in intertropical Africa, and nowadays, most KS cases worldwide occur in persons who are immunosuppressed. In 2010, the KS number is estimated to be around 43,000 representing thus around 0.4 % of all the world cancers [3, 4].

The histological features of the four epidemiological forms of KS are indistinguishable. This complex tumor, of mixed cellularity, is defined histologically by the coexistence at different levels, according to the evolution stage, of the main following features: a vascular proliferation, extravasated erythrocytes, inflammatory

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Table 1 Clinical and epidemiological forms of Kaposi's Sarcoma

Classic (1872)	Elderly men of Eastern, European, or Mediterranean origin	Slow chronic evolution Localized lesions Lower extremities
Endemic: three different forms (1914–1950)	Adults (mostly men) but also some children in Central, East, and South Africa	1. Slow evolution as classic KS 2. Usually more aggressive than classic KS with disseminated lesions with lymph node 3. Children form with lymph node
Immunosuppression associated/iatrogenic (1970)	Organ-transplant recipients	1. Chronic 2. Rapid aggressive evolution 3. Regressive in some cases after removal of immunosuppression
AIDS-associated epidemic (1981)	HIV-infected persons Homosexual men in Occident Heterosexual men and women in Africa	Aggressive Frequent disseminated lesions Visceral mucosal involvement Lymph node

infiltration, and the presence of tumor cells (spindle cells) [5]. At the early stage lesion (patch-stage KS), a macular lesion of the reticular dermis is observed with proliferation of small irregular endothelium-lined spaces with a variable inflammatory lymphocytic infiltrate. During the progression of the disease (plaque-stage KS), a small palpable lesion exists with expansion of a spindle cell vascular process in the entire dermis associated with a perivascular inflammatory infiltrate. At a late stage, lesion (nodular-stage KS), nodules, and tumors (skin, lymph node, etc.) are associated with proliferation of spindle cells (sheets, fascicles, etc.). The cellular origin of the spindle cells (the main proliferative elements of KS) remains a matter of debate; however it is suspected that HHV-8 infects circulating endothelial precursor cells driving them toward a lymphatic lineage [6].

2 Discovery of HHV-8

A viral etiology for KS has been suspected for a long time, and several viruses were detected in some KS lesions such as CMV, HHV-6, BK, etc. In the 1990, solid epidemiological studies indicate that an as-yet unidentified infectious agent, transmitted mainly by sexual contact, may cause Kaposi's sarcoma in persons with AIDS, especially in MSM [7]. In 1994, a new herpesvirus was first identified in a tumor biopsy from an AIDS-KS and called human herpesvirus-8 (HHV-8) or Kaposi's sarcoma-associated herpesvirus (KSHV) [8]. It is now considered as the causing agent of all forms of Kaposi's sarcoma. HHV-8/KSHV is a *Gammaherpesvirus* and the only known *Rhadinovirus* infecting humans. The 165 kb HHV-8 genome is notable for molecular piracy of several genes homologous to cellular regulatory genes that are likely to contribute to KS pathogenesis of KS [9].

3 HHV-8 Epidemiology, Geographical Distribution, and Modes of Transmission

Diagnosis of an HHV-8 infection is mostly based on the demonstration of specific antibodies directed against latent and/or lytic HHV-8 antigens in the plasma/sera of infected persons [10, 11]. While both assays perform very well in epidemiological studies, the latter are generally considered less specific than the anti-latent ones. This implies that seroprevalences are frequently lower in studies using anti-latent assays. Both ELISA, using different specific peptides, and immunofluorescence assay, using different HHV-8 infected cell lines, are used for serology. Direct detection of fragments of genomic DNA of HHV-8 is performed by specific polymerase chain reaction targeting different HHV-8 genes [11]. Sequencing of such amplicons, especially of the K1 gene (around 900 bp), is very useful for genotype determination and molecular epidemiological studies [12, 13]. Antibody titer determination, as well as viral load quantification, can be useful, especially for biological follow-up of some patients.

HHV-8 is not a ubiquitous virus and the viral global distribution is quite heterogeneous (Fig. 1). Generally speaking, areas of high or very high endemicity correspond mostly to the regions of classic and endemic KS forms. For instance, HHV-8 seroprevalence ranges from 20 to 80 % in the general adult population in sub-Saharan Africa, especially Central and East Africa [14], and in parts of South America [15], parts of China [16], and Melanesia [17]. Mediterranean countries have a global seroprevalence in adults ranging from 5 to 30 %, depending on the areas [18]. The low endemic regions are North America and most of European and Asian countries.

Fig. 1 Geographical repartition of HHV-8 seroprevalence. Relatively few studies were performed either in representative general population or among blood donors. Most studies were conducted to evaluate HHV-8 prevalence among high-risk populations (men who have sex with men (*MSM*) and HIV individuals) and to study mother-to-child transmission

However, in these regions, HHV-8 is often endemic in the homosexual male population. Indeed, MSM represent an important HHV-8 endemic population with a seroprevalence level ranging from 15 to more than 50 % in some countries [19, 20].

The epidemiological determinants, including the modes of transmission, are quite different depending on the studied population and the level of endemicity. In highly endemic areas, HHV-8 infection is mainly acquired during childhood and is very probably transmitted during mother-to-child contacts and between young siblings [21, 22] (Fig. 2). Indeed, in endemic population of African origin, studies have demonstrated a high level of familial aggregation, with strong evidence for transmission between children of the same family (especially in siblings with an age difference of less than 5 years) and from mother to child [22, 24]. It is also worth to note that in central, and mostly in East Africa, endemic KS can also occur in children [1, 2]. Interestingly, HHV-8 infection can be unevenly distributed from one region to another, suggesting nonuniform specificities in transmission modes [25].

In endemic areas, as rural general populations of Central and East Africa, adult HHV-8 prevalence is generally similar in men and women and increases slightly with age. In such populations, nonsexual transmission of HHV-8 is considered as

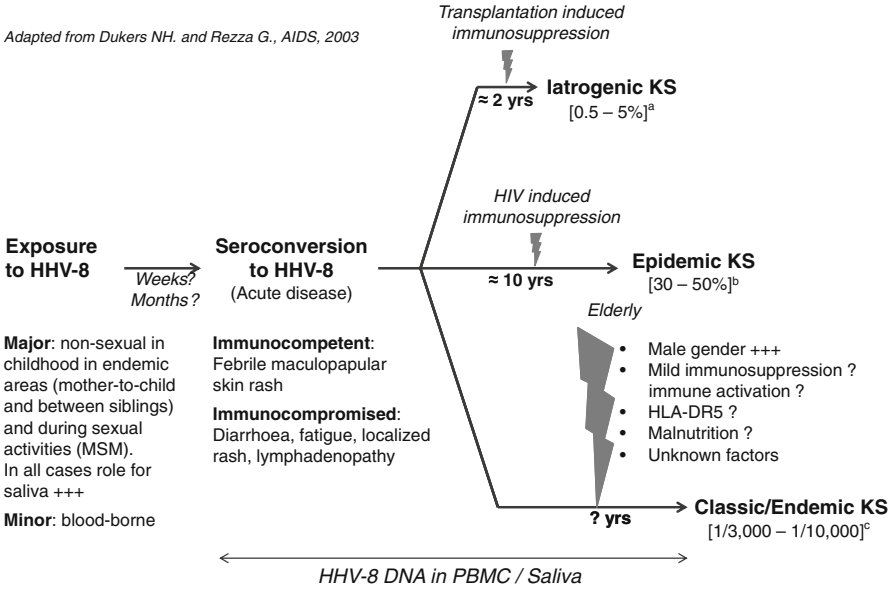

Fig. 2 Natural history of HHV-8 infection and KS development: Determinants and risks (Adapted from Dukers and Rezza [23]). (a) The incidence of KS after organ transplantation depends on the geographical origin of HHV-8-infected individuals (mostly patients of Mediterranean, Jewish, and Arabic ancestry) as well as the type of transplanted organ. (b) The risk of KS among HIV-infected individuals is higher when HHV-8 seroconversion occurs after HIV seroconversion. (c) The risk of KS among immunocompetent individuals over 50 years of age varies according to gender suggesting the existence of sex-related factors. *MSM* men who have sex with men

the major mode of viral acquisition. However, little remains known about HHV-8 spread in adult African population. This feature appears to greatly differ to that of industrialized/occidental countries where most of the infection seems to be acquired after adolescence, especially in high-risk groups. Indeed, it is clear that in MSM, HHV-8 is associated with sexual risk factors, such as number or partners and history of sexual transmitted disease [26]. In both high endemic areas, as Central Africa, and in high-risk population, as MSM, saliva is considered as the main vector of HHV-8 infection [27]. Transmission via blood transfusion seems rare, while transmission via solid organ donation has been clearly documented (for review on the different modes of transmission, see [9, 23, 28–30]).

As demonstrated for Epstein-Bar virus, some studies have suggested that HHV-8 prevalence may also be related to the socioeconomic level of the studied populations. In highly endemic areas of East Africa, HHV-8 infection is associated to factors such as low socioeconomic level, common living standard, water supply, and promiscuity [31]. Furthermore, few studies, conducted in another environment, show that populations that kept a traditional way of life show high prevalence for HHV-8. However, these data remain yet scarce, and other studies are necessary to appreciate the different items (environmental cofactors, specificities in ways of life influencing transmission modes, or even genetic features), which can lead to the apparent HHV-8 seroprevalence differences observed in different populations, especially in Africa.

4 Molecular Epidemiology

Molecular epidemiology studies on HHV-8 have mainly focused on the variable K1 region (ORF-K1), a region encoding a membrane protein-expressed during the early lytic phase of the viral cycle [32]. This has led to the identification of five main viral subtypes (A, B, C, D, E) that exhibit a geographical clustering. There is a 15–30 % amino acid difference overall among those subtypes and a 30–60 % amino acid difference within two K1 highly variable regions VR1 and VR2, which encode the areas usually targeted by the immune system on the K1 protein [32]. Subgroup A1–4 and subtype C are predominant among populations of European descent but also in North Africa, in the Mediterranean Basin, and in some regions of Asia. Subgroup B1–4 and clade A5 are predominant in sub-Saharan Africa. The reported subtype D sequences have been described in Southeast Asia (Japan, Taiwan) and in the Pacific (Australia, New Zealand, Wallis, Vanuatu), while subtype E is restricted to the Amerindian populations. Thus, HHV-8 appears to be a very ancient virus infecting the human population [13, 32, 33]. Its genetic variability can be used as a molecular mean to better understand population migrations. HHV-8 has several distinct simian counterparts that have been characterized both in nonhuman primates from the Old World (gorillas, chimpanzees, and macaques) and the New World (squirrel monkeys, marmosets, and tamarins) [34].

5 Other Cancers Associated with HHV-8

HHV-8 has been associated with other tumors such as primary effusion lymphoma (PEL) [35], most multicentric Castleman diseases (MCD) [36], and other rare associated lymphomas.

PEL is a rare and aggressive B-cell non-Hodgkin lymphoma that usually present with malignant effusion without tumor mass. An extracavitary or solid variant has also been described. PEL is always associated with HHV-8 infection and also frequently with EBV. Most PEL occur in the context of HIV infection or during an immunosuppressive therapy. PEL can also occur in elderly persons from a high HHV-8 endemic area. PEL cells typically express a hemato-lymphoid marker, CD45, but they usually lack expression of B-cell markers. Furthermore, they express plasma cell markers such as CD138. PEL is generally resistant to chemotherapy with a median of survival of less than 6 months (for review, see [35]).

MCD is an uncommon lymphoproliferative disorder, corresponding mainly to the histological plasma cell variant of CD. It is a systemic disease that commonly occurs in the setting of HIV infection and is always associated with HHV-8 infection in this case. MCD is clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, and systemic inflammatory symptoms. Both human and HHV-8-associated interleukin 6 are crucial in MCD pathogenesis. The management of MCD remains complex (for review, see [36]).

6 Evidences Linking HHV-8 to Kaposi's Sarcoma

HHV-8 is now clearly considered as the causative agent of KS. This is based on the numerous following evidences: HHV-8 DNA (with a high viral load) is present in all KS biopsies but rarely in other tumors; the detection of HHV-8 DNA in PBMCs of HIV patients is predictive of those who will develop KS; the populations at risk for KS have a higher seroprevalence than those at low risk; in advanced tumor KS lesions, HHV-8 is latently expressed in most of the cells; tumoral KS lesions have a clonal HHV-8 pattern; lastly, HHV-8 fulfill several of the Bradford-Hill criteria for causality. HHV-8 is thus the necessary, albeit not sufficient, causal agent of KS [1].

It is also worthwhile to note that several features concerning KS spindle cell biology, clinical involvement, and evolution after therapy, as well as KS clonal pattern, indicate that KS is not a typical cancer (reviewed in [6]). How HHV-8 gene expression promote such quite peculiar tumor is not the matter of this chapter and has been reviewed [1, 6, 9, 37].

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Epidemiology and Mechanism of Carcinogenesis of Schistosomiasis

Birgitte Jyding Vennervald

Schistosomiasis is a water-related vector-borne disease caused by blood-dwelling trematodes (blood flukes) of various species. The infection is widespread with 85 % of the infections occurring in sub-Saharan Africa. It is estimated that 230 million people are actively infected and a similar number are suffering from postinfection morbidity [7]. It is a poverty-related disease, and it is highly prevalent in areas where adequate facilities with respect to water and sanitation are scarce [1]. Of the several species of human schistosomes, only *Schistosoma haematobium,* which causes urogenital schistosomiasis, has been classified as a carcinogen, and urogenital schistosomasis is associated with squamous cell carcinoma (SCC) of the urinary bladder [5, 13].

1 Epidemiology of Schistosomiasis

People get infected by contact with infested freshwater bodies such as natural rivers, streams, lakes and ponds as well as man-made irrigation schemes and dams where infected intermediate host snails are living and the infective stage of the parasite, the cercaria, will penetrate the skin of people when in contact with the water [1]. Water contact activities differ with respect to age and gender and will typically be related to domestic activities, recreational activities such as playing in water, and occupational activities where contact with water is inevitable. Often the occupation of the local population, such as fishing and farming, makes them particularly vulnerable to contracting infections. In such areas, the infection levels are often very high and

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transmission of the infection is intense. The infection is a result of often many years of exposure to the infested water, and children start getting infected as soon as they are old enough to have water contact. Adult worm pairs accumulate with time, and it has been estimated that worms have a lifespan of approximately 3–5 years. The infection levels typically peak around puberty where after infection levels drop to a low level in adults. Immunity develops slowly and is indicated by the fact that adults get reinfected to a much lesser extent than children despite contact with infested water. Furthermore, resistance to reinfection is correlated with specific immune responses against parasite antigens [8].

S. haematobium worms are located in the urogenital venous plexus especially the veins surrounding the urinary bladder, and parasite eggs accumulate in the bladder where they give rise to an intense inflammatory response in the mucosa. Children harbour active infections characterised by excretion of parasite eggs in urine, very frequently accompanied by haematuria, dysuria and inflammation-related urinary tract pathology such as bladder polyps, bladder wall thickening and sometimes hydronephrosis caused by intense local granulomatous inflammation caused by eggs deposited around the ureter ostia [8]. The infections observed in adults are most often chronic in nature, and parasite egg excretion may be low or absent. However, since schistosomiasis-associated cancer of the urinary bladder is found in adults, the occurrence of a cancer is not necessarily associated with detectable parasite eggs in the urine. The bladder cancer is a result of many years of exposure to infection and a steady accumulation of parasite eggs in the urinary tract tissue, resulting in long-term chronic inflammation [26].

The fact that the infection is poverty related and highly prevalent in rural areas where access to clean water and adequate sanitary facilities is very limited means that the cancer patients are found in areas where local health facilities are poorly equipped to diagnose and treat cancer and the patients often have a very long way to a secondary health facility or a hospital. In some instances, the patients are referred to the larger university hospitals in the capital. This is often a serious logistic and financial constraint for patients from rural areas.

2 Epidemiology of *Schistosoma haematobium*-Associated Cancer

It has been observed that bladder cancer and especially squamous cell carcinoma (SCC) is geographically associated with *S. haematobium* [6]. This is indicated by the fact that bladder cancer was reported as the most common type of cancer in men and the second most common in women in Egypt where it constituted approximately 30 % of the total cancer incidence [16]. This trend was also observed in other *S. haematobium* endemic countries. There are especially two points which characterise the *S. haematobium*-related bladder cancers. In infection endemic areas, the most frequent histological type is SCC, whereas transitional cell carcinomas (TCC) are predominant in non-endemic areas [9, 16, 20]. Secondly, patients with schistosomiasis-related SCC tend to be considerable younger than patients with TCC [20].

So far, no cohort studies on urinary bladder cancer and *S. haematobium* infections have been published, but significant positive associations between the occurrence of urinary bladder cancer and infection with *S. haematobium* have been reported in several case studies with estimated risks ranging from 2.0 to 14 [13]. Smoking is recognised as a factor playing a role in the development of bladder cancer in non-endemic countries, and recent case-control studies have taken this into consideration as a possible confounding factor. *S. haematobium* eggs can cause cervical lesions [14], but so far no significant positive associations have been demonstrated between cervical cancer and *S. haematobium* infection [13]. However, it has been proposed that egg-induced lesions may serve as an entry point for other carcinogenic agents such as human papillomavirus (HPV). *S. haematobium* may thus as such contribute indirectly to the increase of the number of HPV-associated cancers.

3 Mechanisms of Carcinogenesis

When *S. haematobium* eggs are deposited in the urinary bladder wall by the female worm, they give rise to an intense inflammatory response with the accumulation of lymphocytes, macrophages and eosinophils around the eggs [8]. Continuous infection and reinfection can lead to a state of chronic inflammation which seems to be associated with an increased risk of cancer initiation at the site of inflammation, and chronic inflammation plays a central role in *S. haematobium*-related cancer [12, 15, 17]. During the inflammatory response, cells like macrophages and eosinophils generate free oxygen radicals and nitrogen species in response to parasite eggs resulting in increased oxidative stress [22]. Eosinophils are found in high concentration in urine from people infected with *S. haematobium* during the stage of active infection, and the number of eosinophils in urine correlates positively with the degree of urinary tract inflammation [21]. Increased levels of oxidative stress in *S. haematobium-related* cancer correlate with genotoxicity, and this indicates a mechanism where oxidative stress induced by chronic inflammation and response to schistosome eggs results in nitric-oxide-mediated DNA alterations which may lead to genetic instabilities with potential malignant transformation [12].

By studying bladder tissue samples from cancer patients with *S. haematobium* eggs in the bladder tissue and/or a history of exposure to schistosomiasis, several genotoxic mechanisms have been described. Mutations in the tumour suppressor gene p53 are more frequent in tissue samples from patients with schistosomiasis-associated bladder cancer than in bladder cancer not related to schistosomiasis [2, 18]. Other mechanisms include DNA adducts [4, 10], gene methylation [11] deletions and/or mutations in tumour suppressor genes, oncogenes or genes associated with cell cycle control [4, 28]. Inflammation and passage of parasites eggs through the tissue result in repeated tissue damage which lead to restorative hyperplasia of the damaged tissue. This may promote the propagation of cells in which genotoxic DNA damage has been completed. Then it may become a matter of time and further genotoxic damage before a potential cancer occurs [16].

Furthermore, it has been speculated that *N*-nitroso compounds may play a role in schistosomiasis associated carcinogenesis. It is known that bacteria can reduce dietary nitrate to nitrite which may react with compounds in urine to produce *N*-nitroso compounds, and *S. haematobium*-infected individuals have been shown to have high levels of *N*-nitroso compounds in urine. Likewise, the level of *N*-nitrosodimethylamine in urine was significantly higher in *S. haematobium-infected* bladder cancer patients compared with controls [3].

4 Diagnosis of *S. haematobium* Infection

During the active stage, urogenital schistosomiasis is diagnosed by detection of parasite eggs in urine. Another indication of active infection is the presence of circulating antigens from the worms in serum or urine, whereas antibody measurements are of limited use in schistosomiasis endemic areas [7]. Ultrasound examination of the urinary tract reveals schistosomiasis-related pathology of the urinary tract such as bladder wall thickening, polyps and hydronephrosis and has been used as a non-invasive technique to document urinary tract morbidity and the impact of anti-schistosomal treatment on morbidity in school or community-based field studies or control programmes [27].

It is important to keep in mind that the above-mentioned diagnostic tools are useful when it comes to detecting active infections. By the time the bladder cancer has developed, the infection is most likely chronic or absent with very low or no egg excretion in urine.

5 Biomarkers in Urine

Although several studies have investigated urine biomarkers associated with schistosomiasis infection and related bladder cancer [24], there are currently no urine biomarkers which have been tested in larger clinical studies or follow-up studies assessing the cancer predictive or prognostic value of the tests. A recent study among patients treated with radical cystectomy for squamous cell carcinoma of the bladder showed that an increased number of altered tissue biomarkers had significant potential to predict the outcome of radical cystectomy for squamous cell carcinoma and might identify patients at high risk who would benefit from additional treatment approaches [28].

6 Management and Control

The development of schistosomiasis-related cancer of the bladder requires exposure to the infection for many years, and it is thus reasonable to believe that reducing the level of infection by regular treatment and the risk of getting (re)infected by

reducing the risk of exposure will reduce the risk of developing schistosomiasis related cancer later in life [7, 19, 25]. In Egypt, where schistosomiasis control programmes have been implemented through decades, the patterns of schistosomiasis-associated bladder cancer has changed from 2001 to 2010 with a decline in the frequency of schistosomiasis associated cancers and SCC and increase in the frequency of transitional cell carcinoma and the mean age of the patients [23].

Praziquantel is the drug of choice for schistosomiasis, and a dose of 40 mg per kg body weight as a single dose is the treatment for *S. haematobium.* It can safely be administered to pregnant women, and large-scale control programmes are based on yearly or every second year treatment of school-aged children and vulnerable groups [7]. From a public health perspective, schistosomiasis infections are preventable causes of cancer, emphasising the need for sustainable schistosomiasis control in endemic areas. World health Assembly resolution 65.21 recommends that schistosomiasis endemic countries intensify interventions to control schistosomiasis and embark on elimination programmes with a vision of eliminating schistosomiasis as a public health problem in 2025. This will no doubt reduce the number of new cases of schistosomiasis-associated bladder cancer with time, but it should be borne in mind that the cancer seen today is the result of heavy exposure and infection through the last 20–30 years. We will still have patients presenting with schistosomiasis-associated bladder cancer for many years to come. These patients are predominantly from poorer rural areas and have very limited resources to spend on seeking medical care. Improved diagnosis, management and care for these patients are warranted and should not be forgotten when we talk about eliminating schistosomiasis.

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Epidemiology of *Helicobacter pylori* and Mechanisms of Carcinogenesis

Philippe Lehours, Emilie Bessède, Francis Mégraud, and Christine Varon

1 Epidemiology

Soon after the discovery of *H. pylori*, numerous studies based on serological surveys highlighted an increasing prevalence of *H. pylori* infection with age within a population, which was inversely related to the socio-economic status [14]. This was related to the so-called cohort phenomenon: each age group has a different prevalence of an infection acquired primarily during childhood and lasting lifelong. The risk of acquiring the infection has decreased over the years due to improvement in socio-economic conditions.

Regarding Europe, the prevalence of *H. pylori* infection according to the year of birth has decreased quickly and dramatically in countries from Northern Europe (e.g. Finland), whereas it remains high in some countries from Southern Europe (especially Portugal) [11]. Indeed, *H. pylori* infection remains a frequent and early event in Portugal [13].

A gastric biopsy-based study conducted in the Brussels area (Belgium) over a 20-year period has also nicely shown that the prevalence was much higher in children (0–9 years old) with a North African origin compared to children with Western European origin. Therefore, these data show the effects of time, age and ethnicity on

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the prevalence of *H. pylori* infection and its complex heterogeneity in the same cosmopolitan urban area [15].

It has been estimated that approximately 50 % of the world's population harbours *H. pylori*. Are there any populations which are *H. pylori* free? The answer is clearly no, even if some countries show surprisingly low prevalence such as the Malay population [23].

The main reservoir remains the human stomach. The transmission between humans is mainly intrafamilial. The role of parents has been nicely investigated in particular by Dominici et al. in a prevalence-based study which assessed the presence of IgG antibodies; results showed a higher prevalence in children living in families where the two parents were infected compared to those living in a one parent-infected family. The predominant role of the mother in transmission was also noticed [5]. The study of transmission in families was further investigated on three families using microarrays and sequencing of two housekeeping genes [22]. The authors showed that two to five strains circulated within a given family. Identical strains were present in at least two members of all three families supporting the accepted model of intrafamilial transmission, but they also showed that sibling-to-sibling transmission and acquisition of *H. pylori* from outside the family were also probable.

The possible vehicles of *H. pylori* transmission are vomit, saliva and faeces; therefore, the routes of transmission are mainly gastro-oral, oral-oral or faecal-oral. *H. pylori* can indeed be found in viable form in vomit [21], and therefore, we now have strong arguments in favour of a gastro-oral transmission.

The publication of anecdotal reports of positive culture from saliva as well as PCR results points to saliva as another source of *H. pylori* transmission following regurgitation and vomiting.

H. pylori can be detected in faeces of infected individuals, and accordingly, an antigen stool test or even PCR detection can be performed to diagnose the infection. However, is *H. pylori* viable in faeces? Although *H. pylori* stool culture is extremely difficult, it is possible in case of a short intestinal transit that can be induced or spontaneous [21]. Therefore a faecal-oral transmission is possible mainly in developing countries where frequent diarrhoeal episodes are found, faecal hygiene is lacking and water to be used in the household is not well treated.

2 *H. pylori* Infection at the Origin of Malignant Diseases

H. pylori is a non-invasive bacterium that survives and multiplies in the mucus and on the gastric epithelial surface thanks to the production of a urease which allows it to neutralise the mucus acidity in the microenvironment.

H. pylori infection consistently induces a chronic inflammation of the gastric mucosa. In approximately 1 % of cases, the infection leads to two types of stomach cancer, gastric adenocarcinoma and gastric MALT lymphoma (Fig. 1).

At the cellular level, *H. pylori* infection leads to a Th1 immune response and to a chronic gastritis, followed by an increase in the apoptosis of the gastric epithelial cells resulting in atrophy and leading to a compensative cellular hyperproliferation and an alteration of the differentiation, which is at the origin of the intestinal

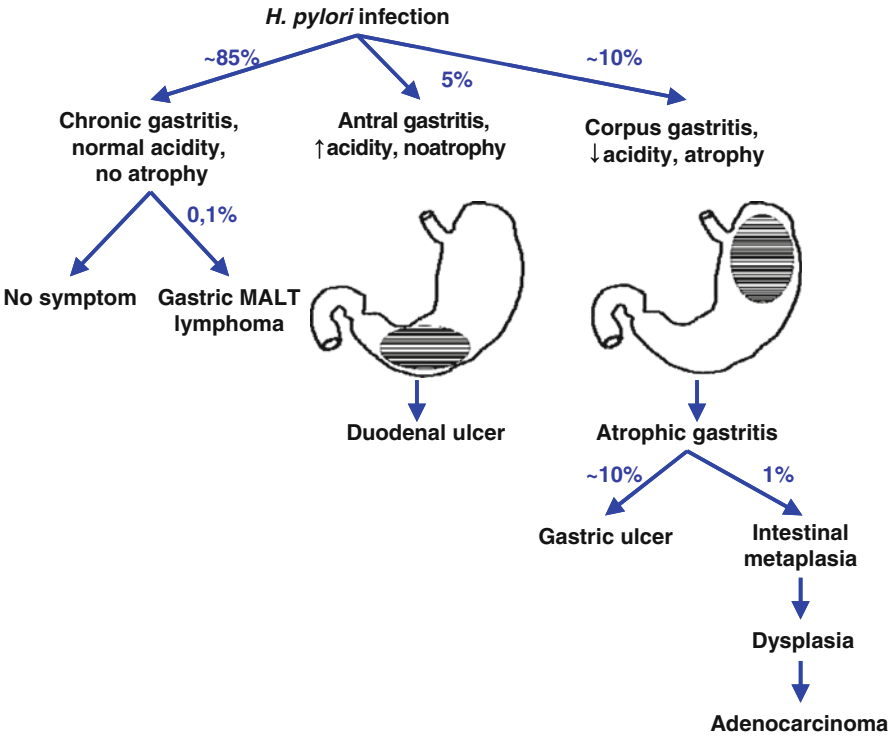

Fig. 1 Gastric pathologies induced by *Helicobacter pylori* infection

metaplasia [3]. These metaplastic lesions can further evolve into dysplasia, in situ carcinoma and finally an invasive adenocarcinoma.

Gastric MALT lymphoma (GML) caused by *H. pylori* infection in humans is one of the most beautiful examples of the role of a chronic infection and inflammation in cancer [26]. MALT-type lymphomas are the most frequent extranodal entities usually found in organs normally devoid of lymphoid tissue such as the stomach. The development of GML in humans is directly related to infection by *H. pylori* and appears in nearly 1 % of infected individuals. The association of *H. pylori* infection with GML is strong and causal: it is indeed currently the only cancer which can be cured at an early stage by an antibiotic treatment [25]. Chronic antigenic stimulation exerted by *H. pylori* on the gastric mucosa induces dense lymphoid infiltrates containing small centrocytic B cells expressing several surface markers typical of marginal zone B cells in normal MALT.

No bacterial virulence factor has yet been clearly associated with this disease [12]. A better understanding of the pathophysiology of this lymphoma has been hampered by the difficulty in obtaining primary xenografts from surgical specimens of GML patients. Based on the use of animal models, it is now admitted that the inflammatory, molecular and immunological contexts of the host prior to *H. pylori* infection are probably essential contributors to GML pathogenesis [4].

3 *H. pylori* Virulence Factors

H. pylori has developed a unique set of factors (Table 1), actively supporting its successful survival and persistence in its natural hostile ecological niche, the human stomach, throughout the individual's life, unless treated. In the human stomach, the vast majority of *H. pylori* cells are moving in the mucus layer lining, but a small percentage adhere to the epithelial cell surfaces.

H. pylori is one of the most genetically diverse bacterial species known, and it is equipped with an extraordinarily large set of outer membrane proteins (OMPs), whose role in the infection and persistence process is crucial. The large group of OMPs contains adhesins (BabA and SabA), adherence-associated lipoproteins (AlpA/B) and inflammatory OMPs (OipA or HomB) that mediate *H. pylori* binding to the host cell membrane. Some of these OMPs are associated with more severe pathologies, such as HomB in ulcers [19] and cancer [10]. The *babA* genotype correlates with the highest incidence of ulceration and gastric cancer [24].

One of the most extensively studied toxins produced by *H. pylori* is the vacuolating cytotoxin A (VacA). Infection with *H. pylori* strains containing the toxigenic allelic s1 form of VacA is associated with an increased risk of peptic ulceration and gastric cancer. Once internalised into the cell, VacA induces severe "vacuolation" characterised by the accumulation of large vesicles. VacA also exerts effects on target cells, including disruption of mitochondrial functions, stimulation of apoptosis and blockade of T-cell proliferation [20].

The oncoprotein CagA encoded by the *cag*A gene of the *cag* pathogenicity island (*cag*PAI) is one of the most studied virulence factors for *H. pylori*. The *cag*PAI encodes proteins assembling a type 4 secretion system (T4SS), which interacts with

Table 1 List of bacterial factors of *H. pylori* associated with gastric adenocarcinoma

Name	Function	Targets	Bacterial genotype associated with cancer
BabA	Adhesin	Lewis antigen	*bab*A2+
SabA	Adhesin	Sialyl-Lewis antigen	*sab*A+
OipA	Adhesin	Unknown	*oip*A+
HopQ	Adhesin	Unknown	*hop*Q1
HomB	Adhesin	Unknown	*hom*b+
VacA	Vacuolating cytotoxin	RTPβ receptor	*vacA* s1m1
T4SS	Type 4 secretion system encoded by the *cag*PAI	β1 integrin	*cag*PAI+
CagA	Oncoprotein	Cell-cell junctions proteins (ZO-1, JAM and E-cadherin), β-catenin, kinase PAR1, Src kinases, Erk1/2 kinases, SHP2 phosphatase, c-Met receptors	*cag*A+

cagPAI cag pathogenicity island

the α5ß1 integrin at the surface of the gastric epithelial cells and allows the injection of different bacterial effectors including CagA and pro-inflammatory components of the bacterial peptidoglycan directly into the cytoplasm of the host cell [29]. CagA thereby affects several signalling pathways and cell proliferation and differentiation states [1]. A direct causal link between CagA and gastric carcinogenesis was proven in transgenic mice expressing CagA: these mice spontaneously develop gastric polyps and adenocarcinoma, revealing CagA as the first bacterial oncoprotein [18].

4 *H. pylori*-Mediated Inflammatory Response

The role of inflammation in *H. pylori* infection is also of major importance as it triggers the outcome of this chronic infection.

The activity of the inflammatory response (polymorphonuclear and lymphoplasmacytic infiltration) as well as the preneoplastic lesions such as atrophy or intestinal metaplasia is evaluated during histological examination of gastric biopsies according to the Sydney system. The development of chronic atrophic gastritis and other preneoplastic lesions is associated with decreased pepsinogen I/II ratio, increased plasma gastrin concentration and a Th1 polarisation of the immune response (IFN, IL-1β, IL-8 and TNF) that will inhibit somatostatin production and therefore stimulate gastrin production. The TNF and IL-1β also inhibit the acid production by the parietal cells.

The tendency of an immune response to become polarised towards Th1 or Th2 effectors is influenced by a combination of host genetic factors and the type and amount of antigen that is encountered. IL-12 and IFN-γ are important for induction of Th1 response, whereas IL-4 and IL-13 play critical roles in promoting Th2 response. However, in many cases, it is still not understood why a Th1 or Th2 response is preferentially induced. Of particular interest, the immune response to Helicobacter infection can be modulated experimentally in mice by co-infection with nematodes towards a Th2 type that protects against gastric atrophy [8]. Such modulation is mediated by downregulation of the Th1 cytokines TNFα and IL-1β and higher levels of the Th2 cytokines IL-4 and IL-10 [9].

Polarisation towards a Th1 profile can contribute to the development of peptic ulcers and other severe mucosal pathology, while on the other hand, activation of a Th2 cell response results in amelioration of the gastritis. Therefore, it has been deduced that an uncontrolled Th1 cell response to *H. pylori* infection results in persistence of inflammation and disease, whereas, in contrast, a Th2-mediated response reduces the pro-inflammatory immune effects [17].

In humans, the innate immune response caused by the infection is not sufficient to eliminate the pathogen. Regulatory T cells recruited in the gastric mucosa during infection could also play a role in the development and persistence of chronic inflammation via the production of cytokines that regulate the inflammatory response such as TGFβ and IL-10. Moreover, immune response contributes to chronic gastritis ultimately leading to the development of more severe disease in some individuals.

H. pylori strains from East Asia are associated with a high cancer risk and African strains with a low cancer risk in African populations despite the fact they are highly infected. This so-called African enigma probably reflects the modulation of the inflammatory process initiated by the infection, towards a non-neoplastic outcome. The available scientific evidence supports the role of the following factors, listed in order of their possible importance in explaining the enigma: the oncogenic potential of different bacterial genotypes, the modulation of the immune response to Helicobacter infection towards a Th2 type and dietary influences and host genetic susceptibility [9].

5 Mechanisms of *H. pylori*-Mediated Gastric Carcinogenesis: The Disease

Gastric adenocarcinoma is a poor prognosis disease, with a survival rate of less than 20 % at 5 years, and apart from surgery (partial or total gastrectomy), no specific therapy is recommended. Gastric adenocarcinomas are histologically heterogeneous. Except for rare cases of family cancers found in young adults associated with mutations in the *cdh*1 gene, gastric adenocarcinomas are sporadic, occur in people over 60 years old and almost always develop over a mucosal inflammation resulting from chronic infection by *H. pylori*.

Preneoplastic lesions and gastric cancers are induced by *H. pylori* infection. The stomach cancers are essentially adenocarcinomas originating from the transformation of gastric epithelial cells and in rare cases (approximately 5 %) sarcoma (gastrointestinal stromal tumours or GIST) of stromal origin. Distal gastric adenocarcinomas associated with *H. pylori* infection can be separated into two main histological types: the diffuse type (70 %) and the intestinal type (30 %). The diffuse type is a poorly differentiated adenocarcinoma wherein glandular architecture disappears. Diffuse type adenocarcinomas are in most cases associated with sporadic or inherited mutations in the *cdh*1 gene encoding E-cadherin, which inhibit the expression of this molecule at the adherent cell junctions, producing often highly invasive independent cell tumours. Adenocarcinomas of intestinal type have a preserved glandular architecture which is more or less well differentiated. While the development of adenocarcinomas of diffuse type is brutal, without frontrunner precancerous lesions, development of intestinal type adenocarcinomas undergoes a cascade of well-characterised histological events, allowing one to anticipate its appearance when preneoplastic lesions are detectable. *H. pylori* infection causes a Th1-type immune response and gastritis. The consequence is an increase in apoptosis of gastric epithelial cells (atrophy) generating a compensatory cell hyperproliferation and an altered differentiation leading to metaplasia [16]. Production of cyclooxygenase 2 (COX2), NO synthase, reactive oxygen and nitrogen species following the infection combined with the Th1 immune response are sources of errors during mitosis and participate in the accumulation of mutations [27].

6 The Stem Cell Hypothesis

The role of bone marrow-derived mesenchymal stem cells (BMDCs) in the neoplastic process has been recently highlighted. These cells which are recruited into the gastric mucosa following chronic inflammation and epithelial damage induced by *H. pylori* infection appear to be involved in about a quarter of the cells found in preneoplastic lesions [28], suggesting that gastric carcinoma may originate from both local epithelial stem cells and BMDC. Once recruited, these cells home in the gastric mucosa and fuse with local gastric epithelial cells, bearing local stem cell failure and participating in tissue regeneration. The context of chronic infection and inflammation leads to an epithelial mesenchymal transition (EMT) and altered tissue regeneration and differentiation from both local epithelial stem cells and BMDC. EMT induces the emergence of CD44-positive cells possessing mesenchymal and stem cell properties, resulting in metaplastic and dysplastic lesions to give rise, after additional epigenetic and mutational events, to the emergence of cancer stem cells (CSC) and adenocarcinoma [6, 7, 28, 2].

7 Conclusion

The association and the causal relationship between *H. pylori* infection and gastric adenocarcinoma as well as gastric MALT lymphoma is clearly established. Environmental factors and host genetic factors play probably an important role. However, for gastric adenocarcinoma, bacterial factors play a key role in the cascade of events leading to cancer. The CagA protein, specific for *H. pylori* and having no homology to other known proteins, is now regarded as a true oncogene. Host factors involved in gastric MALT lymphoma pathogenesis have to be determined, and new animal models of this disease will help to better investigate the mechanisms of deregulation of the inflammatory response.

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Part III
Hemopathies

Adult T-Cell Leukaemia/Lymphoma (ATL)

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1 ATL Classification, Diagnosis, Response Criteria and Prognosis

Adult T-cell leukaemia/lymphoma (ATL) is a T-cell lymphoproliferation due to human T-cell lymphotropic virus type I (HTLV-1) infection that bears dismal prognosis. Diagnosis can be easily performed in the presence of tumour mass including lymph nodes, splenomegaly, skin tumours and abnormal lymphocytes in the peripheral blood with or without hyperlymphocytosis, with typical cytological features (flower cells or clover leaf) with a phenotype of activated T cells (CD2+CD3+, CD4+, CD25+) and often in aggressive forms, an hypercalcemia. No recurrent karyotype abnormalities have been found in ATL, and thus, it is not recommended for diagnosis. A tumour biopsy is mandatory if the diagnosis is not made on the basis of peripheral blood analysis. No histological features are pathognomonic of ATL: it may be similar to other peripheral T-cell lymphoma depending on the cytological (large cells, Sezary-like cells, anaplastic, immunoblastic, etc.) and histological features and immunohistochemistry (as in peripheral blood CD3+, CD4+, CD25+). Although in theory the demonstration of a clonal integration of the virus in these tumour cells allows a definitive diagnosis; HTLV-1-positive serology, if other features are present, is generally sufficient. Once the diagnosis is made, staging

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Table 1 Shimoyama classification defining four ATL subtypes

	Smouldering	Chronic	Lymphoma	Acute
Lymphocyte count ($\times 10^3$/L)	**<4**	**≥4**	**<4**	**é**
% flower cells	**<5 %**	**≥5 %**	**≤1 %**	é
LDH	≤1.5 N	<2.5 N	é	é
Ca^{2+}	Normal	Normal	é	é
Skin and/or lung involvement	±	±	±	±
Lymph node involvement	No	±	Yes	±
Spleen/liver involvement	No	±	±	±
Central nervous system/bone/pleural/ascites	No	No	±	±

should be performed. Bone marrow aspiration or biopsies are not required in case of peripheral hyperlymphocytosis; CT scans of the head, neck, thorax, abdomen and pelvis to detect nodal and extra nodal lesions and potential opportunistic infections should be performed. Gastrointestinal endoscopies should be performed if available in case of clinical symptoms. In all aggressive forms of the disease, central nervous system (CNS) should be evaluated by CT scan and/or lumbar puncture to evaluate both CNS involvement and/or opportunistic infections. Classification, first described by Shimoyama [1], used for the initial staging, distinguishes four subtypes, which differ regarding their presentation and outcome (Table 1). The overall survival is 36, 30, 10 and 8 months, for smouldering, chronic, lymphoma and acute forms, respectively [1]. The complex presentation with both leukaemic and lymphomatous components makes response assessment difficult. Recently, an international consensus meeting established new response criteria [2].

Complete response (CR) is defined as the disappearance of all measurable tumour lesions (including normalization of lymph node size) and normalization of absolute lymphocyte (including flower cells) count below 4×10^9/L. Unconfirmed CR is defined as a reduction of 75 % of the tumour size and normalization of absolute lymphocyte (including flower cells) count below 4×10^9/L. Partial response (PR) is defined as a reduction of 50 % of tumour size and absolute lymphocyte count. Progressive disease is defined as an increase of 50 % of the tumour size and/or absolute lymphocyte count. These response criteria require that each criterion is present for at least 4 weeks.

2 Treatment of ATL

Treatment of ATL is usually dependent on the ATL subtype. Patients with aggressive forms (acute and lymphoma) have a very poor prognosis because of intrinsic chemo-resistance, a large tumour burden, hypercalcemia and/or frequent infectious complications due to profound immune deficiency. Multiple Japanese trials in aggressive ATL clearly demonstrated that although combinations of chemotherapy, in particular those designed for treatment of aggressive non-Hodgkin lymphomas,

have improved the response rates particularly in ATL lymphoma, they failed to achieve a significant impact on long-term survival. Patients with indolent ATL (chronic or smouldering subtypes) have a better prognosis. However, recent Japanese data showed a poor long-term outcome when patients were managed with a watchful-waiting policy until progression, and even worse when patients were treated by upfront chemotherapy [3].

2.1 Conventional Chemotherapy

Since 1978, the Japan Clinical Oncology Group (JCOG) has conducted six successive prospective clinical trials. All these trials were based on conventional chemotherapy, with various dose and administration modalities. The first trial JCOG 7801 used VEPA (a CHOP-like regimen that contained vincristine, cyclophosphamide, prednisolone and doxorubicin). The CR rate was only 17 % with a median survival time of 5 months. The second trial, JCOG 8101, was a randomized phase III study which included 54 patients and compared VEPA regimen with VEPA-M (VEPA plus methotrexate) [4]. Although the CR rate was improved in the VEPA-M group (36.7 %), no difference in median survival time (7.5 months) and overall survival (8 % at 4 years) was noted.

The third trial, JCOG 8701, was a phase II study with a more aggressive regimen (LSG 4), which combined three successive regimens: VEPA-B (VEPA plus bleomycin), M-FEPA (MTX, vindesine, cyclophosphamide, prednisolone, and doxorubicin) and VEPP-B (vincristine, etoposide, procarbazine, prednisolone and bleomycin). The CR rate was improved to 42 %. However, median survival rate and overall survival (OS) were poor with a median survival time (MST) of 8 months and overall survival rate of 12 % at 4 years. These trials enrolled also patients with other subtypes of NHL. MST was 44 months in NHL versus 8 months in the ATL group.

Following these initial trials, the JCOG designed specific regimens targeting ATL. The JCOG9109 trial (a phase II study conducted between 1991 and 1993) used pentostatin-containing regimen but did not show any improvement (MST 7, 4 months and 2 years overall survival rate: 15 %) [5].

The next protocol named JCOG 9303 was conducted between 1994 and 1996 and used more intensive multi-agent chemotherapy regimens [6]. Treatment was designed as follows: VCAP (vincristine, cyclophosphamide, doxorubicin and prednisolone), AMP (doxorubicin, ranimustine, prednisolone) and VCEP (vindesine, etoposide, carboplatin, prednisolone). It included intrathecal injection of methotrexate and aracytine. The use of granulocyte colony-stimulating factor (G-CSF) was systematic. Results were encouraging with a CR rate of 35 %, a MST of 13 months (versus 8 months in historical controls treated by CHOP-like regimens). The 2-year OS was 31 %. MCNU and carboplatin were used because their activities were not affected by the expression of P-glycoprotein, a product of MDR1, which is frequently expressed by ATL cells.

In order to confirm theses results, a phase III study (JCOG9801) was conducted between 1998 and 2003. This study compared two arms of treatment: VCAP-AMP-VECP versus biweekly CHOP. It included 118 patients (81 acute subtype and 26 lymphoma subtype) [7]. Response rate was higher in the experimental arm (40 % vs. 25 %). Progression-free survival at 1 year was 28 % versus 16 %, and overall survival was 24 % versus 13 % in the two arms respectively. There was a statistically significant difference only in a subgroup analysis (patients younger than 56 years, poor performance status).

2.2 Allogeneic Stem Cell Transplantation

As most of patients relapse after conventional chemotherapy, allogeneic stem cell transplantation (alloSCT) seems to be an attractive option as consolidation treatment. Most of the reports come from Japan. A number of retrospective studies have confirmed alloSCT using either myelo-ablative conditioning or reduced-intensity conditioning as a feasible treatment option for ATL patients. The largest retrospective study has been reported in 2010 [8]. This study included 386 patients who received alloSCT between 1995 and 2005, either with standard or reduced intensity conditionings. After a median follow-up of 41 months, 3-year overall survival was 33 %. Among patients who received family-related transplants, donor HTLV-I seropositivity adversely affected disease-associated mortality. Recently, the long-term results of a series of 30 patients who received reduced intensity conditionings were reported. Overall survival rate and progression-free survival rates were 36 % (95 % CI, 21–25 %) and 31 % (95 % CI, 17–45 %) respectively [9].

The response after donor lymphocyte infusion (DLI) is often considered being the best proof of a graft-versus-disease effect. Recently, the Nagasaki Transplant Group has reported objective responses for patients relapsing after alloSCT who have been treated with DLI. Moreover, the responses were durable, with three cases of long-term remission of more than 3 years [10]. A graft-versus-ATL effect is also suggested by the results of the national Japanese retrospective study, but results are less convincing [11].

However, the number of ATL patients eligible for alloSCT is very limited because of the low CR rate especially in the acute form, poor performance status, severe immunosuppression and low probability of finding a suitable donor in patients from ethnic minorities.

2.3 Antiviral Therapy: Alpha Interferon (Zidovudine) AZT

The combination of zidovudine (AZT) and alpha interferon (IFN) was first reported in two phase II studies [12–14]. High response rate was observed particularly in previously untreated acute ATL. The efficacy of this combination was confirmed in

a French trial using AZT/IFN in 19 newly diagnosed ATL patients and in a UK clinical trial using AZT/IFN in 15 ATL patients [15, 16]. A meta-analysis was performed on ATL patient survival between 1995 and 2008 in three countries (the United States, the United Kingdom, Martinique and continental France) [17]. Two hundred and fifty-four patients have been enrolled in this study; they had various ATL subtypes: 116 acute ATL, 18 chronic ATL, 11 smouldering ATL and 100 ATL lymphoma. Different treatment strategies have been compared, namely, antiviral therapy alone (AZT-IFN), chemotherapy alone and chemotherapy followed by maintenance antiviral therapy. On the 207 patients for whom the first-line therapy was reported, 5-year OS rates were 46 % in 75 patients who received first-line antiviral therapy, 20 % in 77 patients who received first-line chemotherapy and 12 % in 55 patients who received first-line chemotherapy followed by antiviral therapy. Patients with leukaemic subtype significantly benefited from first-line antiviral therapy, whereas patients with ATL lymphoma had a better outcome with chemotherapy. In acute ATL, first-line antiviral therapy alone resulted in a significant survival advantage (5-year OS of 28 %) as compared with first-line chemotherapy with or without maintenance antiviral therapy (5-year OS of 10 %). Achievement of CR with antiviral therapy resulted in 82 % 5-year survival. In chronic and smouldering ATL, antiviral therapy resulted in 100 % 5-year survival. In ATL lymphoma, first-line antiviral therapy resulted in a significant survival disadvantage (median and 5-year OS of 7 months and 0 %, respectively) compared to first-line chemotherapy with or without maintenance antiviral therapy (median and 5-year OS of 16 months and 18 %, respectively). Finally, a multivariate analysis confirmed that first-line antiviral therapy significantly improved overall survival of ATL patients (HR 0.47; 95 % CI 0.27–0.83; $p=0.021$). The presence of a functional p53 in tumour cells is associated with a better response [18].

A recent English study has reported the efficacy of the association of chemotherapy with AZT-IFN combination [19]. Seventy-three patients with aggressive subtypes (29 acute and 44 lymphoma subtypes) were retrospectively analysed. Sixty-seven patients received chemotherapy as first-line treatment, mostly CHOP-like regimen. Forty received the association of AZT-IFN including 27 as first-line therapy in association with chemotherapy (concurrent with chemotherapy or sequential).

Belonging to 65 patients for whom response was available, response rate was 81 % for patients who received combined regimen (chemotherapy plus AZT-IFN) versus 49 % for those who received chemotherapy alone. This seems to translate in a doubling PFS when compared patients treated with combined regimen to patients treated with chemotherapy alone (8 months versus 4 months respectively). This last result did not however reach statistical significance. Nevertheless, it was observed a better OS with prolonged median OS in acute ($p=0.0081$) and in lymphoma subtypes ($p=0.001$) in patients treated with combined regimen when compared to those treated with chemotherapy alone as first-line therapy. Moreover, exposure to AZT-IFN combination at any time was associated with a better prognosis for both ATL subtypes with reduced hazard ratio risk of death of 0.23 (95 % CI, (0.091–0.60), $p=0.002$) in multivariate analysis. However, toxicity especially haematological

toxicity was not recorded in this study. We know that AZT-IFN bears haematological toxicity by itself in addition to chemotherapy.

2.4 Arsenic Trioxide (AsO3)

Arsenic trioxide is synergistic with IFN to induce cell cycle arrest and apoptosis in HTLV-I-infected and fresh ATL cells through rapid shut off of the NF-κB pathway and a delayed shut off of cell cycle-associated genes, secondary to Tax degradation by the proteasome [20–22]. Although it has been demonstrated that arsenic and IFN cooperate to cure murine ATL, derived from *Tax* transgenics through selective eradication of leukaemia-initiating cell (LIC) activity. This strongly suggests that LIC activity is dependent on continuous Tax oncogene expression. Hence, addition of arsenic to AZT/IFN, through elimination of LIC activity, may result in long-term disease eradication and potential cure [23]. A recent prospective phase II study evaluated the efficacy and safety of the combination of arsenic, IFN and AZT in 10 newly diagnosed chronic ATL patients. The response rate was 100 % including 7 CR, 2 CR but with more than 5 % circulating atypical lymphocytes, and one partial response. Side effects were moderate and mostly haematological [24]. We have also recently reported a series of 11 patients with ATL (3 lymphoma type, three chronic and five acute) treated with arsenic/IFN after induction chemotherapy [25]. At initiation of AsO3, four patients were in CR, two in PR and five in progression. Ten patients received AsO3 during 3–8 weeks. One progressed 3 days after starting AsO3 and six patients died. All were progressive at time of AsO3 initiation. Five patients survived: 3-lymphoma type in CR (25, 31, 46 months of follow-up), one acute subtype in CR (9 months follow-up) and one chronic subtype in PR (39 months follow-up). Tolerance was acceptable with peripheral neuropathy ($n=4$), hand-foot syndrome ($n=3$), skin eruption ($n=3$, including two toxic epidermolysis). While preliminary, these observations nevertheless suggest that in ATL patients, arsenic/IFN efficiently targets ATL LIC activity and may be useful as a consolidation therapy for those patients achieving a satisfactory response after induction therapy.

2.5 Specific Monoclonal Antibodies

2.5.1 Anti CD25 Antibody

ATL cells express CD25 (alpha-chain of IL2 receptor). A first trial reported the use of anti-CD25 antibody in 19 patients. Authors obtained six responses (two CR, four PR) that lasted from 9 weeks to more than 3 years [26]. A second study used anti-CD25 antibody coupled with YTRIUM-90. Seven of eighteen treated patients (one with chronic ATL and six with acute ATL) obtained a partial remission. The duration

of these partial remissions ranged from 1.6 to 22.4 months (mean, 9.2 months). Two patients achieved CR status. One patient died 36 months after initiation of therapy from a secondary AML, and the other patient was still in CR at time of publication [27]. A neutralizing monoclonal antibody to the transferrin receptor (mAb A24) has been designed and induces apoptosis of ATL cell lines and primary ATL cells [28]. Thus far, only preclinical studies have been performed (Hermine et al., personal communication).

2.5.2 Anti-CC Chemokine Receptor 4 (CCR4)

ATL cells express the CC chemokine receptor 4 (CCR4). KW-0761 is a defucosylated humanized antibody which enhances antibody-dependent cellular cytotoxicity (ADCC) that binds CCR4. A first phase I study of KW-0761 was performed and included 13 patients with CCR4-positive relapsed ATL. Overall response rate (ORR) was 31 % (2 CR and 2 PR) [29]. A pivotal phase II study has been recently presented and published which confirmed the efficacy of this new antibody. Twenty-eight patients with relapsed ATL were enrolled. The primary end point was ORR. Among the 26 pts evaluable for efficacy, the ORR was 50 % with 8 CR and 5 PR; the response rates in each affected lesions were 100 % (13/13) for peripheral blood, 63 % (5/8) for skin and 25 % (3/12) for lymph node disease. Median progression-free and overall survivals were 5.2 and 13.7 months, respectively. The treatment schedule was one weekly perfusion (1.0 mg/kg) for 8 weeks. The most common adverse events were infusion reactions (89 %) and skin rashes (63 %) with one case of Stevens-Johnson syndrome.

2.6 Watch and Wait Policy

Patients with smouldering or chronic ATLL subtypes have a better prognosis than patients with aggressive forms (acute and lymphoma) and have been considered as indolent forms. Many patients have been managed with a watch and wait policy until disease progression or treated with chemotherapy when poor prognostic factors were present. A recent published Japanese study reported on 90 patients with indolent subtypes (65 chronic and 25 smouldering) [3]. Forty-four (49 %) patients progressed to aggressive disease with a median time of transformation of 18.8 months (range 0, 3 months to 17.6 years) and 41 died. Median survival was 4, 1 year. No difference between the two subtypes (chronic and smouldering) was observed. The estimated 10-year survival rate was 25.4 % (95 % CI, 15, 3–36, 8 %). This study shows that even, in the indolent subtype, prognosis is poor. Moreover, patients who received chemotherapy had a worse prognosis and a shorter survival than patients who were managed by watchful waiting. These results underscore the need for further improvement in the treatment of patients with otherwise indolent forms of ATL.

2.7 *Drugs Used in T-cell Lymphoma Outside HTLV-1 Infection*

Currently, it is not yet clear whether or not T-cell lymphoproliferation associated with HTLV-1 infection is, with respect to oncogenic mechanisms, different from other T-cell lymphoma and as such whether or not they may benefit from drugs approved or in development in T-cell lymphoma. We will focus on three drug families that could be interesting to use as part of the induction treatment or as part of consolidation treatment.

2.7.1 Histone Deacetylase Inhibitors (Vorinostat, Romidepsin, Valproic Acid)

Histone deacetylase inhibitors or HDAC inhibitors (HDACI) are a new class of drugs which activity was initially designed on transcriptional activity by acting on chromatin epigenetic modification, histone deacetylation. Two of these agents (vorinostat and romidepsin) have been approved in the United States for the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL). Two pivotal studies show response rates around 30 % (30 % for vorinostat and 34 % for romidepsin) [30, 31]. Romidepsin shows efficacy on peripheral T-cell lymphoma (PTCL) with response rates around 25–40 % in two phase 2 studies. The first study reported on forty-seven patients with relapsed or refractory PTCL. Overall response rate was 38 % (95 % confidence interval 24–53 %) with 8 CR and 9 PR. The median overall response was 8.9 months (range 2–74). Side effects were acceptable [32]. The second study reported on 130 patients with relapsed or refractory PTCL. The ORR was 25 % (33 of 130 patients), including 15 % (19 of 130) CR/Cru, with a median duration of response of 17 months [33]. To our knowledge, these drugs have not been yet evaluated in ATL as single therapy or in combination with other drugs in induction therapy. However, Ramos et al. have reported on a clinical trial using IFN-AZT with valproic acid during the maintenance treatment phase [34]. The authors hypothesized that HDAC inhibitors could reactivate latent HTLV-1 in ATL cells harbouring intact provirus and help eliminate residual disease. Thirteen patients were enrolled. One showed a serial decrease in clonal ATL disease followed by PCR. Using fresh cells from this patient treated ex vivo with vorinostat, the authors showed an increase of HTLV-1 expression and an induction of cell death. However, in this study, induction of a putative immune response against virus-infected cells was not addressed.

2.7.2 Others

Few unpublished case reports have shown some responses with demethylating agents (5-azacytidine), imids (Lenalidomide), PI3 kinase inhibitors, etc. But their role in the therapeutic armamentarium of ATL remains to be determined.

2.8 Monoclonal Antibodies Used in T-cell Lymphoma Outside HTLV-1 Infection

2.8.1 Alemtuzumab

Alemtuzumab (CAMPATH-1H) is an anti-CD52 antibody that is approved for chronic lymphoid leukaemia treatment. It has been shown that it is effective on T-cell prolymphocytic leukaemia (PTLC), with high response rate in a prospective study including 39 patients with T-PLL treated with CAMPATH-1H [35]. The overall response rate was 76 with 60 % CR and 16 % partial remission (PR). These responses were durable with a median disease-free interval of 7 months (range, 4–45 months). In ATL, experience is limited to case reports [36]. In addition, a recent study reported efficacy of the association of alemtuzumab and pentostatin in various type of PTCL including one case of ATL, which was in CR [37]. However, association of CAMPATH with conventional chemotherapy in PTCL has shown relative efficacy but high rate of infections.

2.8.2 SGN-35 (Brentuximab Vedotin)

SGN-35 is a chimeric monoclonal antibody which targets the cell-membrane protein CD30 and which is linked to three to five units of the antimitotic agent monomethyl auristatin. The FDA has recently approved this drug for the treatment of Hodgkin lymphoma and anaplastic T-cell lymphoma. It could have an effect on ATL cells as it has been suggested by recent in vitro and in vivo results [38].

3 Strategy and Challenges in Low-Income and Developing Countries

3.1 Chronic and Smouldering ATL

Patients with chronic and smouldering ATL have a better prognosis compared to patients with aggressive subtypes (acute and lymphoma). However, as it has been shown in a recent Japanese study, long-term survival is dismal when these patients are managed with a watchful-waiting policy until disease progression. Moreover, patients who received chemotherapy alone had a poorer outcome indicating that this may be detrimental in these subtypes [3]. So far, no clear prognostic factors have been yet defined in order to predict transformation to an aggressive form and patient who are at risk of progression. Our point of view is that most of the patients with chronic and smouldering ATL, if possible, should be treated. In the recent worldwide meta-analysis, patients with chronic/smouldering ATL who received first-line therapy by AZT-IFN only had an excellent survival (100 % OS beyond 5 years). Thus, outside the context of clinical trials, the current standard therapy of chronic and smouldering ATL

is combination therapy with AZT and IFN. This requires however continuous therapy. Treatment should not be interrupted as relapse always occurs when treatment is stopped. The recommended starting dose is AZT 600–900 mg/day (in three divided doses) and interferon- alpha (5–6 million IU/m^2/day). Usually, after 1 month, AZT dose can be titrated down to 600 mg/day in two divided doses, and IFN dose can be reduced to 3–5 millions IU/day or alternatively 1.5 μg/kg of pegylated IFN weekly. Based on preclinical studies, clinical trials are testing the effect of adding arsenic to the AZT/IFN combination as a consolidation therapy with the aim of stopping therapy and achieving cure by potential elimination of leukaemia-initiating cells [20–23].

3.2 ATL Lymphoma

As it has been shown in the recent meta-analysis, the combination of AZT-IFN is less effective than first-line chemotherapy in ATL lymphoma [17]. Therefore, chemotherapy should be the preferred option. However, the recent work from the United Kingdom has shown that the combination of antiviral therapy with CHOP regimen (cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1, prednisone 60 mg/m^2 day 1) is superior to CHOP regimen alone in patients with ATL lymphoma subtype [19]. The use of chemotherapy is based on the Japanese experience across different trials. The LSG15 protocol is the 'standard of care'. It is based on multiple drugs. When treated with this LSG15 protocol, ATL lymphoma patients achieve a better CR rate (66.7 %) than acute subtype (19.6 %) or chronic-type patients (40.0 %). It remains to be determined if as in other T-cell lymphoma addition of etoposide (150 mg/m^2/day) to CHOP could increase response rate and duration of response. However, relapse occurs rapidly and overall survival rate is low [6]. Therefore, a consolidation therapy is critical. Whenever possible, Allogeneic SCT should be considered, but its expansive and the small number of available sibling donors in developing countries reduce significantly the interest of this option [8]. Alternatively, based on preclinical data, we currently are testing the efficacy of two cycles of arsenic (0.15 mg/kg/day during 4–6 weeks)/IFN (pegylated 1.5 μg/kg/week or 3–6 MUI/day) maintenance as a consolidation procedure following achievement of CR; there are encouraging preliminary results. This strategy in theory is possible in developing countries where the arsenic is available at a low coast. Moreover, the addition of AZT/IFN or other novel therapies to chemotherapy may help to achieve remission. HDAC inhibitor might be tested in this indication to induce an immune response against residual tumour cells, and some patients may experience long remission by taking valproic acid. In case of poor access to high-dose chemotherapy, low dose of daily oral etoposide (50 mg/day) or weekly injection of vinblastine (6 mg/m^2) may provide a control of the disease. This type of chemotherapy might be also used in relapsing patients as a palliative treatment.

3.3 Acute ATL

Combination chemotherapy regimens have little effect in acute ATL. Even if the most intensive regimen (LSG-15) have increased response rate, MST and OS are low [6, 7]. In the recently published meta-analysis on antiviral therapy for ATL, treatment of acute ATL patients with AZT and IFN showed a higher response rate and significantly prolonged survival. Moreover, patients who achieved CR had a long-term response [17]. Outside the context of clinical trials, the current standard therapy of acute ATL is combination therapy with AZT and IFN. However, it can be difficult to manage patients presenting with bulky tumour or severe hypercalcaemia not responding to bisphosphonates; initial chemotherapy (CHOP-like) is sometimes required. It would be helpful to predict which patients with the acute subtype will benefit from this approach. Preliminary results indicate that patients with wild-type functional p53 are more likely to respond to AZT/IFN combination [18]. We therefore recommend evaluating p53 by a functional assay in all patients while the treatment is initiated, but this test is not available everywhere [39]. Long-term disease control requires however continuous therapy, since relapse is always noted when treatment is stopped. The recommended dose of AZT/IFN is the same than in chronic/smouldering subtypes. As in lymphoma subtype, allogeneic SCT should be considered in young patients with acute ATL who have a suitable donor [39]. As in other ATL subtypes, based on preclinical data, ongoing clinical trials are testing the efficacy of arsenic/IFN maintenance following achievement of CR.

3.4 Supportive Therapy in ATL

Hypercalcaemia associated with aggressive ATL should be managed together with the treatment of the disease, hyperhydration, and biphosphonates therapy and when not available, although they may increase the risk of infections, corticosteroids may be used. Trimethoprim-sulfamethoxazole, valacyclovir and antifungal agents are recommended for the prophylaxis of *Pneumocystis jiroveci* pneumonia, viral and fungal infections, respectively. In endemic area, anti-strongyloides agents, such as ivermectin or albendazole, should be always considered to avoid systemic infection particularly in patients with a history of past and/or present exposure to the parasite. Intrathecal prophylaxis with chemotherapy should be considered for patients with aggressive ATL even in the absence of clinical symptoms because more than half of relapses after chemotherapy occur in the central nervous system (Fig. 1).

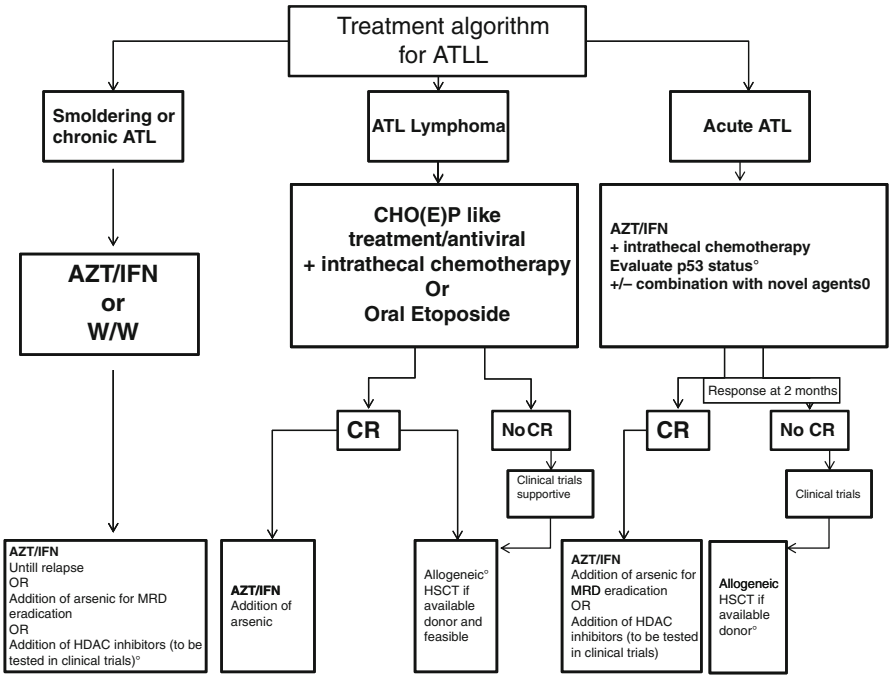

Fig. 1 Recommended treatment strategy for patients with acute, lymphoma or chronic/smouldering ATL. *CR* complete remission, *MRD* minimal residual disease, *AZT* zidovudine, *IFN* interferon-alpha, *alloSCT* allogeneic stem cell transplantation, *W/W* watch and wait, *CHO(E)P* cyclophosphamide, oncovin, etoposide, prednisone (if available)

4 Perspectives and Conclusions

The treatment of ATL has to be adapted according clinical presentation and the level of the health system. Unfortunately particularly in countries where allogeneic stem cell transplantation is not available, the probability of cure is rare in this disease. The combination of AZT and IFN is effective in the leukaemic subtypes of ATL and should be considered as standard of care in first-line therapy in that setting. This combination has clearly changed the natural history of the disease through achievement of a significantly improved long- term survival in patients with smouldering and chronic ATL as well as a subset of patients with acute ATL. Prior exposure to chemotherapy increases the rate of complications and of acquiring a resistant phenotype. We therefore recommend that the combination of AZT and IFN is used as a first-line treatment in the leukaemic forms and that treatment is initiated with high doses of both agents since reduced doses are often not effective. Conversely, patients with lymphoma subtype benefit from initial induction therapy based on conventional chemotherapy regimen but constantly relapse and have

a poor prognosis. Addition of AZT-IFN in combination with chemotherapy may increase response rate and outcome but is associated with a significant risk of infection and increase of the cost of treatment. Consolidation treatment with AsO3 may be considered, followed by maintenance therapy with AZT/IFN. In order to prevent the occurrence of resistance and relapse, clinical trials assessing additional targeted therapies such as arsenic/IFN combination or monoclonal antibodies, particularly the promising anti CCR4 antibody, are mandatory after achieving CR, but for the later special programme would be necessary to get access to the drug in developing countries. Finally, HDAC inhibitors, such as valproic acid, which is not expensive and is available virtually everywhere, may be also an interesting option in induction or in maintenance. Hopefully in the future, new drugs or targeted therapies will be available at low cost to help to treat this disease with a dismal prognosis. An antitumour vaccination programme, using virus proteins, is currently setting up in Europe, the United States and Japan. Meanwhile an effort, when possible, should be made to prevent the risk of infection through breast feeding which is the major cause of contamination and risk of developing lymphoproliferative disorders.

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Extranodal NK/T Cell Lymphoma, Nasal Type

Ritsuro Suzuki

1 Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is a distinct lymphoma characterized by predominant occurrence in nasal/paranasal area, skin/soft tissue, or gastrointestinal tract [1, 2]. The clinical course is aggressive, notably for disseminated cases, and used to result in poor prognosis [3–6]. Tumor cells of ENKL express multidrug resistance (MDR)-associated P-glycoprotein which actively export several cytotoxic agents such as doxorubicin, vincristine, or etoposide [7, 8]. This resulted in the poor response to conventional chemotherapy of lymphoma, mostly including anthracyclines [3–6]. After the extensive recognition of this lymphoma all over the world, the treatment paradigm has changed to simultaneous chemoradiotherapy for limited disease [9, 10] and L-asparaginase-containing chemotherapy for extensive disease [11, 12]. Currently, the prognosis of ENKL has been improved to be categorized in intermediate group and even better than that of mature T-cell lymphomas [2]. In this chapter, the particular features of this lymphoma are described.

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2 Epidemiology of NK/T-Cell Lymphoma

ENKL is an uncommon form of lymphoma which is much more prevalent in East Asia and Latin America. The incidence among all types of lymphoma is also different within the endemic areas; in East Asia, the rate of occurrence was 3 % in Japan [13] and in Malaysia [14], 4 % in Thailand [15], 6 % in Taiwan [16] and in Hong Kong [17], 9 % in Korea [18], and 11 % in China [19] (Fig. 1). In Western countries, although the subjected numbers are small, the incidence of ENKL was 2 % in France (4 of 192 patients), but 0 % in other countries [20]. Other anecdotal reports suggest that the rate ranges from 0 to 1 % in India, Australia, Greece, or Canada [21–24]. Although systematic incidence of lymphoma subtypes has not been reported from countries in Latin America, several studies suggest that considerable numbers of patients with ENKL do exist in Mexico, Peru, Brazil, and Singapore [25–28].

3 Pathology and Phenotype

Histologically, lymphoma cells of ENKL show diffuse proliferation with angiocentric or angiodestructive growth pattern (Fig. 2a). The cytological spectrum is rather broad, and cell sizes range from small to large. Varying degree of infiltration of inflammatory cells is presented and sometimes accompanies necrotic changes. These conditions caused the misunderstanding of this tumor as a nonneoplastic

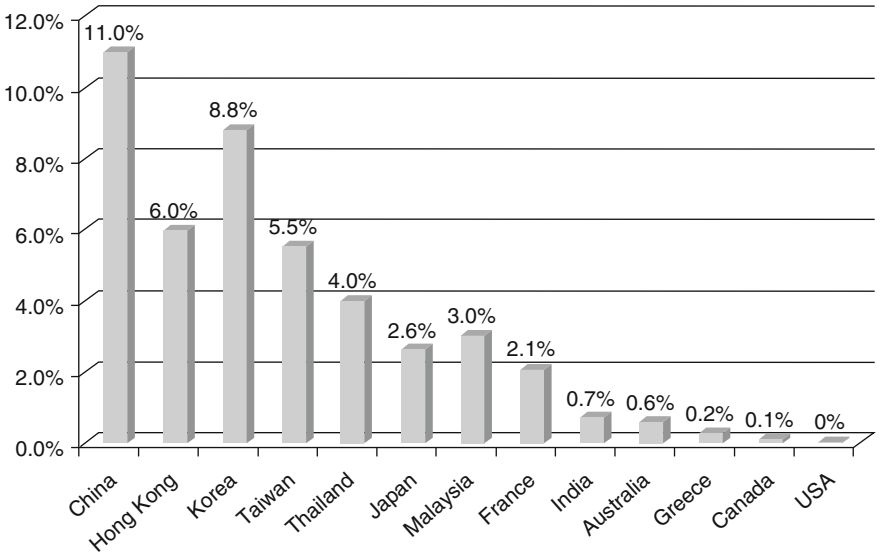

Fig. 1 Ratio of ENKL in malignant lymphoma among each country

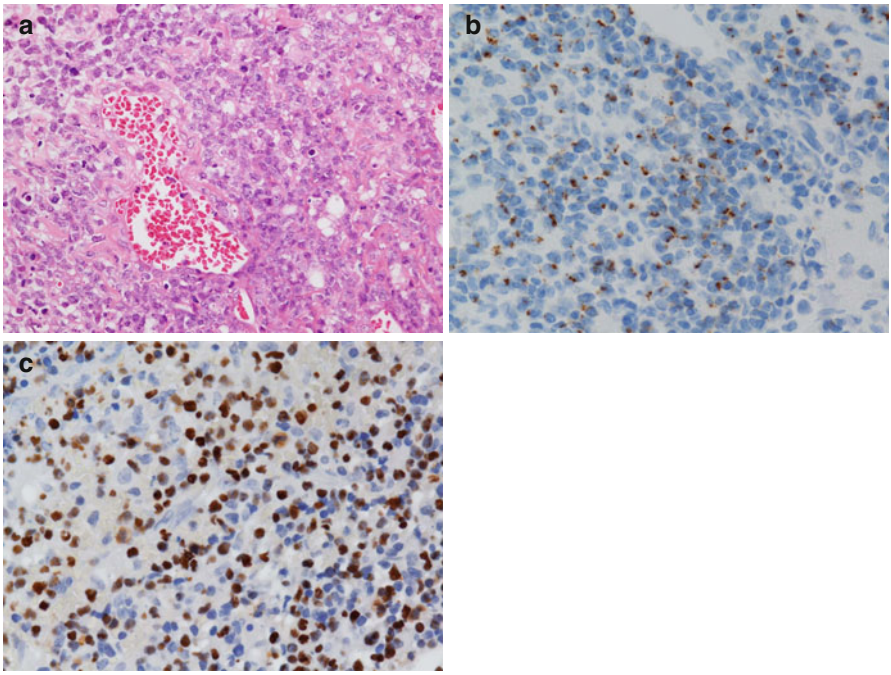

Fig. 2 Histologic features of ENKL. Tumor cells show an angiocentric growth pattern with infiltrating inflammatory cells and necrosis (**a**). The neoplastic cells are positive for granzyme B (**b**) and Epstein-Barr virus, detected by EBER in situ hybridization (**c**)

condition, particularly for nasal lymphomas [1, 29]. Repeated biopsies are important for precise diagnosis of those cases. Uncommon case of ENKL with intravenous lymphoma is recognized occasionally (Fig. 3) [30]. This suggests that intravascular form of lymphoma is not B-cell specific.

The lymphoma cells express NK-cell markers that include CD2, cytoplasmic CD3 (cyCD3), CD7, and CD56. Surface CD3 (sCD3), CD5, and T-cell receptor (TCR) are generally negative, and TCR genes show germline configurations. Cytotoxic molecules such as TIA-1, granzyme B, and perforin are also positive in this lymphoma (Fig. 2b). Lymphoma cells are also positive for Epstein-Barr virus (EBV), which is currently regarded as a hallmark of ENKLs [30]. The EBV in specimens can be detected by EBER in situ hybridization (Fig. 2c).

4 Clinical Presentation

ENKL mostly occurs in adults with median age of 40s to 50s and shows remarkable male predominance [3–6, 25–28, 31–34]. Upper aerodigestive tract, typically nose or paranasal area, is the most affected site of origin, followed by the skin and

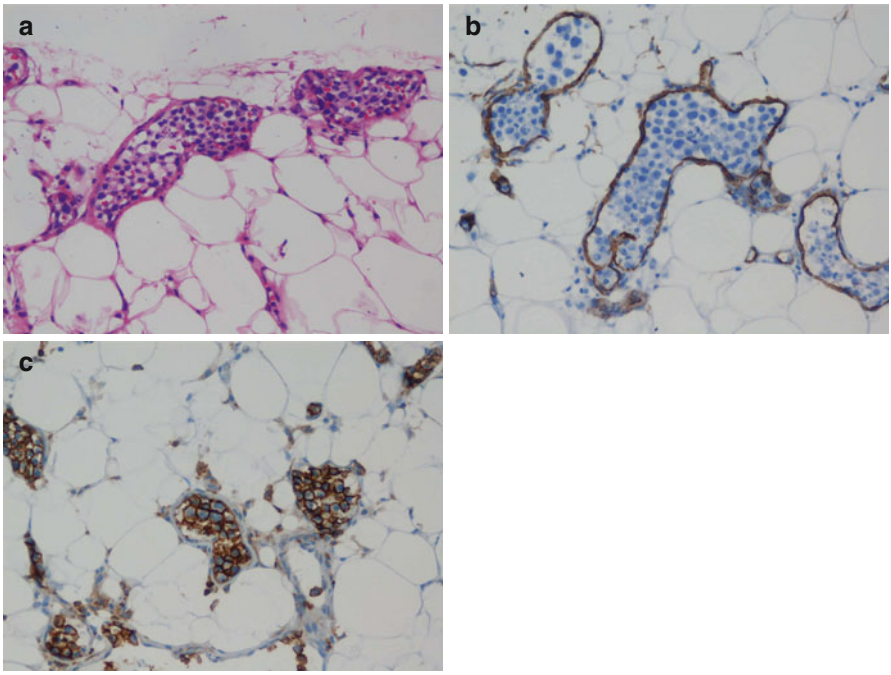

Fig. 3 ENKL of intravascular lymphoma. A rare form of ENKL presents with intravascular lymphoma (**a**). The CD34 staining highlights the localization of lymphoma cells in the vessels (**b**). Lymphoma cells are positive for CD56 (**c**)

gastrointestinal tract. For ENKL with nasal origin, approximately half of the patients present with stage I disease and one fourth with stage II [3, 5, 26–28, 32]. Some patients show long-term limitation to the original site, mimicking chronic sinusitis. On the other hand, extensive-stage disease can rapidly progress with fever, bone marrow involvement, hemophagocytosis, and disseminated intravascular coagulation. In contrast to nasal cases, two thirds of extra-nasal ENKLs present with advanced stage [5, 6]. In the 4th WHO classification, both nasal and extra-nasal ENKLs are included in the same category of disease [1] but should separately be assessed for clinical management.

5 Differential Diagnosis

For precise diagnosis of ENKL, several NK-cell-associated diseases should differentially be diagnosed. Those include aggressive NK-cell leukemia (ANKL), lymphomatoid gastroenteropathy (LyGa), and chronic NK-cell lymphocytosis (CNKL).

5.1 Aggressive NK-Cell Leukemia

ANKL is a leukemic form of NK-cell malignancy and accounts for less than 1 % of the lymphoid malignancies [13, 19]. It predominantly occurs in younger patients than ENKL with a median age around 40 years without any sex predominance [35]. The disease progression is rapid, and patients frequently present with B symptoms, such as fever, night sweat, or body weight loss. Hematological manifestation of ANKL is that of leukemia, which includes circulating and bone marrow leukemic cells, neutropenia, anemia, and thrombocytopenia, but hepatosplenomegaly is also frequently recognized. Cutaneous or central nervous system involvement is uncommon. Leukemic cells present as large granular lymphocytes and express NK-cell antigens including CD2+, cytoplasmic CD3, CD7, CD16, and CD56. EBV is usually positive, but not exclusively [35, 36]. Expression of CD16 is more frequent in ANKL than in ENKL, reflecting the different maturation stage of NK-cells: the former from cytotoxic NK-cells and the latter from immunoregulatory NK-cells [37]. The genetic differences of ANKL and ENKL including genomic gain and loss were revealed by array-based comparative genomic hybridization [38]. Anthracycline-based chemotherapy showed only limited response, but efficacy of L-asparaginase has recently been documented. Dose-reduced SMILE or L-asparaginase mono-induction is recommended for treatment [39].

5.2 Lymphomatoid Gastroenteropathy

The LyGa or NK-cell enteropathy is characterized by a localized proliferation of NK-cells, mostly in the stomach, but less frequently in the intestine [40, 41]. Patients do not show specific symptoms, and most are found by chance through endoscopic examination or follow-up of gastric cancer. Macroscopic findings show protruded lesion(s) in the stomach with around 1 cm diameter with or without depression or ulcers. Histologic specimens show sheeted proliferation of NK-cells without any accompanying necrotic areas. EBV is negative and can be a hallmark of differential diagnosis from ENKL. Lymphoepithelial lesions are occasionally found, and eosinophilic granules are seen in proliferating NK-cells. *Helicobacter pylori* infection is often accompanied, but its significance remains uncertain. The lesions usually disappear without any medications, and the recurrences are rare. The most important point for this disease is to avoid chemotherapy for lymphoma.

5.3 Chronic NK-Cell Lymphocytosis

CNKL is characterized by a chronic increase of blood NK-cells without lymphadenopathy or organomegaly [42]. The term “lymphocytosis” is derived from its non-neoplastic nature without any cytogenetic abnormalities. However, peripheral blood

counts and morphology of increased NK-cells resemble those of ANKL. EBV is usually undetectable in CNKL; hence, the examination of EBV may help the differential diagnosis [43]. Rare cases of CNKL were reported to develop to ANKL [44], but these may represent occult ANKLs in the category of CNKL rather than transformation. CNKL is sometimes associated with reactive conditions against viral infections or underlying solid tumors [42]. Examinations of whole body and watchful observations are thus recommended as managements of CNKL.

6 Treatment of ENKL

6.1 Limited Stages

Radiotherapy has been the mainstay for the treatment of ENKL with limited stage disease. Since anthracyclines and vincristine are exported from lymphoma cells of ENKL by p-glycoprotein [7, 8], the efficacy of CHOP/CHOP-like regimen was unsatisfactory [5, 45]. Radiotherapy should be given prior to [46] or simultaneous with chemotherapy [9, 10]. The chemotherapy to be combined with radiotherapy is not determined, but platinum-based regimens are preferentially used. The Japanese Clinical Oncology group conducted a phase II study of simultaneous chemoradiotherapy (SCRT) with 50 Gy irradiation and the 2/3 dose of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) (Table 1) [9]. Two thirds of DeVIC was repeated 3 cycles, and the total treatment period was 9 weeks. The study by Korean group adopted a cisplatin monotherapy for SCRT followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) regimen [10]. Both studies showed satisfactory results with 2-year OS of approximately 80 % (Table 2), and the long-term follow-up study of RT-2/3 DeVIC confirmed the durable efficacy with 5-year OS of 70 % [47].

6.2 Advanced Stages, Relapsed or Refractory State

Systemic chemotherapy is required for advanced stage, relapsed or refractory ENKL patients. However, the efficacy of CHOP/CHOP-like regimen is limited because of the expression of p-glycoprotein [5]. Based on the clinical experience and in vitro

Table 1 RT-2/3 DeVIC regimen

Agent	Dose	Administration	Days
Radiotherapy	1.8–2.0 Gy	(Total 50 Gy)	Days 1–33 or 38 (5–6 weeks)
Carboplatin	200 mg/m^2	30 min div	Day 1 (22, 43)
Etoposide	67 mg/m^2	2 h div	Days 1–3 (22–24, 43–45)
Ifosfamide	1000 mg/m^2	3 h div	Days 1–3 (22–24, 43–45)
Dexamethasone	40 mg/body	30 min div	Days 1–3 (22–24, 43–45)

2/3 DeVIC should be repeated every 3 weeks

Table 2 Comparison of simultaneous chemoradiotherapy (SCRT) for localized ENKL

Regimen	RT-2/3 DeVIC	Korean CCRT
Treatment period	9 weeks	16–20 weeks
Radiation dose	50 Gy	40–50.8 Gy (median: 40 Gy)
Cytotoxic agents	CBDCA	CDDP
	ETP	ETP
	IFM	IFM
	Dexa	Dexa
Chemotherapy	3 courses	SCRT + 3 courses
Number of patients	27	30
Stage I ratio	67 %	50 %
CR rate	77 %	73 % → 90 % (best response)
ORR	81 %	100 %
2y OS	78 %	86 %
95 % CI	(57–89 %)	(74–99 %)
Median f/u	32 months	23.7 months
Range	(24–62 months)	(17.3–37 months)
5y OS	70 %	–
95 % CI	(49–84 %)	–
Median f/u	67 months	–
Range	(61–94 months)	–

Abbreviations: *JCOG* Japan Clinical Oncology Group, *CCRT* concurrent chemoradiotherapy, *CBDCA* carboplatin, *ETP* etoposide, *IFM* ifosfamide, *Dexa* dexamethasone, *CDDP* cisplatin, *CR* complete response, *ORR* overall response rate, *OS* overall survival, *CI* confidence interval, *f/u* follow-up

Table 3 SMILE regimen

Agent	Dose	Administration	Days
Methotrexate	2 g/m^2	6 h div	Day 1
Ifosfamide	1500 mg/m^2	3 h div	Days 2–4
Etoposide	100 mg/m^2	2 h div	Days 2–4
Dexamethasone	40 mg/body	30 min div	Days 2–4
L-asparaginase	6000 IU/m^2	2 h div	Days 8, 10, 12, 14, 16, 18, 20

SMILE should be repeated every 4 weeks

sensitivity studies, L-asparaginase-containing regimens have been established and became the first choice for these patients [48]. L-asparaginase is an enzyme that digests serum L-asparagine and acts as an antitumor agent through asparagine starvation of tumors with low expression levels of asparagine synthetase [49]. The SMILE regimen consists of steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (Table 3) [50]. The phase II SMILE study showed an excellent antitumor activity to ENKL (Fig. 4) [11], and the efficacy was further verified by a long-term follow-up with a 3-year OS of 50 % (95 % CI, 33–65 %) [51]. Another L-asparaginase-containing regimen, AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) was studied by GELA (Groupe d'Etude des Lymphomes de l'Adulte) and GOELAMS (Groupe Ouest-Est des Leuce'mies et des Autres Maladies du Sang) [52].

Table 4 Comparison of L-asparaginase-containing regimens for ENKL

Regimen	SMILE	AspaMetDex
Agents	MTX	MTX
	L-asp	L-asp
	Dexa	Dexa
	ETP	
	IFM	
Number of patients	38	19
Course	2 courses	3 courses
Chemotherapy interval	4 weeks	3 weeks
Rate of stage III/IV patients	71 %	37 %
CR rate	45 %	61 % (1 patient excluded)
ORR	79 %	78 %
2y OS	51 %	41 %
Median f/u	24 months	26 months
Range	(13–35 months)	(17–49 months)
In case of L-asp allergy	SMILE head is strong enough	MTX monotherapy

Abbreviations: *NKTSG* NK-cell Tumor Study Group, *MTX* methotrexate, *L-asp* L-asparaginase, *Dexa* dexamethasone, *ETP* etoposide, *IFM* ifosfamide, *CR* complete response, *ORR* overall response rate, *OS* overall survival, *f/u* follow-up

The phase II study of AspaMetDex for relapsed or refractory ENKL also showed a good overall response rate and 1-year OS [12]. However, results of a later-conducted study for newly diagnosed ENKL patients were rather unsatisfactory [53]. Although more than half of the patients were in localized stage, the ORR was 55 % (95 % CI, 32–77 %) and OS was less than 50 %. All patients examined developed an anti-asparaginase antibody, partly due to the low-intensity chemotherapy before L-asparaginase. The comparison of these two L-asparaginase-based chemotherapy is shown in Table 4. SMILE is sometimes myelotoxic to ENKL patients, but the duration of neutropenia is generally not so long (Fig. 5). It is therefore needed to identify patients who develop severe leukopenia and neutropenia after SMILE regimen.

6.3 Hematopoietic Stem Cell Transplantation

Previously, prognosis of ENKL was recognized as poor even for limited stage patients. Therefore, both autologous and allogeneic hematopoietic stem cell transplantations (HSCTs) were conducted for ENKL with every situation [54]. A long-term survival for ENKL patients who received upfront autologous HSCT ranged from 50 to 70 % [54–56]. The matched-control study comparing autologous HSCT and conventional radiochemotherapy showed that the advantage of autologous HSCT was evident only for patients with high-risk prognostic index [57]. Allogeneic HSCT showed a long-term survival rate ranging from 30 to 40 % [54, 58], but the patient background characters were worth than those of autologous HSCT. Patients who received allogeneic

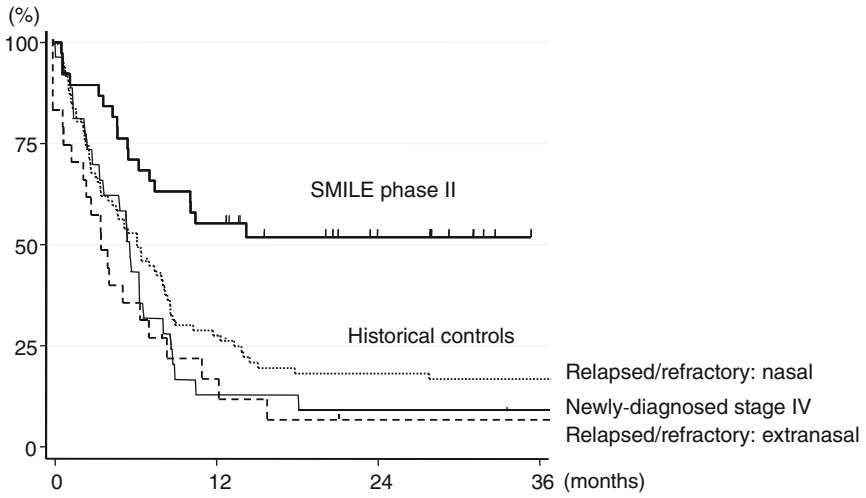

Fig. 4 Survival of newly diagnosed stage IV or relapsed/refractory ENKL. The survival curve of SMILE phase II study is overlaid on those of historical control and is markedly improved. However, these curves are not exactly comparable because of background differences

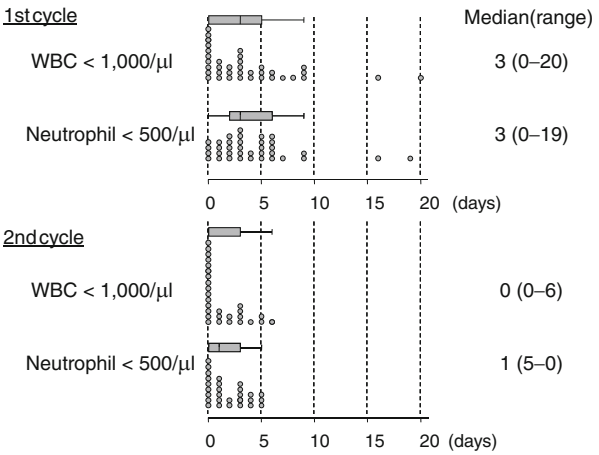

Fig. 5 Duration of cytopenia after SMILE. Although several patients developed prolonged leukocytopenia and neutropenia, the durations of cytopenia were generally not so long. Both the median of leukocyte less than 1,000/μl and that of neutropenia less than 500/μl were 3 days. The durations of cytopenia were rather short after the second course of SMILE as compared with the first course

HSCT were more likely to be in non-CR condition and to have higher clinical stage at diagnosis, although the age was lower. No superiority of either autologous or allogeneic HSCT has been identified, as well as the conditioning intensity of reduced vs. myeloablative conditioning [59, 60]. In the current decade, the treatment modality was changed and prognosis was improved by an introduction of SCRT and L-asparaginase-containing chemotherapy; hence, new questions are raised for the significance and methodology of HSCT for ENKL. Further investigations and prospective evaluations are needed to clarify the indication of HSCT for NK/T-cell lymphoma.

7 EBV-DNA in Peripheral Blood

In the process of tumor growth, cell-free DNA fragments are released from apoptotic/necrotic tumor cells to circulating peripheral blood. For patients with ENKL, the EBV-DNA can be detected as a part of tumor DNA [61]. These viral DNA fragments are usually less than 500 bp in length and can be detected by polymerase chain reaction [62]. Measurement of the circulating EBV-DNA copy numbers is useful for diagnosis, monitoring, and prognostication of the disease [63–65]. There are several choices of source tissue for analysis including mononuclear cells, plasma, and whole blood, and each choice represents a different outcome [64]. The SMILE-EBV study further identified that the amount of EBV-DNA predicted the degree of adverse reactions by SMILE chemotherapy [66]. One reason for this phenomenon is that the toxicity by chemotherapy is mediated by certain toxic substances released from tumor cells, such as cytotoxic molecules. This is also important for patient case, since the initial dose of chemotherapy for patients with high tumor burden may be decreased to avoid excessive toxicity.

8 Prognostic Factors for ENKL

The International Prognostic Index (IPI) score is a good indicator for prognosis of ENKL [3–6], like most of other types of lymphoma. However, among the components of IPI, the age is not prognostic in many observations [4, 5]. Other adverse prognostic factors specific for ENKL are the non-nasal origin of lymphoma [5, 6], local tumor invasiveness [67], and the regional lymph node involvement [4]. Poor prognosis of the non-nasal origin is partly due to the difference in stage distribution [68], but is still prognostic after adjustment by multivariate analysis [5]. This warrants future division of disease subtypes of nasal and non-nasal ENKLs in the lymphoma classification. The local tumor invasiveness included bony invasion or perforation or invasion of the skin based on computed tomography or physical findings [67]. However, these extreme local progressions are currently rare due to the early disease recognition and reference to specialized physicians. The regional lymph node involvement was defined as the involvement of lymph nodes corresponding to N1, N2, or N3, but not M1 of the TNM staging system [4]. The incidence of regional lymph node swelling ranges from 30 to 50 %.

9 Future Perspectives

Several new insights have been developed for ENKL. The disease is currently recognized to belong to intermediate prognosis [2]. Further improvement for diagnosis and treatment should be explored by prospective clinical studies.

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Diagnosis of Diffuse Large B-Cell Lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) and accounts for 25–30 % of adult NHL in Western countries. However, its relative proportion varies across the world (25–75 % of all NHL), being higher in the tropical countries and in the resource-poor setting. While there could be environmental or genetic basis for this difference, precision of applying WHO classification can also account for the difference. Though it is more common in elderly (peak incidence in seventh decade), it can occur at all ages. While the majority of DLBCLs arise de novo, a significant proportion represents progression from another type of B-cell lymphoma [1–4].

DLBCL is a heterogeneous group of B-cell lymphomas. Several distinctive subsets of DLBCL have been defined. However, most DLBCLs do not belong to these specific subcategories and are classified as DLBCL, not otherwise specified (NOS). About 40 % of DLBCLs, NOS, occur at extranodal sites that include the gastrointestinal tract, bone, testis, spleen, Waldeyer's ring, salivary gland, thyroid, liver, kidney, adrenal gland and central nervous system (CNS). Almost any organ can be involved by DLBCL [5].

While in most cases of DLBCL an apparent causative risk factor is not identifiable, a minority of cases show underlying immune deficiency. Immune deficiency could be

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congenital or acquired, the latter being in the context of human immunodeficiency virus (HIV) infection, transplantation or immunosuppressive medication [6–8].

DLBCL is defined in the WHO classification as a neoplasm of medium or large B lymphoid cells with a diffuse growth pattern. The nuclear size of the tumour cells is equal to or exceeds the size of a normal macrophage nucleus or is more than twice the size of a normal lymphocyte nucleus. By definition, DLBCL expresses B-cell antigens—CD20, CD19, CD79a, PAX5, CD22 and immunoglobulin. The demonstration of one or more of these antigens is essential for the diagnosis [5].

1 DLBCL-NOS

1.1 Morphology

In tissue samples (lymph nodes and extranodal sites), there is partial or more commonly diffuse infiltration by medium/large lymphoid cells. In some lymph nodes, infiltrate may be seen in an interfollicular distribution or rarely in a sinusoidal distribution. A variable amount of background fibrosis is noted. Perinodal extension is frequently seen. Cell size varies between cases. Cases are also heterogeneous with respect to pleomorphism among the tumour cells. While some cases are relatively monomorphic, others show variation in cell/nuclear size and shape. Prominent pleomorphism and tumour giant cells may be seen in some cases. In some cases, tumour cells can be cohesive, thereby mimicking a carcinoma. Variable amounts of small reactive lymphoid cells are seen in the background.

Areas of necrosis including coagulative necrosis can be seen. Some cases show a starry-sky appearance, a pattern produced by the presence of phagocytic histiocytes amidst the monomorphic neoplastic infiltrate. Sclerosis is particularly common in mediastinal and retroperitoneal sites [5].

1.2 Common Morphological Variants

- Centroblastic variant—centroblasts are medium/large lymphoid cells with oval to round vesicular nuclei with fine chromatin. They have 2–4 basophilic nucleoli placed close to nuclear membrane. They have scanty basophilic/amphophilic cytoplasm. Some cases show lobulated or angulated nuclei [5].
- Immunoblastic variant—immunoblasts are large lymphoid cells with a round or oval vesicular nuclei, single centrally located large nucleolus and relatively abundant basophilic cytoplasm. Some of the cells also show plasmacytic differentiation. For a diagnosis of immunoblastic variant, >90 % cells should have morphology of immunoblasts. This subset is associated with poor prognosis. Those with <90 % immunoblasts are considered as centroblastic variant [5].

- Anaplastic variant—the subset is characterised by cohesive very large tumour cells with bizarre pleomorphic nuclei, some of the cells resembling Hodgkin cells. In some cases, sinusoidal distribution may be seen. A significant proportion of these cases may express CD30. ALK is negative [5, 9].

1.3 Molecular Variants

Based on gene expression profiling, DLBCL can be subtyped into germinal centre B-cell-like (GCB) and activated B-cell-like (ABC) subsets. Assigning a cell of origin subset is based on mRNA expression and was initially identified on microarray studies [10–12]. Before the introduction of rituximab, 5-year survival for the GCB and the ABC subsets was approximately 60 and 35 %, respectively. Regimens containing rituximab demonstrate a 5-year survival of about 90 % for GCB subset and about 45 % for the ABC subset. There are currently ongoing clinical trials to assess the impact of differential therapy on the subsets. As of now, mRNA expression analysis is not a part of routine clinical diagnosis.

1.4 Immunohistochemical Variants

- CD5-positive DLBCL: About 10 % of DLBCLs express CD5. Most cases have centroblastic appearance. About 20 % cases show an intravascular or intrasinusoidal distribution of tumour cells. These cases are usually CD10-negative and express BCL2 and BCL6. Most of these cases do not express cyclin D1, a feature useful in distinction from blastoid mantle cell lymphoma. The subset is associated with poor prognosis. Patients are prone for CNS relapse [13].
- Germinal centre B-cell-like: This subset expresses CD10. In the absence of CD10, these cases express BCL6 and lack MUM1/IRF4 expression (Hans algorithm). A 30 % cutoff is used for scoring immunostains. Approximately, the subset would account for one-half of DLBCL-NOS [10].
- Non-germinal centre B-cell-like: This subset does not express CD10 and expresses MUM1/IRF4 or does not express both BCL6 and CD10 (Hans algorithm). A 30 % cutoff is used for scoring immunostains. The subset has relatively poor prognosis. Approximately, the subset would account for one-half of DLBCL-NOS [10].

BCL2 expression is seen in about 50 % of DLBCLs. CD10 expression is seen in about 20–40 % of DLBCLs, and BCL6 expression is seen in about 60 % cases. Several immunostains serve as surrogate markers in classification of DLBCL into germinal centre B-cell-like and non-germinal centre B-cell like subsets. The original Hans-classifier used three molecules—CD10, BCL6 and MUM1/IRF4 for subtyping DLBCL. Subsequently several other immunohistochemistry-based algorithms were published. While all algorithms published follow a similar

direction and demonstrate better survival for GCB subset, there are issues with reproducibility. Furthermore, a proportion of cases show discrepant results between immunohistochemistry and gene expression approaches [10, 11, 14].

1.5 Other Immunohistochemical Features of DLBCL

- About 2 % of DLBCLs express cyclin D1. This is often seen as weak expression in a proportion of cells and is not associated with CCND1 translocation. In some cases CCND1 amplification has been demonstrated. In such cases differential diagnosis includes blastoid and pleomorphic variants of mantle cell lymphoma [15].
- Most cases of DLBCL are negative for MYC protein. In a minority of cases, MYC expression (>40 % cells positive) is noted. Such cases should be investigated for MYC translocation [16, 17].
- About 10–20 % of DLBCLs express CD30 in a variable proportion of cells. In CD30-positive DLBCLs, dependent on clinical presentation and other histological features, primary mediastinal large B-cell lymphoma and classical Hodgkin lymphoma need exclusion.
- Evaluation of Ki67 expression is generally undertaken. Ki67 expression is highly variable and varies between 20 and 90 %. Most cases however have Ki67 expression >50 %. In general, Ki67 expression does not show definite impact on prognosis. In a minority of cases, Ki67 expression can approach 100 % and require exclusion of Burkitt lymphoma and grey zone lymphoma. Similarly, cases with <50 % Ki67 expression require careful consideration and exclusion of other indolent B-cell lymphomas [8, 18].
- Cases co-expressing c-MYC and BCL2 have worse prognosis [18].

1.6 Chromosomal Translocations in DLBCL *[5, 18, 19]*

- *BCL6* translocation is seen in about 30 % cases.
- *BCL2* translocation is seen in 20–30 % cases.
- *MYC* translocation is seen in about 10 % cases. *IG* gene partners *MYC* in 60 % cases.
- *MYC* and *BCL2* translocations are seen in less than 5 % of cases.
- *TP53* mutations are identified in about 20 % cases.

1.7 Microenvironment in DLBCL

Cells in the microenvironment of DLBCL play an important role. The presence of MHC class II gene expression pattern correlates with better survival.

2 T-Cell/Histiocyte-Rich Large B-Cell Lymphoma (THRLBCL)

THRLBCL is characterised by the presence of small numbers of large atypical B cells (<10 % of the overall population) in a background of abundant reactive small T cells and histiocytes. THRLBCL is a predominantly nodal lymphoma. Involvement of the liver, spleen and bone marrow is frequent. However, other extranodal presentations are not common. The disease shows male predominance. Most patients are symptomatic, and they often present in high stage with a relatively high IPI score.

Morphology demonstrates the presence of large atypical lymphoid cells with features of centroblasts, immunoblasts or neoplastic lymphocyte-predominant cells (similar to the neoplastic cells of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)) in a background of small lymphocytes and histiocytes. Plasma cells and eosinophils are not prominent. Variable degree of pleomorphism is noted among the large atypical cells, and some of the cells resemble Hodgkin cells. Proportion of histiocytes is also variable. Composition of the infiltrate in THRLBCL overlaps with those of NLPHL. However, a distinct nodular pattern is absent. In a given case, if an area with morphological features of NLPHL is identifiable, the case should be classified as NLPHL. Some cases of NLPHL progress to THRLBCL. Cases with splenic involvement show multifocal/micronodular involvement of white pulp. Cases with hepatic involvement show localisation of abnormal infiltrate to portal tracts. Some cases may show evolution to conventional DLBCL [5].

Atypical cells in THRLBCL express B-cell markers CD19, CD20, CD79a, CD22 and PAX5 and also express BCL6. In a proportion of cases, neoplastic cells express BCL2. Background T cells express various pan-T-cell markers, with a significant proportion of cells being CD8 positive. Histiocytes are highlighted by CD68R. The absence of follicular dendritic cells (on CD21 and CD23 immunostains) and follicular mantle cells (on IgD immunostain) is helpful in distinction from NLPHL. Tumour cells are negative for CD15 and CD30, and this helps distinction from classical Hodgkin lymphoma. In some cases, CD30+ cells can be seen. EBV association is not seen [5].

3 Primary DLBCL of the CNS

This refers to primary intracerebral or intraocular DLBCL and excludes lymphomas of dura and intravascular large B-cell lymphoma, CNS involvement in systemic lymphoma or immune deficiency-associated lymphomas.

CNS-DLBCL is rare (<1 % of NHLs). About 20–40 % are multifocal, and about 60 % occur in supratentorial sites. Morphology demonstrates a diffuse infiltrate of large atypical lymphoid cells characteristically seen involving perivascular spaces. In most cases, tumour cells have features of centroblasts. Morphology could be altered by prior treatment with steroids. Tumour cells are admixed with variable

numbers of small lymphocytes, histiocytes, microglial cells and reactive astrocytes. Lesions with prior steroid treatment may also show large areas of necrosis.

CNS-DLBCLs express B-cell markers CD19, CD20, CD79a, CD22 and PAX5 and frequently express MUM1/IRF4 and BCL2. BCL6 expression is seen in about 20 % cases; CD10 expression is rare. EBV association is usually not seen in general population, while it is frequently observed in CNS lymphoma related to immunodeficiency [20].

4 Primary Cutaneous DLBCL, Leg Type

These account for 4 % of primary cutaneous lymphomas and about 20 % of primary cutaneous B-cell lymphomas. Patients are usually elderly and predominantly women. While most occur in legs, a small minority (10–15 %) occur in other sites. They typically present as red or bluish red tumours on one or both legs.

Morphological features are those of DLBCL with centroblasts and immunoblasts occupying the dermis and extending to subcutis. Epidermotropism is not seen. Tumour cells typically express BCL6, BCL2, MUM1/IRF4 and FOX-P1 and are negative for CD10. Translocations involving *BCL6*, *c-MYC* and *IGH*, amplification of 18q21 and deletion of 9p21 are frequent [5].

This is an aggressive disease with a 5-year survival of approximately 50 %. During later stages, extracutaneous spread of disease is frequent.

5 EBV Positive DLBCL of the Elderly

This entity refers to DLBCL occurring in patients of >50 years of age, in whom there is no documentable evidence of immune deficiency or a prior lymphoma. Other well-defined EBV-positive large B-cell lymphomas such as those arising in the background of lymphomatoid granulomatosis, plasmablastic lymphoma or primary effusion lymphoma also need to be excluded. In Asia, this entity accounts for approximately 10 % of DLBCL. In the Western countries, they account for <5 % of DLBCL. EBV association is seen in nearly one-quarter of DLBCLs among patients >90 years of age. Nearly 70 % of patients present with extranodal lesions, and the rest with nodal lesions. This is an aggressive disease with the median survival of about 2 years.

Morphology is variable. While some of the cases show features of monomorphic DLBCL, others show a polymorphic infiltrate composed of a broad range of B cells (variation in size and in maturation) accompanied by a reactive small lymphocytic, plasma cell and histiocytic infiltrate. Areas of geographic necrosis and cells resembling Hodgkin cells are frequently seen. Immunophenotype is that of non-germinal centre subtype of DLBCL. Frequently they show detectable cytoplasmic immunoglobulin. Rare cases may lack CD20 expression. They are variably positive for CD30. They consistently express EBER and frequently express EBV-LMP 1. A proportion of cases express EBNA2 [21].

6 Primary Mediastinal (Thymic) Large B-Cell Lymphoma (PMLBL)

PMLBLs account for 2–4 % of NHLs. It is predominantly seen in women (male/female ratio of about 1:2). Most patients are in third or fourth decade of life. Patients typically present with a large anterosuperior mediastinal mass, frequently invading adjacent structures and producing superior vena cava syndrome. Involvement of supraclavicular lymph node and other cervical lymph nodes can occur. However, disease is restricted to these sites at presentation. In later stages of disease, involvement of other extranodal sites is relatively common.

In most cases, the diagnosis is based on a needle core biopsy. Typically, groups of medium/large cells are seen surrounded by compartmentalising alveolar fibrosis. Tumour cells have pale-staining cytoplasm. In some cases, tumour cells have lobulated nuclei resembling lacunar cells and Hodgkin cells. Apart from expressing B-cell markers, tumour cells frequently express CD30, CD23 and p63. Tumour cells are also frequently positive for MUM1/IRF4 and variably positive for BCL2 and BCL6. They also express transcription factors OCT2, BOB.1 and PU.1. They are usually negative for CD10. Most cases are negative for CD15, although occasional cases may be positive. Tumour cells also express MAL antigen, TRAF1 and nuclear REL. PMLBL shows gains of 9p24 (*JAK2*, *PD1* and *PDL2*) and 2p15 (includes *REL* and *BCL11A*) [22].

7 Intravascular Large B-Cell Lymphoma (IVLBCL)

This is an extranodal DLBCL where tumour cells are restricted to the lumina of blood vessels, especially capillaries. Involvement is usually widespread including bone marrow; lymph nodes are often spared. Larger arteries and veins are not involved. Median age of presentation is 67 years. Patients in Western countries predominantly present with neurological and cutaneous manifestations. Patients in Asia present with multiorgan failure, hepatosplenomegaly, multiple cytopenias and haemophagocytic syndrome. Disease course is aggressive with poor responses to chemotherapy.

Immunophenotype of IVLBCL is that of DLBCL of non-germinal centre subtype, and one-third of cases express CD5. The peculiar pattern of involvement is likely to be due to lack of CD29 and CD54 in the tumour cells [5].

8 ALK-Positive Large B-Cell Lymphoma

This is a rare tumour that can be mistaken for other large-cell lymphomas or large-cell malignancies. Though this is predominantly nodal disease, extranodal presentations are also documented. Most patients present in advanced stages. Typically, histological examination demonstrates sheets of immunoblast/plasmablasts-like cells filling lymph node sinuses. Diagnostic difficulty stems from lack of expression of

B-cell markers such as CD20 and CD79a. CD45 expression is weak or absent. There is often weak expression of PAX5; however some may be negative. They are also negative for CD30. Most cases show expression of cytoplasmic immunoglobulin (mostly IgA and less frequently IgG). Light chain restriction is demonstrable. They express MUM1, EMA, CD138 and CD38; hence, plasmablastic lymphoma enters differential diagnosis. They can also express CD4, CD57, CD43 and perforin, thereby mimicking T-cell lymphomas. They are EBV-negative. Diagnosis is based on expression of ALK protein, which is typically seen as granular cytoplasmic positivity. FISH analysis demonstrates *Clathrin-ALK* translocation. This is generally an aggressive disease [5, 9].

Other lymphomas with large B cells include DLBCL associated with chronic inflammation (associated with EBV) such as in pleural localisation after tuberculosis [5], DLBCL arising in the background of lymphomatoid granulomatosis (associated with EBV) [5], plasmablastic lymphoma (associated with EBV) [5], large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (associated with HHV8) and primary effusion lymphoma (positive for both HHV8 and EBV) [5, 23]. DLBCL can also show overlapping features with Burkitt lymphoma (B-cell lymphoma unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma) [5, 18] and classical Hodgkin lymphoma (B-cell lymphoma unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma) [5]. These entities are not discussed in this review.

While in most cases DLBCL is de novo, a minority of cases represent transformation from an underlying indolent lymphoma such as follicular lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma. EBV-positive DLBCL can also arise as a second malignancy associated with immune suppression in the background of angioimmunoblastic T-cell lymphoma. These are also not discussed in this review.

The diagnosis in countries with limited resources, is mainly based on morphology. However, the use of a limited panel of immunohistochemistry (one including CD20, CD10, BCL2, Ki67, CD38 and CD44) improves diagnostic accuracy. In a small minority, FISH analysis of *MYC* and *BCL2* would be essential [18, 24, 25].

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Burkitt's Lymphoma: Physiopathology and Treatment of EBV-Associated Lymphomas

Saliou Diop and Felipe Suarez

1 Introduction

Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin's lymphoma (NHL) derived from germinal center B-cells [1]. Three categories of BL are recognized. Endemic BL (eBL) occurs in the equatorial belt of sub-Saharan Africa, with an estimated incidence of 50 cases per million per year and a strong predominance in children (median age of 6 years). eBL represents half of all the pediatric cancers and over 90 % of pediatric lymphomas in sub-Saharan Africa [2, 3]. The geographic distribution of eBL overlaps with that of malaria. Sporadic BL (sBL) occurs in the northern hemisphere and Asia with a lower incidence and affects children as well as young adults. Immunodeficiency-associated BL (iBL) is the third type of BL and has emerged in the 1980s with the human immunodeficiency virus (HIV) pandemic. iBL occurs in HIV-infected patients with moderate immunosuppression (CD4 cell counts above 200/mm^3).

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2 Clinical Presentation of BL

BL often presents as an advanced disease with extranodal, CNS, and bone marrow involvement. The classic presentation of eBL includes facial involvement (mandibular and periorbital tumors) and/or abdominal tumors. sBL also frequently presents with an abdominal involvement (often ileocecal). sBL and iBL may also present as typical high-grade nodal lymphomas.

3 Pathology of BL

Tumors are characterized by monomorphic, highly proliferative medium-sized lymphoid cells of B-cell phenotype (Fig. 1a, b). The phenotype is $CD20^{+}$, $CD10^{+}$, $BCL2^{-}$. BL is one of the most rapidly proliferating human tumor with a doubling time of 24–48 h, and numerous mitotic cells and apoptotic figures are salient

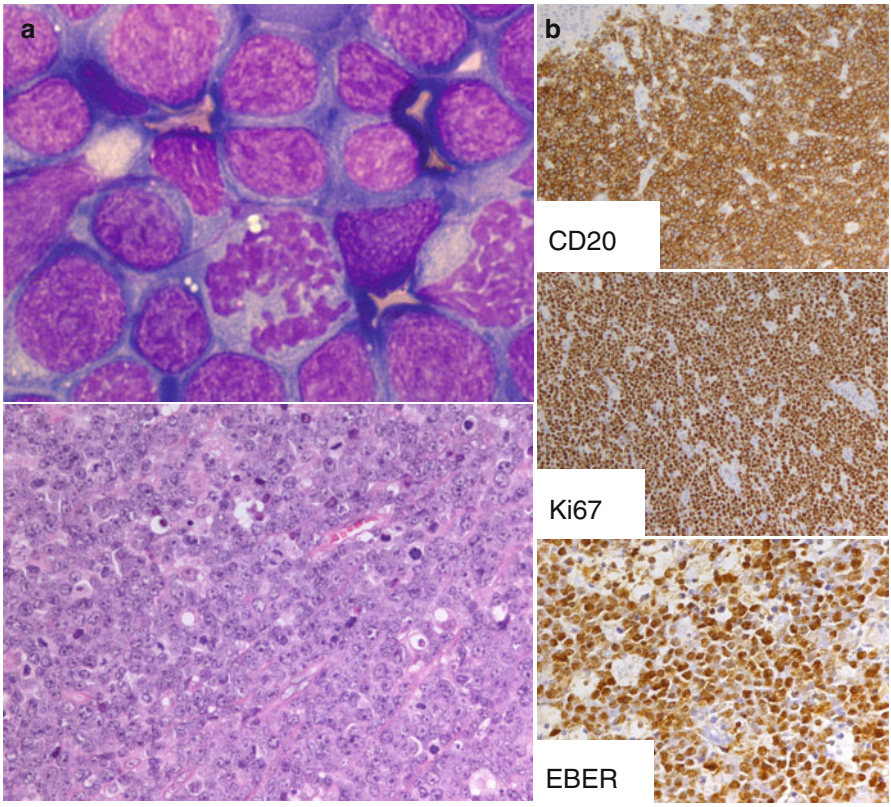

Fig. 1 (**a**) *Top*: cytology on a fine-needle aspiration. Note the 2 mitotic figures. *Botton*: H&E stain of a lymph node biopsy showing BL. (**b**) *Top*: CD20, middle Ki67 immunohistochemistry. *Bottom* EBER in situ hybridization

cytological and pathologic features of BL. Ki67 is expressed in virtually all cells. In cases associated with Epstein-Barr virus (EBV; see below), EBER is detected in tumor cells by in situ hybridization (Fig. 1b).

4 Pathophysiology of BL

4.1 BL and MYC *Rearrangements*

BL is derived from post-germinal B-cells. Translocations involving the *MYC* oncogene are the cytogenetical hallmarks of BL and are found in over 90 % of the cases [4]. In about 80 % of BL, the t(8;14)(q24;q32) involve *MYC* on chromosome 8 and the immunoglobulin heavy-chain locus (IgH) on chromosome 14. Less frequent translocations include t(2;8)(p12;q24) and t(8;22)(q24;q11) involving *MYC* and the kappa and lambda immunoglobulin light-chain loci (IgL), respectively. As a result, *MYC* is transcriptionally activated in B-cells leading to cell proliferation. The translocations are thought to be facilitated by AID, an enzyme responsible for somatic hypermutations and class-switch recombination in B-cells during the germinal center reaction [5]. Mechanisms associated with defective apoptosis in BL include frequent abrogation of p53 function by mutations of the *TP53* gene [6] and inhibition of BIM [7].

4.2 BL and EBV

EBV was isolated from endemic BL tissue in 1964 [8] and was later epidemiologically associated with the development of BL [9]. The distribution of EBV is worldwide and over 90 % of the adult population is infected. Acquisition of EBV occurs around 2 years of age in sub-Saharan Africa and during adolescence and young adulthood in the northern hemisphere [10]. EBV-infected individuals remain lifelong carriers of the virus. EBV infects epithelial cells (usually of the oropharynx) where it establishes a lytic infection and B-cells where it establishes a persisting latent infection [11]. B-cells infected in vitro with EBV are transformed and proliferate indefinitely as lymphoblastoid cell lines (LCL). During latency, the viral genome is maintained as an episome in the nuclei of B-cells and only a handful of viral genes are expressed. These can interfere with normal cellular pathways. Latent membrane proteins (LMP) 1 and 2 are expressed at the cellular membrane of B-cells infected with EBV and drive their proliferation and differentiation by mimicking the signals that normal B-cells receive during the germinal center reaction (LMP1 acts as a constitutively active CD40 signal [12] and LMP2 as a constitutively active B-cell receptor signal [13]). Other intracellular latent genes include EBNA1, EBNA2, EBNA3A-C, EBNA-LP, and virally encoded small RNA transcripts (EBER). The expression pattern of the EBV latent genes is tightly regulated. After naive B-cells become infected with EBV, LMP1

and LMP2 drive B-cell proliferation and their differentiation [14]. Infected B-cells expressing the full repertoire of EBV latent genes are highly immunogenic and give rise to a strong cytotoxic T-cell response that eventually opposes B-cell proliferation. Simultaneously, the EBV latent program switches to a restricted pattern, ultimately leading to infected B-cells acquiring a memory phenotype and harboring EBV with a very restricted pattern of gene expression. These cells are the reservoir of EBV infection and persist during the lifetime of the infected individual. Occasionally, EBV-infected memory B-cells are driven to differentiate into plasma cells, triggering the lytic program [15]. There are three distinct types of EBV latency programs occurring in EBV-associated lymphomas [16]. In immunodeficiency-associated lymphomas (posttransplant lymphoproliferative disorders and HIV-associated lymphomas in severely immunocompromised patients), type III latency is observed and closely resembles that observed in vitro in LCL, where most of the latent genes are expressed and drive the B-cell proliferation. In EBV-associated Hodgkin's lymphoma, a more restricted type II latency is observed, where LMP1 and LMP2 are expressed and contribute to the survival of malignant cells. EBV is universally associated with eBL, and a restricted-type I latency is observed, similar to that observed in EBV-infected memory B-cells in healthy carriers [17]. A minority of sBL and iBL are also associated with EBV infection and a type I latency. During type I latency, only EBNA1 is expressed. Although eBL has been linked to EBV infection for over 40 years, the precise oncogenic role of the virus has remained elusive. EBNA1 is not directly oncogenic but may exert an antiapoptotic role that contributes to the malignant phenotype [16]. Nevertheless, the universal presence of EBV in eBL cells, as well as experimental evidence, points to a pathogenic role of EBV in the development of eBL. EBV may cooperate with MYC in BL and may provide at least part of the antiapoptotic machinery required for cells that overexpress deregulated MYC.

4.3 eBL and Malaria

There is strong epidemiological evidence associating malaria with eBL [18]. Extensive infection with *Plasmodium* sp. may serve as a cofactor to EBV in the development of BL in equatorial regions. Chronic infection with *Plasmodium* sp. leads to polyclonal B-cell activation, favoring the emergence of the *MYC* rearrangements characteristic of BL. Moreover, *Plasmodium* sp. contributes to immunodepression and plasmodial factors can lead to reactivation of the EBV lytic cycle [19].

4.4 eBL and HIV Infection

HIV infection also leads to chronic polyclonal B-cell activation and may contribute to BL development [20], as is the case for malaria.

5 Diagnosis and Initial Workup

Evaluation of BL in high-income countries relies on histological examination of surgical biopsies of involved tissue and staging using bone marrow and cerebrospinal fluid (CSF) examination and thoracic and abdominal computed tomography. Complete biological workup with complete blood count and blood chemistry with creatinine, electrolytes, uric acid, and lactate dehydrogenase (LDH) is mandatory given the high proliferative rate and the high risk of spontaneous and therapy-induced tumor lysis syndrome.

6 Treatment

BL was one of the first lymphomas to be cured solely by chemotherapy. Despite its very aggressive presentation, BL is a highly curable form of NHL. Improved outcome has been achieved over the last two decades with the use of intensive chemotherapy following the protocols developed by the LMB and the BFM cooperative groups. These protocols rely on an initial cytoreduction, followed by a combination of intensive chemotherapy, and include high-dose methotrexate and intrathecal chemotherapy to address the frequent CNS involvement [21]. Chemotherapy induces profound neutropenia, anemia, and thrombocytopenia that require antibacterial therapy for frequent neutropenic fever and transfusions of packed red blood cells and platelets. Several courses of chemotherapy are required and the entire treatment period lasts approximately 4 to 6 months with frequent hospitalizations. Overall survival and cure extends from 70 % to over 90 % depending on age and initial stage.

7 Challenges in Low-Income and Developing Countries

Low income of parents of affected children, poor or absent health insurance policies, sparse hospital infrastructure, and lack of appropriate health networks constitute tremendous challenges to the care of eBL in low-income countries [22–24]. Recommended diagnostic procedures, supportive care, and intensive chemotherapy required to guarantee the curability of this otherwise highly treatable lymphoma are unrealistic in equatorial Africa. Intense efforts have been made by medical researchers in affected countries and have led to the development of strategies that can be adapted to the various situations. The cost-effectiveness of treating pediatric cancer, particularly BL in low-income countries, has been evaluated and found to be favorable [25]. Current overall survival with such approaches is in the range of 50 % in children [26]. Therapy for adults is more complicated and has not been extensively studied in these regions.

Diagnostic pathology and hematopathology is not readily available in equatorial Africa (0.1–1.3 pathologists per million population versus 62 in the USA) [27]. Diagnosis of BL on surgically removed biopsies is generally not feasible. Cytopathological evaluation of fine-needle aspirates (FNA) is almost universally available and has a good diagnostic value [28]. Even if eBL is by far the most frequent NHL in children in these regions and its clinical presentation is typical, a FNA is recommended for the diagnosis. In recent protocols undertaken in equatorial Africa, FNA was used for diagnosis of eBL in over 75 % of the cases [26]. In some cases, patients are treated solely on the basis of a clinical diagnosis highly suggestive of eBL. Staging includes CSF evaluation imaging procedures that are usually limited to chest X-ray and abdominal ultrasonography. Complete staging should be performed when feasible, to determine the St Jude stage as some protocols use risk-adapted chemotherapy. As expected, most studies have found poorer outcomes for more advanced disease.

Table 1 Chemotherapy strategies for children with eBL in low-income countries

Protocol	Phase	Drugs	Schedule
Malawi 2000 [29]	*COP1* (d1)	Vincristine 1 mg/m^2 IV CPM 300 mg/m^2 IV MTX + HC IT PDN 60 mg/m^2 PO	d1 d1 d1 d1–7
	COP2 (d8 if advanced)	Vincristine 2 mg/m^2 IV CPM 500 mg/m^2 IV MTX + HC IT PDN 60 mg/m^2 PO	d1 d1 d1 d1–7
	COMP1 and COMP2 (d22 and d36 if limited d30 and d42 if advanced)	Vincristine 2 mg/m^2 IV MTX 2 g/m^2 IV Leucovorin rescue CPM 500 mg/m^2 IV PDN 60 mg/m^2 PO	d1 d1 d2–3 d2 d1–7
Malawi 28 day [26]		CPM 40 mg/m^2 IV CPM 60 mg/m^2 IV or PO MTX + HC IT	d1 d8–d18–d28 d1–d8–d18–d28
GFAOP [30]	*First line*	CPM 1.2 g/m^2 IV	d1–d8–d15
	Second line (if relapse of absence of CR):		
	COPM1 and COPM2	Vincristine 2 mg/m^2 IV PDN 60 mg/m^2 PO CPM 500 mg/m^2 IV MTX 3 g/m^2 IV Leucovorin rescue MTX + HC IT	d1 d1–5 d2–4 d1 d2–3 d2 & 6
	CYM1 and CYM2 (Interval between course approximately 18 d)	MTX 3 g/m^2 IV AraC 100 mg/m^2 SC MTX + HC IT AraC + HC IT	d1 d2–6 d2 d6

Abbreviations: *IV* intravenous, *PO* oral, *IT* intrathecal, *SC* subcutaneous, *CPM* cyclophosphamide, *MTX* methotrexate, *HC* hydrocortisone, *PDN* prednisone, *AraC* cytarabine

Chemotherapy strategies for children with eBL in low-income countries have evolved over the years (Table 1). Initial attempts based on protocols used in high-income countries were developed around the use of cyclophosphamide, vincristine, and intravenous methotrexate, together with steroids and intrathecal methotrexate. Such protocols have excessive toxicities in these settings and are difficult to implement, as they require prolonged hospitalization, are often complicated by infection, and need transfusions which are generally not available. Furthermore, such approaches are costly, in the region of 500 USD per patient, several orders of magnitude above the estimated per capita health care expenditures in these countries [29, 30]. Lately, even simpler protocols have been tested. Hesseling et al. developed a short-course (28-day) schedule of cyclophosphamide monotherapy, associated with intrathecal methotrexate. This approach has been evaluated in Malawi [26] and in several other countries with minor modifications (treatment adaptation according to disease risk) [31]. Complete responses are over 80 %. Relapses or primary refractory diseases occur in around in approximately 30 % of the patients, yielding a 1-year EFS of approximately 50 %. As fewer than 5 % of the patients' relapse after 1 year, the cure rate is approximately 50 %. The cost of this approach is less than 50 USD per patient.

Supportive care should include intravenous fluid infusion (3 L/m^2) to ensure proper urinary output over the first few days following chemotherapy to cope with tumor lysis syndrome [32]. The latter should also be prevented with allopurinol starting ideally 24 h before initiating chemotherapy, as urate oxidase is not available in most of these countries. Emesis can be controlled by metoclopramide or other available drugs. Additionally, antiparasitic drugs should be given systematically along with cotrimoxazole prophylaxis. Neutropenic fever should be treated with the available broad-spectrum antibiotics (usually ampicillin or ceftriaxone). A malaria blood smear should be performed and antimalarial drugs prescribed if needed. Transfusions when available are restricted to life-threatening anemia.

8 Perspective and Conclusion

eBL is the single most frequent pediatric cancer and represents the vast majority of pediatric lymphomas in sub-Saharan Africa. Pathophysiology of eBL involves latent EBV infection and malaria. EBV would represent a logical therapeutic target, but thus far, no readily available antiviral therapy targets latent cells. Chemotherapy-based approaches remain the mainstay of the treatment of BL. Despite the major challenges posed to the treatment of BL in high-endemicity and low-income countries, progress has been made, and treatment should be proposed. Current therapy of eBL yields cure rates in the range of 30–50 %, still largely inferior to the 70–90 % achievable in higher-income countries.

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Mantle Cell Lymphoma

Catherine Thieblemont

1 Epidemiology

The MCL represents approximately 4–10 % of all cases of non-Hodgkin lymphoma (NHL) [1]. The distribution seems lower in developing countries than in West European countries. For example, the frequency of MCL is reported lower in Algeria (2.5 %), in Pakistan (1.3 %), and in sub-Saharan Africa (1.4 %) compared with WEU (8.3 %) [2–4]. However this may reflect the difficulties to diagnose this lymphoma subtype. In Taiwan and in China, MCL represents 4 and 2.6 % of all NHL, respectively [5, 6].

MCL occurs primarily among elderly individuals with a median age of approximately 60 years. It is a rare disease in patients less than 30 years old. This tumor has a male predominance with a male/female ratio around 2–7:1.

Similar to chronic lymphocytic leukemia (CLL) and other lymphoid neoplasms, occasional cases of MCL have been observed in families in which a first-degree relative developed an MCL or other lymphoid malignancies [7]. The neoplasm in the second generation tends to appear at an earlier age than in the parents, suggesting a genetic predisposition. Genetic studies in MCL patients have identified certain single-nucleotide polymorphism (SNP) of the AURKA, TNFRSF10A, and TNFRSF10B genes at higher frequency in MCL patients than in healthy controls, but the number of samples examined was limited [8, 9]. Mutations in genes of the DNA damage response pathway such as ATM and CHEK2 have been detected in the germ line of some patients with MCL, suggesting that alterations in this pathway may play a predisposing role in the development of the disease [10, 11].

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2 Physiopathology

Mantle cell lymphoma (MCL) is genetically characterized by the translocation t(11;14)(q13;q32) and the overexpression of cyclin (CCND1) that probably facilitate the transformation of the cells by deregulation the cell cycle [12]. This initial event is acquired in pre-B cells of the bone marrow and seems to be followed by two different molecular pathways that configure two clinical and biological subtypes of the disease (Fig. 1). The classical and most common of MCL derives from mature B cells that do not enter the follicular germinal center and carry no or limited number of *IGHV* somatic mutations. Theses tumors express the transcription factor SOX11, are genetically unstable, and tend to accumulate alterations in cell cycle regulatory genes, DNA alteration damage response pathway, and cell survival mechanisms [13]. The acquisition of these alterations results in a more aggressive behavior. The second less common subtype of MCL is characterized by cells that also carry the t(11;14) and CCND1 overexpression but have experienced the follicular germinal center and carry IGHV with somatic hypermutations [14]. These cells are genetically stable, SOX11 expression is negative or very low, and the tumor tends to disseminate to the peripheral blood and spleen more than to the lymph nodes [14].

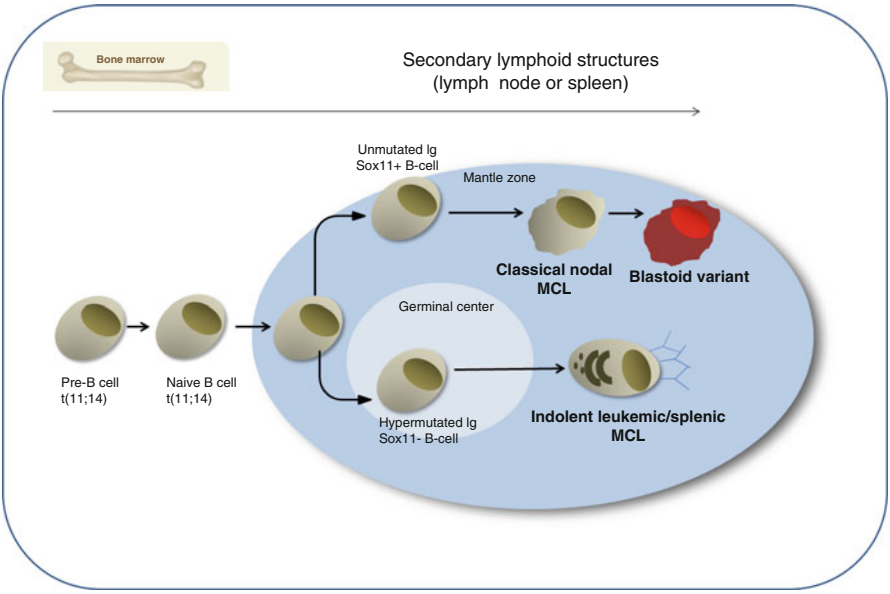

Fig. 1 Pathophysiology in the subentities and variants of MCL. MCL regroups at least three diseases: the classical nodal MCL, the most common entity, the indolent leukemic/splenic MCL, and the blastoid variant associated with a very aggressive behavior with poor response to treatment. The translocation t(11;14)(q13;q32) and the overexpression of cyclin (CCND1) is acquired in pre-B cells of the bone marrow and is followed by two different molecular pathways that configure the two clinical and biological subtypes of the disease: the nodal MCL and the leukemic/splenic MCL. The blastoid variant may be diagnosed either at the beginning of the evolution or later during the course of the disease. The outcome is very poor

The disease seems to be stable and asymptomatic for long periods of time but some tumors may acquire additional alterations in gene such as *TP53* that lead to the progression of the disease and transformation to a more aggressive variant [14].

A subset of MCL does not carry the t(11;14) translocation and CCND1 expression but they have the same pathological and clinical characteristics of MCL with this genetic alteration [15].

The most common alterations further deregulating cell cycle in MCL involve the *INK4a/CDK4/RB1* and *ARF/MDM2/TP53* pathways [13]. The relevance of cell cycle deregulation in MCL is highlighted by the poor prognosis conferred by high proliferative activity measured either by a gene expression signature or the Ki-67 index [16]. Recent genome-wide study using next-generation sequencing (NGS) has expanded the perspective of genes and pathways involved in the development of MCL. These studies have confirmed that the most common secondary alteration in MCL is the mutation of the DNA damage sensor *ATM*, usually associated with 11q deletions and a high number of chromosomal alterations [17]. These alterations seem to accumulate in tumors expressing SOX11 [17]. Novel mechanisms identified include activating mutations in NOTCH1/2 in around 10 % of the tumors associated with an aggressive evolution [18]. Mutations in several chromatin modifiers such as *WHSK1*, *MLL2*, and *MEF2B* have been also detected almost exclusively in MCL expressing SOX11 [17]. Somatic mutations in regulatory genes of the NFKB pathway have been identified in around 10–15 % of MCL [17]. *BIRC3* is the most commonly affected gene (6–10 %). Other alterations in both canonical and alternative NFKB pathways include recurrent inactivating mutations of *TRAF2*, activating mutations of *TLR2*, and occasional mutations of *CARD11*, *MAP3K1* (*NIK*), and *IKBKB* (*IKKB*), suggesting that NFKB pathway may be activated by genetic alterations in a higher number of cases that initially thought. A practical consequence of these alterations is their possible relationship with resistance of MCL cells to inhibitors of the BCR pathway as demonstrated in MCL cell lines [19].

In addition to frequent genetic alterations, MCL has deregulation of different signaling pathways that may be important targets of new drugs [13].

The promising results obtained with the inhibitors of the BCR signaling suggest that survival of MCL cells depends on the activation of this pathway, although the mechanisms are not entirely understood [20]. Activation of the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway has been observed in MCLs and is an effective target for new therapies [13]. Recent studies are emphasizing the potential relevance of the interactions between MCL cells and the microenvironment [21, 22].

3 Clinical Presentation

The clinical presentation of MCL is very different regarding the subtypes: nodal or leukemic/splenic. In the classical nodal MCL, representing 80 % of the patients, the disease is nodal and disseminated, including generalized lymphadenopathies and bone marrow involvement. The Ann Arbor is stage III or IV. Bulky disease and B symptoms are uncommon [23]. Extranodal involvement is almost constant, the most

frequent sites involved being the bone marrow, blood, and colon. This intestinal involvement is usually asymptomatic. The clinical behavior of MCL patients is aggressive with a median overall survival (OS) of around 3–4 years 10 ago. However the OS has been dramatically improved with median at around 7 years in 2015 based on recent advances in therapeutics [24, 25].

Leukemic involvement may also appear during the evolution of the disease and could represent a manifestation of progression to blastoid variant. These cases are usually associated with a median survival of only 3 months [26].

The patients with an indolent leukemic/splenic MCL present with an indolent disease and no B symptoms. The clinical exam confirms the presence of a splenomegaly that may be massive and no lymphadenopathy. This small proportion of patients has longer survival, even without the need of any treatment.

4 Diagnosis

The diagnosis of MCL is established according to the criteria of the WHO classification of hematological neoplasms [1] based on a nodal biopsy. In the case of indolent leukemic/splenic MCL subtype, diagnosis is based on the immunophenotype of the peripheral blood B cells and bone marrow biopsy. Besides the classical immunophenotype (CD5+/CD19+/CD20+/CD22+ and CD10−/CD23−/CD200−), the detection of the pathognomonic cyclin D1 overexpression (immunohistochemistry) or the chromosomal translocation t(11;14) by fluorescent in situ hybridization is crucial, since histomorphological phenotypes may differ significantly. In addition, rare cases of cyclin D1-negative variant of MCL have been recognized, characterized by a similar gene expression profile and numerous secondary genomic alterations as classical MCL. SOX11, a transcription factor expressed in 90 % of MCL, might be helpful to identify the cyclin D1-negative variants.

Moreover, both the cell proliferation gene expression pattern and the Ki-67 proliferative index staining represent powerful prognostic indicators of long-term outcome.

The indolent leukemic/splenic MCLs also exhibit the chromosomal translocation t(11;14) and the overexpression of CCD1. They predominantly display hypermutated immunoglobulin genes, non-complex karyotypes, and a peculiar gene expression profile.

5 Prognostic Parameters

The different therapeutic approaches do not consider the high heterogeneity in the evolution of the disease in MCL patients. The increasing number of therapeutic options is opening new perspectives for patients but the evaluation of these approaches will require a correct stratification of the patients according to the specific biological risk of their disease. Recently, a specific MCL prognostic index (MIPI, Mantle Cell Lymphoma International Prognostic Index) based on four

independent prognostic factors [age, Eastern Cooperative Oncology Group (ECOG) performance score, lactate dehydrogenase (LDH), and leukocyte count] has shown the capacity to clearly separate MCL patients into three groups with significantly different prognoses [27].

As described in the chapter describing the physiopathology of MCL, the proliferation of the tumor evaluated either as the mitotic index or cells expressing the proliferation-associated antigen Ki-67 is the best predictor of survival in MCL patients and has an independent prognostic value from the MIPI [28]. The analysis of gene expression profiling in MCL has identified a proliferation signature based on the expression of 20 genes able to clearly discriminate patients with different median survival, confirming that increased proliferation was the best predictor of poor survival [29]. New markers independent of the proliferation have been recently reported to influence the behavior of the disease or the response to the current treatment. Thus the concomitant inactivation of the two regulatory pathways, INK4a/CDK4 and ARF/p53 in MCL, was associated with a poor survival that was independent of Ki-67 proliferation index [30].

6 Treatment

In countries where treatment is available, the initial therapeutic decision for a patient with MCL is dictated by the age and, more importantly, the fitness of the patients (Fig. 2). For years the standard treatment was the classical CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone) for fit patients or chlorambucil for frail patients. The complete remission rate was 20–50 % and the median OS of around 3 years. The intensive leukemic regimen hyper-CVAD (a dose-intense, hyperfractionated cyclophosphamide in a CHOP-like combination plus high-dose methotrexate and cytarabine) improved the results of CHOP in non-randomized studies in younger patients [31]. Fludarabine-containing regimens and other polychemotherapy combinations were also used with no substantial modifications on the outcome of the patients. More recently, the strategies for the management of MCL patients have changed due to the introduction of immunotherapy and new drugs that are more targeted to molecular mechanisms of the disease. The combination of chemotherapy regimens such as CHOP, hyper-CVAD, or FCM (fludarabine, cyclophosphamide, mitoxantrone) with rituximab, a chimeric monoclonal anti-CD20 antibody with limited efficacy as a single agent, has been shown to produce impressive overall response rates of up to 80–95 % and CR rates of up to 30–87 % in previously untreated patients [32–34].

These progressive therapeutic improvements are now the basis of the MCL treatment in first line. For the fit patients eligible for high-dose therapy and autologous stem cell transplantation (HDT/ASCT), the treatment of choice involves a cytarabine-based regimen (R-DHAP/X/C (rituximab, dexamethasone, high-dose aracytine + cisplatin, or oxaliplatin or carboplatin) or hyper-CVAD), which is consolidated with a high-dose therapy associated with an autologous transplant. This strategy produces

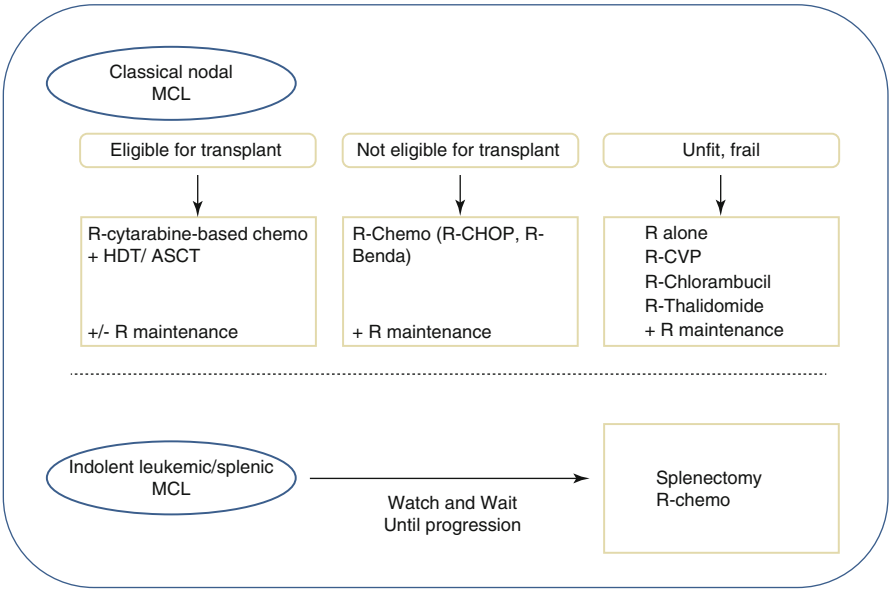

Fig. 2 Treatment strategies in MCL. The initial therapeutic decision for a patient with MCL is dictated by the age and, more importantly, the fitness of the patients. For the fit patients eligible for high-dose therapy and autologous stem cell transplantation (HDT/ASCT), the treatment of choice involves a cytarabine-based regimen (R-DHAP/X/C (rituximab, dexamethasone, high-dose aracytine + cisplatin, or oxaliplatin or carboplatin) or hyper-CVAD), which is consolidated with a high-dose therapy associated with an autologous transplant. Rituximab in maintenance has been recently proved to increase PFS. For patients in whom an intensive approach to management is not feasible, several possibilities of immunochemotherapy may be proposed to the patients such as R-CHOP and R-bendamustine. In this population, there is a clear benefit of rituximab as maintenance after R-CHOP. For frail and unfit patients, a number of less intensive therapies are available, including rituximab alone as well as CVP, cladribine, or thalidomide, usually in combination with rituximab. For patients with indolent leukemic/splenic MCL, watch and wait should be observed until progression. At time of treatment decision, several options may be proposed such as splenectomy and R-chemotherapy. *HDT/ASCT* high-dose therapy and autologous stem cell transplantation

impressive results with a CR/CRu rate before transplant at 77 % and after transplant 92 % (Cheson 1999 criteria) [35], further improved by a rituximab maintenance after transplant with a 2y-EFS of 93.2 % (95 % CI, 86.9–96.6) in the rituximab arm versus 81.5 % (95 % CI, 72.7–87.7) in the WW arm (HR = 2.1) [36]

For patients in whom an intensive approach to management is not feasible, several possibilities of immunochemotherapy may be proposed. The most commonly used are R-CHOP [33], R-fludarabine and cyclophosphamide (FC) [37], and R-bendamustine [38]. A large randomized study recently demonstrated a survival benefit for the use of R-CHOP over rituximab and FC (R-FC) in older patients with MCL [39]. This study also demonstrated the clear benefit of rituximab as maintenance after R-CHOP, where it doubled remission duration in responding patients. The use of the R-CHOP/R-cyclophosphamide, vincristine, and prednisolone (CVP) regimens in comparison with R-bendamustine (R-B) has been assessed across a range of lymphomas including MCL in two randomized trials [38, 40]. For the

MCL cohorts, the R-B combination demonstrated a superior PFS [38] and response rate [40] but no difference in OS. Neither trial involved rituximab maintenance; because the addition of this significantly improves the outcome following R-CHOP and there are currently no available data on maintenance after R-B, it is not clear which of these two regimens is superior. Recently it has been shown in a randomized trial that the association of bortezomib to R-CHOP improves the response rate and the PFS compared to R-CHOP alone [41].

For the more frail patients where it is not possible to use either of these approaches, a number of less intensive therapies are available, including rituximab alone as well as CVP, chlorambucil, cladribine, or thalidomide, usually in combination with rituximab [25].

7 New Therapies

The growing insights into the molecular biology of MCL lead to the systematic exploration of targeted approaches. Interestingly, in contrary to the short-term remissions after chemotherapy, various molecular approaches achieve the highest response rates in this distinct lymphoma subtype. Thus, proteasome inhibitors (bortezomib), immune modulatory drugs (lenalidomide), or mTOR inhibitors (temsirolimus) have been meanwhile registered in relapsed MCL [25] for review. Inhibitors targeting BCR signaling pathway are highly active in mantle cell lymphoma. In an international phase II trial, the Bruton's kinase (BTK) inhibitor ibrutinib achieved an overall response of 68 % (CR 21 %) [20]. Results of phase III trials are eagerly awaited comparing ibrutinib vs. temsirolimus in relapsed disease and assessing BR schedule +/− ibrutinib in first line. Another inhibitor of the BCR signal cascade, the delta-specific PI3K inhibitor (idelalisib) also achieved a promising ORR of 32 % in relapsed MCL, but duration of remission seems to be limited [42]. Two cell cycle targeted drugs, flavopiridol and PD0332991 (direct inhibitor of cyclin-dependent kinase 4 and 6), showed also activity in relapsed MCL alone and in combination with fludarabine, rituximab, or bortezomib. Finally, promising results have been recently reported for an oral second-generation BCL-2-specific MH3-mimetic ABT-199.

8 Conclusion

For many years, MCL was considered as a poor-prognosis disease. Things are changing a lot since 10 years, thanks to the biology that allowed us to better understand this disease and lead us to the systematic exploration of targeted approaches. A tailored therapy concept, based on individual risk profile, should be now the basis of treatment of patients with MCL. However this is the concept in countries that have the chance to have a developed healthcare system. How this will impact treatment in other countries is a real challenge.

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Indolent Lymphomas: Follicular Lymphoma, HVC-Associated Marginal Zone B-Cell Lymphoma, and Waldenstrom's Macroglobulinemia

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1 Indolent Lymphomas

Among indolent, low-grade B-cell lymphomas, the REAL classification in 1994 [1], as well as the subsequent WHO classifications in 2001 [2] and 2008 [3], comprised follicular lymphoma (FL), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL) (of MALT, nodal, and splenic type), and lymphoplasmacytic lymphoma (LPL)/Waldenstrom's macroglobulinemia (WM).

2 Follicular Lymphoma

FL is the most frequent low-grade lymphoma in western countries, accounting for 25 % of all cases [4]. FL is generally considered a long-lasting indolent disease, but survival duration is quite heterogeneous. Among possible options, patients may be observed without any specific treatment until disease progression or may receive immunotherapy (rituximab alone) or immunochemotherapy (combination of rituximab and cytotoxic chemotherapy). Cooperative groups such as the *Groupe d'Etude*

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des Lymphomes Folliculaires (GELF) from France [5] and the *British National Lymphoma Investigation Group* (BNLI) proposed criteria for initiating treatment in FL patients.

Prognostic factors in FL reflect different aspects of the disease; some are directly related to the lymphoma biology such as histological features (pattern, grading) or genetic alterations and tumor microenvironment. Other factors are connected with the tumor spread (stage, tumor burden, bone marrow involvement, symptoms) or indirect laboratory parameters (LDH, anemia, β_2-microglobulin). Other factors are related to disease modifications after treatment (clinical response, minimal residual disease). $^{[18F]}$fluorodeoxyglucose–positron emission tomography (FDG-PET) is a powerful functional imaging tool in staging and response assessment in Hodgkin lymphoma and in diffuse large B-cell lymphoma. Recent data from a large multicenter clinical trial in advanced FL patients (PRIMA trial) showed that FDG-PET status at the end of immunochemotherapy is strongly predictive of outcome [6].

The Follicular Lymphoma International Prognostic Index (FLIPI) was proposed from the retrospective analysis of more than 4,000 patients with FL patients treated between 1985 and 1992 [7]. After a multivariate analysis, 5 parameters resulted predictive: age >60 years, serum LDH level > upper limit of normal (UNL), number of nodal areas >4, and hemoglobin level <12 g/dl. Three risk groups (low, intermediate, and high) were distinguished. In 2004, an international consortium established the FLIPI2 composed by 5 prognostic parameters: longest diameter of the largest tumor mass >6 cm, serum β_2-microglobulin level > UNL, bone marrow involvement, hemoglobin ≤12 g/L, and age >60 years [8].

It has been clearly shown that a significant improvement in overall survival of FL patients occurred in the last 15 years when compared to historical controls [9]. This improvement is mainly related to the introduction of anti-CD20 monoclonal antibodies.

Nowadays, for patients with limited disease stages (I-II), radiotherapy is the treatment of choice; on the other side, for patients with advanced stages with a high tumor burden, immunochemotherapy followed by 2 years of rituximab maintenance is widely accepted as standard therapy. In the near future, novel therapeutic options will arrive from new antibodies, from immunomodulatory drugs (lenalidomide), and from new agents targeting oncogenic pathways such as B-cell receptor signaling pathways or inhibition of bcl 2.

3 HVC-Associated Marginal Zone B-Cell Lymphomas

Several clinical-pathological studies investigated the association of HCV infection with specific indolent NHL subtypes. Within indolent NHL subtypes reported in the WHO classification [3], the association with HCV infection has been best characterized in MZLs. Many infectious agents have been involved in the pathogenesis of specific types of MZLs [10]: *Helicobacter pylori* for gastric MALT lymphoma, *Borrelia burgdorferi* for MALT lymphoma of the skin, *Chlamydophila psittaci* for

MALT lymphoma of the orbit, and *Campylobacter jejuni* for immunoproliferative small intestine disease. In these disorders, the eradication of the antigen after antimicrobial therapy may lead to a regression of the underlying lymphoma.

Accordingly to this scenario, also chronic stimulation by HCV may play a role in development of a subgroup of MZL cases; however, the role of HCV in marginal zone lymphomagenesis can reflect geographic difference considering the relatively high seroprevalence in some series of MZL [11] and the rarity of HCV-positive cases in others [12].

Splenic marginal zone lymphoma (SMZL) is an indolent lymphoma, which accounts for less than 2 % of all NHL [13]. SMZL is clinically characterized by splenic, peripheral blood, and bone marrow involvement with small lymphocytes that occasionally show cytoplasmic villi (the so-called villous lymphocytes). In a large Italian series, HCV serology was positive in 19 % and cryoglobulins were detected in 10 % [14]. In 2005, French authors described a form of SMZL associated with mixed cryoglobulinemia (MC) and HCV infection [15]: all 18 patients had MC that was symptomatic in 13.

Primary nodal marginal zone lymphoma (NMZL) is comprised in the 2008 edition of WHO lymphoma classification as a distinct clinical-pathologic subtype characterized by exclusive primary lymph node localization in the absence of extranodal site of involvement. This rare form of indolent NHL has been linked to the HCV infection with preferential use of specific immunoglobulin gene segments [16]. In a relatively large Italian series, HCV serology was positive in 24 % and HCV-RNA was detectable in half of NMZL patients studied [17].

Regarding extranodal MALT lymphomas, in an Italian multicenter study, three specific MALT lymphoma sites showed an elevated prevalence of HCV infection: the salivary glands, skin, and orbit [18]. The association of salivary gland lymphoma and HCV infection has been clearly demonstrated [19]. Interestingly, a study on B-cell lymphoma in patients with Sjögren's syndrome and HCV infection reported an elevated occurrence of parotid involvement and a high proportion of MALT lymphomas with primary extranodal involvement (the exocrine glands, stomach, and liver) [20]. A series of 12 HCV-positive subjects showing subcutaneous nodules resembling "lipomas" with a typical histology of extranodal MZL of MALT have been recently reported by our group [21]. From a clinical point of view, the clinical benign appearance of these "lipoma-like" lesions and their indolent clinical behavior may result into a delay of correct diagnosis.

The aim of treatment for patients with HCV-related chronic hepatitis is to prevent disease complications, through the HCV eradication, defined as sustained virologic response (SVR), i.e., undetectable HCV-RNA by a sensitive polymerase chain reaction (PCR)-based assay 24 weeks after discontinuation of therapy.

In 2002, Hermine et al. reported the outcome of 9 patients with splenic lymphoma with villous lymphocytes and HCV infection treated with interferon (IFN). Complete response (CR) and HCV-RNA clearance were obtained in 7 out of 9 patients. Two patients who did not respond were subsequently treated with IFN plus ribavirin (RBV) and obtained the HCV-RNA negativity as well as lymphoma regression. This anti-lymphoma activity was absent in HCV-negative patients with

SMZL. A subsequent report from the same group expanded these results in 18 patients with chronic HCV infection, mixed cryoglobulinemia (MC), and splenic lymphoma with villous lymphocytes [15]. All patients were treated with IFN (plus ribavirin in 10) and 14 patients obtained a CR after clearance of HCV-RNA.

Recently, the Fondazione Italiana Linfomi (FIL) performed a cohort study of 704 consecutive HCV-positive patients with indolent lymphoma diagnosed and treated from 1993 to 2009 in 39 centers of the Fondazione Italiana Linfomi; 134 patients were managed with interferon-based antiviral treatment (AT) for lymphoma control. In multivariate analysis, the use of AT during the patients' life had positive impact on OS. Forty-four of the 100 patients treated with first-line AT achieved a CR and 33 a partial response (PR). HCV-RNA clearance was achieved in 80 patients and was related to lymphoma response. On this basis, AT can be considered an option for patients with indolent lymphomas who do not need immediate cytoreductive treatment [22].

Moreover, after nearly 25 years of improvements of IFN-based therapies, huge research and development efforts have produced new antiviral drugs, including direct-acting antiviral (DAA) such as sofosbuvir. The financial sustainability of these new drugs and activity in indolent lymphomas are to be clarified in the future.

4 Waldenstrom's Macroglobulinemia

Waldenstrom's macroglobulinemia (WM) is a rare indolent B-cell lymphoproliferative disorder, characterized by the presence of a serum IgM monoclonal protein associated with bone marrow infiltration by lymphoplasmacytic lymphoma [23].

WM is a disease of the elderly, with a median age at diagnosis of 65–70 years, and a slight male predominance.

A familial clustering of WM and other lymphoproliferative disorders has been demonstrated in about 20 % of cases, suggesting a role of genetic factors in the pathogenesis of this disease [24].

In some cases, WM is preceded by an IgM-MGUS. The risk of progression of IgM-MGUS to WM is approximately 1.5–2 % per year, the size of the monoclonal protein being the most important risk factor for progression [25].

In recent years, important advances have been made in the understanding of the biology of WM. An oncogenic somatic mutation in the MYD88 gene, leading to change of an amino acid (leucine to proline) at position 265, has been identified in WM patients by whole genome sequencing of paired tumor and germline tissue [26] and subsequently confirmed with Sanger sequencing or allele-specific PCR in more than 90 % of patients with WM [27]. The MYD88 (L265P) mutation is only rarely found in patients with other lymphoproliferative disorders and is detectable in about 50 % of patients with IgM-MGUS.

The clinical presentation of WM is highly heterogeneous, including patients who are asymptomatic. When present, symptoms of WM can be grouped into two categories: (1) symptoms attributable to tumor infiltration, including peripheral

Table 1 Diagnostic workup in patients with suspected WM

Complete blood counts
Serum beta2-microglobulin
Serum albumin
Serum protein electrophoresis
Quantification of IgG, IgA, and IgM
Serum and urine immunofixation
Bone marrow biopsy and immunophenotypic studies
CT scan of the thorax, abdomen, and pelvis
Only when clinically indicated:
Serum viscosity
Fundoscopy
Coombs test
Cryoglobulins
Fat biopsy for amyloid
Anti-MAG, antiganglioside M1, and anti-sulfatide antibodies

cytopenias secondary to bone marrow infiltration; lymphadenopathies, splenomegaly, or, less frequently, infiltration of extranodal sites (bone, kidney, central nervous system); and constitutional symptoms; and (2) symptoms attributable to the serum IgM monoclonal protein, which include (a) symptoms due to the autoimmune properties of the IgM monoclonal protein, e.g., peripheral neuropathy, cold agglutinin anemia, immune thrombocytopenia, acquired von Willebrand disease; (b) symptoms due to the tissue deposition of the monoclonal protein, e.g., AL amyloidosis; and (c) symptoms due to the circulating IgM monoclonal protein, i.e., hyperviscosity syndrome and cryoglobulinemia.

The diagnosis of WM is based on histological demonstration of bone marrow infiltration by lymphoplasmacytic lymphoma. The bone marrow biopsy examination demonstrates an intertrabecular infiltrate constituted by small lymphocytes, lymphoplasmacytoid cells, and plasma cells; a mast cell infiltration may also be present but is not required for diagnosis. The typical phenotypic profile of the lymphocytic infiltrate is CD19+, CD20+, CD22+, sIgM+, CD79+, CD5-, CD10-, and CD23-. The diagnosis of WM requires the presence of a serum IgM monoclonal protein. According to the diagnostic criteria established during the Second International Workshop on WM held in Athens in 2002 [23], there is not a threshold for the serum monoclonal protein. Therefore, the differential diagnosis between WM and IgM-MGUS relies on bone marrow findings, rather than on the concentration of the monoclonal protein. Table 1 shows the diagnostic workup recommended in patients with suspected WM.

WM is still an incurable disease, but the prognosis of the disease has improved over time with a median overall survival, which now exceeds 7 years [28]. Treatment of patients with asymptomatic WM is currently not recommended. Patients who need treatment are those with symptoms attributable either to tumor infiltration or to the IgM monoclonal protein. The size of the serum IgM monoclonal protein is not, per se, an indication to treatment [29].

Treatment recommendations from the VII International Workshop on WM have been recently published [30]. For the majority of patients, the most appropriate first-line treatment of WM is an immunochemotherapy including anti-CD20 monoclonal antibody rituximab. Since there are not randomized studies comparing different immunochemotherapeutic regimens, the choice of first-line therapy mainly depends on patient's individual characteristics (e.g., age, performance status, comorbidities, eligibility to transplant) and disease' presentation (e.g., peripheral cytopenias, hyperviscosity, bulky organomegalies, peripheral neuropathy). The combination of rituximab with cyclophosphamide and dexamethasone (DRC) is effective and well tolerated, either in young patients eligible to transplant or in elderly patients. A suitable alternative to this regimen is the association of rituximab and bendamustine, which seems particularly indicated for those patients who present with bulky disease or hyperviscosity, where a rapid disease control is needed. In these patients, also the combination of the proteasome inhibitor Bortezomib with rituximab is an appropriate choice, since it is associated with a rapid response. The combination of fludarabine, cyclophosphamide, and rituximab is no more considered a first-choice option due to its high short-term and late toxicity. For elderly patients not eligible to intravenous treatment, oral fludarabine or oral chlorambucil should be considered, the first agent being more effective, but associated with a higher incidence of neutropenia and infections. For patients with relapsed disease, a retreatment with the same regimen is reasonable if the duration of response was at least 12 months. Autologous stem cell transplant should be considered for patients with relapsed chemosensitive WM.

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Myeloproliferative Neoplasms

Zeba Aziz

1 Introduction

MPN are an uncommon group of neoplasms with clonal proliferation of one or more mature hematopoietic cells of the myeloid lineage. The prevalence of polycythemia vera (PV)/essential thrombocytosis (ET) in the USA ranges from 39 to 57 cases and myelofibrosis (MF) 1.7–2.4 per 100,000 cases. Unfortunately no data is available from developing countries. PV tends to affect males more, while ET affects more females. Median age is in the sixth decade of life with one third of patients presenting in the fifth decade [1].

The revised WHO 2008 classification of MPNs provides a framework to incorporate these neoplasms with correlation of clinical, genetic, and morphologic findings for diagnosis and classification. MPNs are broadly classified based on chromosomal abnormalities [2].

See Table 1.

All MPNs have one or more shared features:

1. Overproduction of one or more blood cell lines, i.e., platelets, red blood cells, and mature myeloid cells.
2. Hypercellular/fibrotic marrow
3. Cytogenetic abnormalities.
4. Extramedullary hematopoiesis
5. Transformation to acute leukemia
6. Overlapping clinical features

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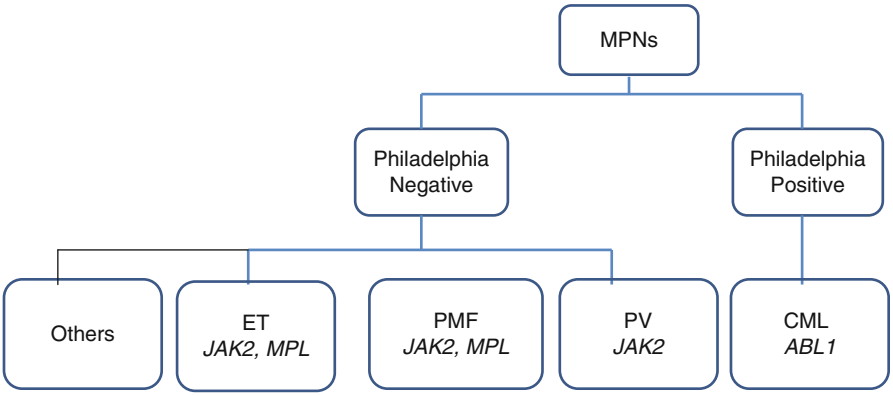
Table 1 Classic myeloproliferative neoplasms (MPN) according to the 2008 WHO classification *ET* **essential thrombocythemia,** *PMF* **primary myelofibrosis,** *PV* **polycythemia vera,** *CML* **chronic myelogenous leukemia. Other = chronic neutrophilic leukemia; chronic eosoniphilic leukemia not other categorized; mastocytosis; and MPNs, unclassified**



2 Mutations in Philadelphia-Negative MPNs (PV, ET, MF)

JAK2, MPL, and CALR are the three major mutations in MPNs occurring in 99 % of patients with PV and 85 % in ET and MF. JAK-STAT pathway is activated in all MPNs regardless of the founding driver mutations [3]. JAK2 belongs to non-receptor tyrosine kinase family and plays a fundamental role in hematopoiesis. Normal JAK2 activation requires ligand binding for signal transduction through the STATS transcriptional pathway. In case of JAK2 mutation ligand binding is not required, continuous down stream signaling occurs. The aberrant activation of the signal transduction pathways results in increased proliferation and inhibition of the apoptotic pathways of the JAK2 mutant myeloid stem cells together with hypersensitivity to several cytokines including erythropoietin, GM-CSF, IL-3, and insulin-like growth factor-1 (IGF-1).

Overall prevalence of JAK2V617F mutations in MPNs is 75 %, with 95 % mutations occurring in PV [4]. Phenotypic differentiation occurs due to differences in host genetic modifications, allele burden, gender, loss of heterozygosity, and qualitative and quantitative differences in downstream signaling pathways. The clones of JAK2V617F-mutated stem cells remain stable over prolonged periods accounting for the indolent nature and clinical stability of PV and ET. MPL10 exon mutations located on the thrombopoietin receptor is present in 5 % ET and PMF.

Somatic mutation of the CALR gene encoding calretinin occurs in ET/MF patients with unmutated JAK2/MPL. Normal functions of CALR include normal folding of newly synthesized glycoproteins, calcium hemostasis, immunogenic cell death, proliferation, and apoptosis. Diverse epigenetic mutations involving other metabolic pathways are acquired during the course of disease, which include DNA methylation genes TET2, DNMT3A, and IDH1/2 and chromatin structure genes EZH2 and ASXLI for evolution of ET/PV into AML [5].

There is NO indication of monitoring bone marrow (BM) response or determining sequential assessment of JAK2V617F allele burden. BM aspirate and biopsy are indicated only if disease progression and transformation to MF/AML are suspected.

Goals of Therapy for PV/ET

1. To avoid occurrence/recurrence of thrombosis or bleeding
2. To minimize/delay disease progression to post ET-MF or acute leukemia
3. To control systemic symptoms
4. To treat complications of hemorrhage/thrombosis
5. To manage special risk situations, e.g., Pregnancy and surgery

3 Polycythemia Vera (PV)

PV is a chronic disorder with increased blood viscosity and sluggish blood flow due to increased red cell production. Median survival is 14.1 years, risk of late progression to PV-MF is 15–20 %, and development to acute leukemia is 3–5 % [5]. The prognosis of patients with PV-acute leukemia is dismal with a median survival of 2–3 months [6].

In peripheral blood there is an increase in all three-cell lines. Thrombocytosis may contribute to bleeding and thrombosis. Platelet aggregation abnormalities are common but do not correlate with bleeding and thrombotic activities.

The bone marrow shows panmyelosis, with increase in the erythroid compartment and to a lesser extent of the myeloid and the megakaryocyte series. The red cell mass is increased and it is extremely sensitive to cytokines such as erythropoietin, IL-3, GM-CSF, and steel factor.

3.1 Criteria for Diagnosis of PV

Proposed WHO diagnostic criteria for PV for 2014 are listed in Tables 2 [7]. These include 3 major and 1 minor criterion.

Secondary polycythemia should be ruled out in patients with isolated erythrocytosis. These include smoking, pulmonary or cardiac problems, overweight with nocturnal dyspnea, hepatic or renal tumors, or hemoglobinopathies.

3.2 PV Signs and Symptoms

In developed countries, patients are frequently diagnosed during a routine peripheral blood smear or for investigations of vague symptoms: unexplained weakness and pruritus (after taking a shower with warm water and physical exercise and at bed time or when changing clothes). *Patients in developing countries* often present

Table 2 2014 proposed revision for World Health Organization (WHO) diagnostic criteria for BCR-ABL negative myeloproliferative neoplasms

Polycythemia vera (PV)[a]	Essential thrombocythemia (ET)[b]	Primary myelofibrosis (PMF)[c]
Major criteria	*Major criteria*	*Major criteria*
1. Hemoglobin > 16.5 g/dl (men) > 16 g/dl (women) or hematrocit >49 % (men) > 48 % (women)	Platelet count ≥450 10^9/l	Megakaryocyte proliferation and atypia·
2. BM trilineage myeloproliferation with pleomorphic megakaryocytes	Megakaryocyte proliferation with large and mature morphology	Accompanied by either reticuline and/or collagen
3. Presence of JAK2 mutations	Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm	Fibrosis
	Presence of JAK2, CALR, or MPL mutation	Not meeting WHO criteria for CML, PV, ET, MDS, or other myeloid neoplasms
	Megakaryocyte proliferation with large and mature morphology	Presence of JAK2, CALR, or MPL mutation
Minor criteria	*Minor Criteria*	*Minor criteria*
1. Subnormal serum erythropoietin level	Presence of a clonal marker (e.g., abnormal karyotype) or absence of evidence for reactive thrombocytosis	Presence of a clonal markers (e.g., abnormal karyotype) or absence of evidence for reactive bone marrow fibrosis
		Presence of anemia or palpable splenomegaly
		Presence of leukoerythroblastosis, or increased lactate dehydrogenase[f]
Requirement for Diagnosis	*Requirement for Diagnosis*	*Requirement for Diagnosis*
Meeting either all 3 major criteria or the first 2 major criteria and 1 minor criterion	Meeting all 4 major criteria or first 3 major criteria and 1 minor criterion	Meeting all 3 majors criteria or the first 2 major criteria and all 3 minor criteria

Table 3 International Prognostic Scoring System for myelofibrosis (IPSS)

Variables	IPSS	DIPSS	DIPSS-plus
Age > 65 years	+	+	+
Constitutional symptoms	+	+	+
Hemoglobin <100 g/L	+	+	+
Leukocyte count > 25 × 10^9/L	+	+	+
Circulating blasts >1	+	+	+
Platelet count <100 × 10^9/L			+
Red blood cell transfusion needed			+

DIPSS Dynamic IPSS, *IPSS* International Prognostic Scoring System for myelofibrosis

with symptoms of hyperviscosity. These include headaches, blurring of vision, plethora, arthralgia, abdominal discomfort, excess sweating erythromelalgia, and cyanosis. Ulceration and gangrene occur due to thrombosis in small blood vessels. Gout, renal stones, and hyperuricemia are due to high red cell turnover. Mild gingival or GI bleeding, stomach ulcers, epistaxis, and bruising may occur occasionally. Splenomegaly is present in 30–40 % patients. Financial constraints, lack of health insurances, and access to medical care are major limitations face by patients in our part of the world from presenting early in the course of disease.

Thrombotic events: The frequency of venous and arterial venous thrombotic events is directly proportional to the rise in hematocrit. Cerebral blood flow also reduces when hematocrit goes above 53 %. Major thrombotic events in PV range from 34 to 39 %; hemorrhagic events are somewhat less common. Both contribute to increased morbidity and mortality in the patients. More severe thrombotic events include myocardial infarction, stroke, and TIA. Rare thrombotic events include splanchnic vein thrombosis (SVC): splenic, hepatic, portal, and mesenteric vein thrombosis and Budd-Chiari syndrome (BCS) [8]. CT/US scans help in determining asymptomatic splanchnic vein thrombosis.

3.3 Treatment for PV

The cornerstone for treatment for PV is to normalize blood counts and to maintain a hematocrit of <45 % in order to decrease blood viscosity and reduce thrombotic episodes. Available therapies do not prevent disease progression to PV-MF or acute leukemia. Patients are stratified according to the risk of thrombosis and not based on survival or disease progression. Prognostic model for PV based on (1) age, (2) prior venous thrombosis is used to stratify patients into low risk (age < 60 years) and high risk (age >60 years) and/or thrombosis [4].

Correction of cardiovascular risk factors: Lifestyle risk factors need to be modified in all patients, so they are not contributory to the already increased risk of vascular complications in PV. These include weight reduction, cessation of smoking, physical exercise, normalizing lipid profile, and avoiding oral contraceptives and situations which increase risk of thrombosis.

Antiplatelet therapy: Low-dose aspirin is recommended to all patients except those with acquired von Willebrand disease, extremely high platelet counts, and peptic ulcer disease. The ECLAP trial randomized patients with PV to low-dose aspirin 100 mg/daily versus placebo. There was a significant reduction in nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular complications (RR = 0.40, CI 0.18-0.91; p = 0.03) [4, 9].

Low-risk patients: Low-risk patients are treated with phlebotomy and aspirin alone to maintain a hematocrit of <45 %. Rates of cardiovascular deaths and major thrombosis [4, 9] are significantly reduced. Systemic symptoms like pruritus and those due to enlarged spleen cannot be controlled by phlebotomy alone. In younger patients phlebotomy is tolerated better and 350–400 mL of blood can be removed safely. Smaller volumes of blood should be removed in older patients.

High-risk patients: Cytoreductive therapy is indicated in patients who present initially with high-risk disease, symptomatic splenomegaly, extremely high platelet counts, and leukocytosis of >20,000 × 10^9/L or those who progress from low-risk to high-risk group.

Therapeutic options for cytoreduction in high-risk patients include HU, interferon alpha, anagrelide, alkylating agents, busulfan, and JAK2 inhibitors which have recently been approved in the USA [10].

Hydroxyurea (HU) is a non-leukemogenic oral antimetabolite that inhibits DNA synthesis and repair. It is the initial treatment of choice for patients requiring cytoreductive therapy. It is cheap, is well tolerated, and effectively reduces elevated counts, spleen size, and thrombotic risks. Initial dose starts from 15 to 20 mg/kg until response to therapy followed by maintenance [11]. Side effects of HU include myelosuppression, macrocytosis, leg and mouth ulcers, raised creatinine, and skin and nail changes.

Interferon/PEG-IFN although not approved are used in patients intolerant or resistant to HU, in patients who are pregnant, and in patients with intractable pruritus. Complete hematologic responses occur in approximately 76 % patients with PV. The mutated JAK2 allele burden is also decreased. In 15–20 % patients IFNs cause complete disappearance of the mutant clone with durable complete remissions [12]. Serious adverse effects include increased risk of depression, hypothyroidism, and retinitis and exacerbation of autoimmune disorders, neuritis, and fatigue.

Based on the RESPONSE trial JAK2 inhibitor ruxolitinib is currently used in patients intolerant/resistant to HU [13]. Precise mechanism of action is unknown, but there is inhibition of JAK2 mutant clones and downregulation of cytokines, but no complete eradication of the malignant clones. Response is not dependent on JAK2 mutational status. Complete hematological response was seen in 24% of patients, symptoms improvement occured in 50% of the patients, 35% of patients had reduction in spleen volume. Thromboembolic events occured lower frequency compared tp patients on hydroxyurea (2.8 events per 100 patients per year).Fewer patients required phlebotomies. Overall Ruxolitinib is well tolerated.

3.3.1 Special Situations

Thrombosis: For splanchnic vein thrombosis, low-molecular-weight heparin (LMWH) followed by lifelong anticoagulation is also indicated [14].

Surgery: Thrombosis or hemorrhage occurs in approximately 8 % of patients with PV/ET after surgery [15]. Prophylactic LMWH and normalization of hematocrit are important for prevention.

Pregnancy: It is uncommon but requires special care. In low-risk patients with no history of abortions, aspirin is given during pregnancy along with 6 weeks of LMWH after delivery. Hematocrit is maintained at < 40 %. For women with pregnancy complications and/or thrombosis, LMWH is used throughout pregnancy and control of hematocrit and thrombocytosis is done through IFN [16].

Pruritus: It may become very debilitating; antihistamines are usually ineffective. IFN, ruxolitinib, and in occasional cases UV light and psoralen are effective.

4 Essential Thrombocythemia (ET)

There is sustained proliferation of megakaryocyte progenitors and increased platelet production, due to extreme susceptibility to cytokines including IL-6, IL-3, and thrombopoietin [17]. Persistent platelets counts $>450\times10^9$/L is the threshold for diagnosis of possible ET. Higher platelet counts are associated with hemorrhagic and thrombotic complications due to acquired von Willebrand disease with abnormalities in platelet aggregation studies [18]. Lowering of platelets counts is associated with correction of defects and cessation of bleeding disorders.

The JAK2V617F occurs in approximately 50–60 % patients with ET. CALR mutation is found in 60–88 % patients with ET with negative JAK2 mutation. CALR-mutated patients with ET are predominantly males, have younger age, have higher platelet count, and have lower WBC counts and hemoglobin with a lower incidence of thrombosis as compared to JAK2-mutated patients [19].

4.1 Diagnosis

The 2014 WHO proposed *major diagnostic criteria* for ET are listed in Table 1

Causes for reactive thrombocytosis have to be excluded, which include iron deficiency anemia, inflammation, infections, malignancies, splenectomy, and cryoglobulinemia. Hemorrhagic or bleeding disorders have to be ruled out.

4.2 Signs and Symptoms

Asymptomatic patients may present with persistently elevated platelet counts. In symptomatic patients clinical *s*igns and symptoms are similar to those with PV. Hemorrhagic or thrombotic episodes occur in both major blood vessels and microvasculature in 20–80 % of patients [17]. Thrombotic episodes occur more frequently in older people due to coexistence of microvascular disease. Pregnancy is associated with a higher incidence of spontaneous abortions due to placental thrombosis.

4.3 Treatment Options

ET is stratified into 3 risk groups.

1. Low-risk group includes asymptomatic patients younger than 60 years with platelet counts of $<1{,}500\times10^9$/L with no history of thrombosis, bleeding, or microvascular disease.

2. High-risk group includes patients older than 60 years with history of thrombosis/bleeding or microvascular disease.
3. Intermediate group includes all patients who cannot be placed in the above risk categories.

Cardiovascular disease and lifestyle modification should be aggressively managed similar to PV.

In *low-risk patients* incidence of thrombosis is similar to that observed in a healthy population [20].

In *high-risk patients* or patients who move from low-risk to high-risk group:

1. Hydroxyurea is the treatment of choice as it lowers thrombotic complications.
2. Patients intolerant/resistant to HU, anagrelide, or interferon are recommended. Side effects of anagrelide include headaches, palpitations, and rarely nonischemic cardiomyopathy [21]. IFN is preferable in young childbearing females. Piprobroman, ^{32}P, and busulfan are sometimes used in patients with short life expectancy.
3. Low-dose aspirin daily for all patients especially with microvascular disease unless contraindicated.
4. Patients with life threatening bleeding/thrombosis may require platelet apheresis along with myelosuppressive therapy. For patients with platelet count $>1{,}500 \times 10^9$/L and acquired von Willebrand disease, withhold aspirin. These patients may require factor VIII concentrates and desmopressin if severe bleeding occurs. In high-risk patients who have to undergo surgery, platelet counts should be normalized prior to surgery.

Patients are monitored according ELN guidelines.

5 Myelofibrosis

Primary myelofibrosis is a rare disorder; post-PV/ET-MF may also occur in 10 % of patients with PV and <1 % from ET [2]. There is abnormal proliferation of megakaryocytes and deposition of fibrous connective in the BM, with abnormal trafficking of the mutant stem cells with production of cytokines PDGF, TGF-B, EGF, and basic fibroblastic growth factor. Extramedullary hematopoiesis occurs especially in the liver and spleen.

JAK2 mutations are found in 65 % of MF patients, CALR mutations occur in 74 % of unmutated JAK2 mutations. CALR-mutated patients with MF have a significant better overall survival compared to patients with JAK2 mutations independent of age and DIPSS-plus prognostic score [22].

WHO 2014 proposed diagnostic criteria for PMF which include 3 major and 3 minor criteria as they are listed in Table 2.

Table 3 shows the three prognostic scoring systems used in myelofibrosis. These includes *the International Prognosis Scoring System* (IPSS) [22] used at the time of

diagnosis includes age >65, leukocyte count $>25 \times 10^9$, hemoglobin < 8 g/dL, constitutional symptoms (weight loss, night sweats, fever >1 month), >1 % blasts in the peripheral blood. Each risk factor +1 worsens prognosis. Median survival time is 135 months in the low-risk category (no risk factor), 95 months (95 % CI 79–114) in the intermediate-1 category (one risk factor), 48 months (95 % CI 43–59) in the intermediate-2 category (two risk factors), and 27 months (95 % CI 23–31) in the high-risk category (three or more risk factors) [23]. *Dynamic* IPSS (DIPSS) also includes unfavorable karyotype (1–2 abnormalities) including +8, −7/7q⁻, inv3, i(17q), 12p-, and 11q23 rearrangements. It can be used at any time during the disease process (28, 29 blood therapy MPN) for prognostication [24].

Refinement of these criteria has been proposed by incorporating other risk factors which include thrombocytopenia, RBC transfusions, and unfavorable karyotypes to establish an updated DIPSS-plus algorithm. Abnormal mutations like JAK2 and CALR are being incorporated in the proposed WHO 2014 guidelines for MPN.

5.1 Signs and Symptoms

Most signs and symptoms are attributable to pancytopenia in MF, which occurs due to decreased hematopoiesis and splenic sequestration. Issues faced by patients include [25]:

1. Severe anemia: requiring frequent transfusions; there is poor increment in increase in hemoglobin because of splenomegaly. Patients may also have associated thrombocytopenia and neutropenia.
2. Marked hepatosplenomegaly: ineffective hematopoiesis accompanied by severe abdominal distension, discomfort, change in bowel habits, splenic infarcts, portal hypertension, ascites, variceal bleeding, cachexia, and decreased mobility and movement.
3. Non-hepatosplenic extramedullary hematopoiesis: may lead to cord compression, ascites, pulmonary hypertension, pleural effusion, skin tumors, and LN enlargement.
4. Thrombo-hemorrhagic complications.
5. On peripheral smear characteristic leukoerythroblastic picture.
6. BM aspirate is often “dry tap” with increased reticulin (trichrome or silver stains for collagen bluish-green).
7. Hypermetabolic symptoms: fever, weight loss, fatigue, cachexia, pruritus, night sweats, and joint pains.

Secondary causes of MF have to be ruled out: metastatic disease, lymphoma, infection, and autonomic disorders. These patients usually do not have splenic enlargement.

5.2 Management of MF

5.2.1 Anemia

Four agents used for treatment of anemia [25]. Treatment is usually started when hemoglobin is <10 g/dL. Response rates are around 20 %.

These include:

1. Corticosteroids: 0.5–1 mg/kg/d.
2. Androgen therapy: testosterone enanthate 400–600 mg/wk, oral fluoxymesterone 10 mg thrice a day, or danazol 600 mg.
3. Low-dose thalidomide 50 mg daily with prednisone 15–30 mg daily.
4. Revilmid is indicated in patients with del[5]9q31in MF. Improvement in anemia is seen in 22% patients, there was 33 % reduction in splenomegaly and 50 % improvement in thrombocytopenia.
5. Recombinant erythropoietin is also effective for treatment of anemia.
6. Iron chelation therapy for patients who require repeated transfusions.

5.2.2 Splenomegaly

1. Hydroxyurea is the preferred treatment option for symptomatic splenomegaly. Spleen size decreases in about 40 % patients. It also controls leukocytosis and thrombocytosis.
2. Busulphan 2–6 mg/day in patients refractory to HU; close monitoring of blood count is required.
3. Cladribine 5 mg/m^2/day for 5 days in a 2-h infusion can be given for 4–6 cycles.
4. Radiation: involved field radiation provides symptomatic relief for 3–6 months. 0.1–0.5Gy in 5–10 fractions is given. Unfortunately it is associated with a >10 % mortality rate due to cytopenias [25].
5. Indications for splenectomy include drug refractory splenomegaly (painful or severe cachexia) and symptomatic portal hypertension: Perioperative mortality is 5–10 %. Post-splenectomy complications occur in 50 % patients. These include surgical site bleeding, thrombosis, subphrenic abscess, hepatomegaly, extreme thrombocytosis, and leukocytosis with excess blasts. Cytoreduction and anticoagulation measures along with an expert surgical team are needed to prevent postoperative complications.

5.2.3 Ruxolitinib

Ruxolitinib, a JAK2 inhibitor, has recently been approved for treatment of PMF. The approval was based on the analysis of 2 COMFORT trials [26]. Significant symptom improvement, decrease in spleen size, and constitutional symptoms due to reversal of the catabolic pathways were noted. Weight gain was seen in 96 % and cholesterol level improved in 97 %. At 3.5 years follow-up, ruxolitinib when compared to the best available therapy resulted in 42 % reduction in risk of death (HR=0.58; 95 % CI, 0.36–0.93).

5.2.4 Bone Marrow Transplantation

There are NO curable options except for allogeneic bone marrow transplant [27]. Most patients are not suitable candidates for transplant due to older age at diagnosis. Younger patients and those with intermediate-2 or high-risk PMF should be considered for transplantation if available.

5.3 Survival with MF

MF has the worst prognosis among MPNs with a median survival of 2.5–3 years. Patients with CALR mutation follow a more indolent course and are associated with younger age ($P<0.0001$), higher platelet count ($P<0.0001$), and lower DIPSS-plus score ($P=0.02$). They are also less likely to be anemic, require transfusions, or display leukocytosis. Patients with non-mutated JAK2, MPL, and CALR (triple negative) have the worst prognosis with high likelihood of transformation to acute leukemia. Overall survival is 3.2 years in triple negative, 9.1 years in MPL mutant, 9.2 years in JAK2 mutants, and 17.7 years with CALR mutations [22]. Common causes of death include myocardial infarction, bleeding, thrombosis, and cerebrovascular and cardiovascular diseases.

6 Therapy and Monitoring of Philadelphia-Negative Neoplasms in Developing Countries

For our indigent patients suspected to have PV/ET, we routinely perform bone marrow aspiration and biopsy to determine cellularity and fibrosis and JAK2 mutation analysis, which is sent to specialized laboratories. Serum erythropoietin levels are done only in case of a JAK2 mutation-negative patient.

Since disease follows an indolent course and management of patients is palliative, we prefer pragmatic use of our limited resources. In low-risk patients, observation, phlebotomy, and aspirin are our treatment of choice. For high-risk patients, we prefer to use HU plus aspirin unless there is contradiction. We treat only young pregnant women with IFN as it is expensive with poor compliance due to side effects. In our indigent patients with thrombotic complications, we use heparin or warfarin as they are cheaper and therefore compliance is better in case of major thrombotic events. For patients with hemorrhagic complications, we use fresh frozen plasma, as it is more accessible and cheaper.

We perform IPSS scoring on all our indigent patients when mutation and cytogenetic analysis cannot be performed. This provides us a reasonably accurate assessment of prognosis.

For MF low-dose thalidomide plus steroids is our initial treatment of choice followed by HU. We use androgens and low-dose steroids for anemia. Splenic irradiation (rarely) only is performed when no other option is available. We use ruxolitinib

as compassionate access programs with subsidized drug by Novartis are available in several low-income countries.

7 Chronic Myeloid Leukemia (CML)

CML accounts for 15–20 % of all adult leukemia. It affects over 100,000 patients worldwide annually and represents a significant global health burden. Median age at diagnosis is 65 years with a male predominance [28]. There is a paucity of reliable data from resource-poor countries [29].

CML is the only Philadelphia-positive MPN; it arises from a reciprocal translocation between the BCR gene on chromosome 22 and the ABL gene on chromosome 9 creating the Philadelphia chromosome t(9;22)(q34;q11).

The resultant BCR-ABL protein product has constitutive kinase activity that drives uncontrolled proliferation, inhibition of apoptosis, and decreased adhesion of hematopoietic stem cells. Patients in chronic phase usually present with fatigue, early satiety, or complications of hyperviscosity such as visual disturbances or priapism. Progression to accelerated phase occurs with progressive loss of white cell differentiation with an accumulation of blasts, terminating into either acute myelogenous leukemia or acute lymphoblastic leukemia. This blast phase is refractory to treatment with a median survival for patients of 3–5 months [7].

TKIs have revolutionized the treatment of CML. With continued use of TKIs, significant fraction of patients achieve deep and long-term responses, with minimal toxicities especially in early-phase CML. In newly diagnosed chronic phase CML, 85 % of patients on IM achieve a complete cytogenetic remission; of these 60 % do so in their first year of therapy [30]. Mortality at 8 years in these patients is 16 %. Once a complete cytogenetic remission is achieved, about 15–20 % of patients on imatinib will develop resistance to their disease, and second-generation TKIs are the treatment of choice in these patients except in patients with 3,151 mutation where ponatinib is the only effective TKI. Resistance to imatinib is due to occurrence of either new mutations or BCR-ABL-independent resistance. Approximately 50 % of patients who are resistant to imatinib will achieve a complete cytogenetic remission to the second-generation TKIs. The responses are durable in about 80 % of patients.

Common toxicities leading to drug discontinuation include nausea, vomiting, diarrhea, and severe muscle cramps. Less common reasons for discontinuing imatinib include edema, heart failure, rash, and arthralgia as well as severe myelosuppression and hepatic toxicity. The toxicity profile remained unchanged after years of use.

Follow-up of patients with CML include hematologic responses, cytogenetic testing, and molecular responses according to ELN guidelines listed in Table 4. Additional chromosomal abnormalities may also be seen in more advanced disease phase. Molecular tests, which include qualitative and quantitative detection of the BCR-ABL gene product, can be performed through either FISH or RQ-PCR for diagnosis and monitoring of the disease status.

Attainment of complete cytogenetic response is critical to prevent disease progression; monitoring needs are minimal and most patients return to a normal productive life. Estimated survival with first-line imatinib is greater than 15 years in early studies and probably longer with more experienced and improved patient management.

Second-generation TKIs include nilotinib 300 mg PO q 12 h for newly diagnosed patients (chronic phase) or 400 mg PO q 12 h for patients resistant/intolerant to IM in patients with advanced disease. The dose for dasatinib is 100 mg PO q 24 h for newly diagnosed patients (chronic phase) and 140 mg PO q 24 h for patients with advanced disease. The dose for bosutinib is 500 mg daily. Ponatinib is recommended for patients with T3151 mutation or Philadelphia-positive acute lymphoblastic leukemia.

7.1 Allogeneic Bone Marrow Transplant (BMT)

Allogeneic bone marrow transplantation (BMT) is associated with long-term survival in 50–70 % patients in chronic phase. Unfortunately, it is extremely expensive and associated with significant treatment morbidity and mortality. Toxicity markedly increases with age and disease stage. Transplant has associated morbidities (infertility, graft-versus-host disease) and mortality (20–50 % at 1 year depending on patient and donor characteristics) [31].

Table 4 European LeukemiaNet guidelines for chronic myeloid leukemia

Time	Optimal response	Suboptimal response	Failure	Warnings
Diagnosis	NA	NA	NA	High-risk CCA/Ph+[3]
3 months	CHR, *at least minor CyR*	*No CyR*	*Less than CHR*	NA
6 months	At least PCyR	Less than PCyR	No CgR	NA
12 months	CCyR	PCyR	Less than PCyR	Less than MMR
18 months	MMR	Less than MMR	Less than CCyR	NA
Any time (during treatment)	*Stable or* improving MMR	Loss of MMR, mutations[1]	Loss of CHR, loss of CCyR, mutations[2] *CCA/Ph+*[3]	↑in transcript levelsCCA/Ph–

New recommendations marked in Italics

BCR-ABL 1kinase domain mutations (1) still sensitive to imatinib and (2) poorly sensitive to imatinib or other TKIs. (3) CCA/Ph+–- "warning" factor at diagnosis, (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least 2 Ph+cells

7.2 Therapy for CML in Developing Countries

Rapid cytoreduction and stabilization of blood counts can be achieved with HU or ARA-C in patients with high white counts. Aggressive supportive care should be given concurrently to prevent tumor lysis syndrome in patients with very high tumor load or with advanced disease. The patient should be advised to drink 3–4 l of fluids daily or IV fluids may be given in case he/she is unable to drink. Allopurinol at 300 mg daily is started to prevent urate nephropathy.

Imatinib 400 mg is started as soon as t(9;22) translocation is detected or BCR-ABL positivity is documented for durable responses with prolonged survival. Novartis/MAX foundation has developed an access program for nearly all low-income countries to provide imatinib at a very subsidized rate. Generic imatinib is also available, but the quality of the drugs is variable. The role of ongoing monitoring of cytogenetic and molecular response is not standardized in developing countries due to lack of resources. If patients are intolerant or fail to achieve a complete cytogenetic response after 18 months, we switch them to second-generation TKIs. We use either cytogenetic responses or BCR-ABL by RQ-PCR to monitor patients. Where not available, it is imperative for centers in the developing world to partner with regional laboratories to have the test performed.

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The Myelodysplastic Syndromes

Vernon Louw

1 Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders, primarily characterized by inefficient hematopoiesis [10]. This results in cytopenias and dysplasia and a variable propensity to transform into acute myeloid leukemia (AML). In most cases, no clear cause is detected, but an important subset of patients may develop MDS after previous exposure to chemotherapy and/or radiation, a condition that is termed therapy-related MDS.

The clinical manifestations are the consequence of variable degrees of bone marrow failure and result in varying degrees to which the production of red blood cells (RBC), mature granulocytes, and platelets is affected. These effects may be both quantitative, resulting in anemia, neutropenia, and thrombocytopenia, and qualitative, resulting in abnormal function and morphology of these cells.

2 Pathogenesis

The pathogenesis of MDS is incompletely understood and extremely variable in nature. The shared element between the different subtypes is the presence of a clonal process that results from a mutation that leads to the transformation of a single hematopoietic progenitor cell [10]. A range of associated and potentially causal mutations have been described, each of which may have a different impact on the

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disease phenotype, prognosis, and sometimes therapy. In addition, there may be stromal and immune factors that affect the development and course of the disease [13]. Environmental factors (e.g., exposure to benzene, tobacco, chemotherapy, radiation, and other chemicals), certain congenital genetic abnormalities (e.g., Fanconi anemia, Down syndrome, Bloom syndrome, etc.), and a range of "benign" hematological diseases (e.g., paroxysmal nocturnal hematuria (PNH), aplastic anemia, polycythemia vera, etc.) have been associated with the development of MDS. Many autoimmune conditions have been described in association with MDS, but it is not clear whether the relationship is causal or not [12].

3 Epidemiology

The incidence of MDS is not clear and most of the available estimates are based on registries and cancer databases from the United States and Europe. Very limited or no information is available from lower income countries. What is known is that it is a disease, predominantly of the elderly, with diagnosis before the age of 50 being very rare, except in cases that are related to previous therapy. The vast majority of patients are older than 65 [7].

4 Clinical Presentation

The signs and symptoms of MDS are generally nonspecific and related to the underlying cytopenias (e.g., tiredness, infection, and bleeding). Many patients are asymptomatic at diagnosis and are diagnosed after abnormalities on a routine full blood count (FBC) or peripheral blood (PB) smear are found. Systemic symptoms (e.g., fever and weight loss) are uncommon and are usually associated with complications of the disease (e.g., infection and/or transformation to AML). Clinical signs are also nonspecific and usually related to cytopenias (e.g., pallor, petechiae, easy bruising, etc.). Hepatosplenomegaly and lymphadenopathy are not common. A small subset of patients may present with Sweet syndrome (acute febrile neutrophilic dermatosis) or myeloid sarcoma, both of which may signal impending transformation to AML.

The most common clinical finding is anemia, with its associated nonspecific symptoms, which often leads to transfusion dependence. Because of the neutropenia and granulocyte dysfunction in many patients, infections (often recurrent), especially bacterial, are common. A range of autoimmune abnormalities have been associated with MDS, with the most common being chronic rheumatic heart disease, rheumatoid arthritis, pernicious anemia, psoriasis, and polymyalgia rheumatica [2]. Acquired hemoglobin H disease (also known as alpha thalassemia myelodysplastic syndrome) has been seen in about 8 % of cases [8]. This condition must be differentiated from other forms of alpha thalassemia.

5 Pathologic Features

MDS is associated with quantitative and qualitative changes in one or more of the blood and bone marrow lineages. Quantitative changes include cytopenias (anemia, neutropenia, and thrombocytopenia) or less commonly an increase in the number of cells of a particular lineage (e.g., thrombocytosis) combined with cytopenia in another (e.g., anemia). Examples include 5q-minus syndrome and refractory anemia with ring sideroblasts associated with thrombocytosis (RARS-T). Qualitative changes usually manifest as dysplasia on blood or bone marrow morphology, with or without measurable functional changes.

5.1 Complete Blood Count

Most patients present with anemia, which is usually associated with a round macrocytosis (mean corpuscular volume (MCV) >100) or normal cell size. The reticulocyte is typically low and the red cell distribution width (RDW) high, in keeping with the variability in red cell size (anisocytosis). About 50 % of patients present with a leukopenia, most often due to a neutropenia, with circulating immature white blood cells sometimes seen in the peripheral blood. Importantly, circulating blasts should be fewer than 20 % of the white blood cell (WBC) differential [9]. About 25 % of patients have thrombocytopenia, which is usually seen in association with other cytopenias and only rarely in isolation. There are rare instances where isolated thrombocytopenia may be confused with immune thrombocytopenic purpura (ITP). Thrombocytosis is seen in less than 10 % of cases and is usually associated with anemia and a specific underlying genetic abnormality (e.g., 5q-minus syndrome, 3q21q26 syndrome, and RARS-T). RARS-T is often associated with activating mutations of Janus kinase 2 (JAK2).

5.2 Peripheral Blood Smear

Dysplastic features are often noted on peripheral blood smear in the RBC and WBC in the peripheral blood. Platelets usually appear normal but may sometimes show changes in size or granularity. A wide range of abnormalities have been described in red blood cells (e.g., changes in size, chromicity (color), and shape, including round macrocytosis, microcytosis, ovalomacrocytosis, basophilic stippling, and many others. The reticulocyte count is usually low. If a reticulocytosis is seen, one should consider autoimmune hemolytic anemia (AIHA). Changes in WBC may include the pseudo-Pelger-Huet abnormality (reduced segmentation) with a range of changes in terms of granularity, the nucleus and its chromatin, and the presence of precursor cells, especially myeloblasts. The presence of Auer rods

in myeloblasts in a patient known with MDS may be a harbinger of AML transformation.

5.3 Bone Marrow Aspirate and Biopsy

The bone marrow aspirate is evaluated for dysplastic features in all three lineages, which may support the diagnosis and assist and subtype classification of MDS, with special emphasis on the percentage of myeloblasts, which should be less than 20 % [9]. The bone marrow biopsy provides an indication of cellularity, which is usually increased as well as the degree of involvement and the presence of fibrosis. This paradox of increased cellularity in the bone marrow with cytopenias in the peripheral blood is usually a reflection of ineffective hematopoiesis, with increased production coupled with increased apoptosis in the bone marrow.

Examples of specific findings in RBC in the bone marrow include the presence or absence of ring sideroblasts, internuclear bridging and erythroid hyperplasia (most common in ineffective erythropoiesis), and hypoplasia or aplasia. A range of changes may be seen in the megakaryocytes (e.g., changes in number, lobularity, granularity, and size). Another feature to be looked for is the abnormal localization of immature granulocyte precursors (ALIPS), where granulopoiesis is displaced from its usual paratrabecular location to more central bone marrow spaces.

A range of cytochemistry, immunocytochemistry, and sometimes flow cytometric evaluations may be required for diagnosis and exclusion of other conditions, including AML. Detection of chromosomal abnormalities by routine cytogenetic analysis is important for classification and treatment and should be done routinely in all cases. In some instances, further evaluation by reverse transcriptase polymerase chain reaction (RT-PCR) and/or fluorescent in situ hybridization (FISH) may be required to distinguish between MDS and AML and has an impact on prognosis or assists in diagnosing subtypes of MDS that may require specific forms of therapy. Importantly, certain cytogenetic abnormalities may indicate the presence of AML, independent of whether the 20 % threshold for myeloblasts has been reached (e.g., t(8;21)(q22;q22); inv(16)(p13.1q22); t(16;16)(p13.1;q22); t(15;17)(q22;q21.1)). In addition, a range of other cytogenetic abnormalities may indicate the presence of MDS in patients with unexplained persistent cytopenias even in the absence of features of dysplasia (e.g., -7/del(7q), -5/del(5q), etc.).

6 Diagnosis

The diagnosis and correct classification and determination of MDS subtype are dependent on careful evaluation by a hematopathologist with experience in the diagnosis of these conditions while taking into account the clinical context.

Diagnosis is based on evaluation of the complete blood count, peripheral blood smear, and bone marrow aspirate and biopsy, coupled with the findings from cytogenetic evaluation, in all patients with unexplained and persistent cytopenias, after exclusion of more common conditions, such as nutritional deficiencies (e.g., B12, folate, copper), human immunodeficiency virus (HIV) infection, alcohol, drugs, and zinc toxicity. All patients should be carefully questioned with regard to occupational exposure to toxins, chemotherapy, radiotherapy, and risk factors for HIV.

In most cases the diagnosis is made based on features as described in the 2008 World Health Organization (WHO) classification after the evaluation for the following three major features [9]:

1. Otherwise unexplained quantitative changes in one or more of the blood cell lineages (i.e., RBC, granulocytes and platelets) with cytopenia defined as:
   - Hemoglobin < 10 g/dL
   - Absolute neutrophil count (ANC) < 1.8×10^9/L
   - Platelets < 100×10^9/L
2. Morphological evidence of significant dysplasia, which is defined as ≥10 % of erythroid precursors, granulocytes or megakaryocytes, as detected after evaluation of the peripheral blood smear and bone marrow aspirate and biopsy, in the absence of other causes of dysplasia.
3. Blast cell percentage in peripheral blood and bone marrow of less than 20 %. Blast cell percentages ≥20 % suggest AML. If certain genetic abnormalities are present (e.g., t(8;21)(q22;q22); inv(16)(p13.1q22); t(16;16)(p13.1;q22); t(15;17)(q22;q21.1)), the diagnosis of AML can be made independent of the blast cell count.

Note that the diagnosis of MDS can be made in the absence of absolute quantitative criteria if there is strong morphological evidence of dysplasia. Similarly, the diagnosis of MDS can be considered in the absence of dysplasia in patients with otherwise unexplained refractory cytopenia combined with certain genetic abnormalities.

7 Differential Diagnosis

A range of conditions may present with features that overlap with MDS and should be considered and excluded before making a diagnosis [9].

These include:

- Idiopathic cytopenia of undetermined significance (ICUS)
- Acute myeloid leukemia (AML), especially where the blast percentage may be less than 20 %, but where AML-defining genetic abnormalities are present
- Myelodysplastic/myeloproliferative neoplasms (MDS/MPN), such as chronic myelomonocytic leukemia (CMML); atypical chronic myeloid leukemia (CML),

BCR-ABL negative; juvenile myelomonocytic leukemia, MDS/MPN unclassifiable; and isolated isochromosome 17p-
- Aplastic anemia
- Myelofibrosis
- HIV infection
- Nutritional abnormalities, including megaloblastic anemias (e.g., vitamin B12 and folate deficiency), copper deficiency, and zinc excess
- Medications, including granulocyte colony-stimulating factor, valproic acid, mycophenolate mofetil, ganciclovir, alemtuzumab, methotrexate, and alkylating agents (e.g., cyclophosphamide)

8 Classification

The myelodysplastic syndromes (MDS) are classified according to the WHO classification system, which is updated from time to time to reflect the most recent understanding of these conditions. A combination of morphological, immunophenotypic, genetic, and clinical features is used in an attempt to classify patients in six general subgroups (Table 1) [9].

9 Prognosis

The natural history of MDS is extremely variable and depends on a range of factors, including the number and degree of cytopenias, the extent of dysplasia, and the specific cytogenetic subtypes. Many other features have been recognized as having an association with outcome, but the most important of these have been combined in prognostic scoring systems, the most common of which are the International Prognostic Scoring System (IPSS), the more recent revised IPSS (IPSS-R), the MD

Table 1 WHO classification of MDS 2008

Entity	Dysplasia	Peripheral blasts	Bone marrow blasts	Ringed sideroblasts	Cytogenetics
5q − syndrome	Mostly DysE	<1 %	<5 %	<15 %	5q − sole
RA, RN,RT, RCUD	DysE, N, T	<1 %	<5 %	<15 %	Various
RARS	Mostly DysE	0	<5 %	>15 %	Various
RCMD	2–3 lineages	Rare	<5 %		Various
RAEB-1	1–3 lineages	<5 %	5–9 %	<15 %	Various
RAEB-2	1–3 lineages	5–19 % Auer rods ±	10–19 % Auer rods ±	<15 %	Various
MDS-U	1 lineage	≤1 %	<5 %	<15 %	Various

DysE dyserythropoiesis, *MDS-U* MDS undefined, *RCMD* refractory cytopenia with multilineage dysplasia, *RCUD* refractory cytopenia with unilineage dysplasia, *RN* refractory neutropenia, *RT* refractory thrombocytopenia, *T* thrombocytes.

Anderson Cancer Center (MDACC) MDS Model, and the WHO Prognostic Scoring Systems (WPSS) [3, 4].

As a general rule, patients are classified into lower and higher risk MDS subgroups with therapeutic decision-making based on where in these subgroupings a patient finds himself/herself.

10 Management

Treatment decisions are usually made based on the need for treating the underlying disease, supportive care, and modifying the natural cause of the disease to prevent, diminish, or delay the development of complications.

Immediate treatment may be indicated for symptomatic cytopenias, such as transfusion for anemia or thrombocytopenia complicated by bleeding. Asymptomatic patients are usually monitored over time for the development of cytopenias or other complications.

Treatment decisions are usually based on the patient's general condition, comorbid diseases, prognosis, and likelihood of developing acute myeloid leukemia. Lower risk MDS patients are usually given supportive care and, depending on specific laboratory findings, may be treated with growth factors (i.e., G-CSF and/or erythropoiesis-stimulating agents (ESAs), immunosuppressive therapies, or specific treatments targeting the underlying disease (e.g., lenalidomide for 5q- syndrome, azacitidine, decitabine, etc.). More definitive treatment strategies for MDS are often very expensive and require significant expertise in its management. Guidelines by the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) are frequently updated and provide practical guidance on decision-making. All patients should be evaluated for the need and practicality of hematopoietic stem cell transplantation as this remains the only form of cure at present [11]. Due to the fact that MDS is mainly a disease of the elderly and often accompanied by comorbid disease, stem cell transplantation is generally limited to a minority of patients [5]. It is advised that all patients be evaluated for enrollment into clinical trials.

The majority of patients become RBC transfusion-dependent over time with the concomitant risk of HLA immunization, transfusion-related reactions, and most iron overload, which can happen after as few as 10–20 RBC transfusions. Red blood cells for transfusion are usually leukocyte-reduced. Irradiation of RBC and platelets is usually required for patients who are candidates for stem cell transplantation. Where available, these patients should also receive cytomegalovirus (CMV) negative transfusions. Patients should be monitored for iron overload and its complications and provided with iron chelation therapy (ICT) where necessary [6]. ICT is usually indicated if a patient has a prognosis longer than 1 year, has received more than 20 units of RBC (or 40 Japanese units), has a serum ferritin >1,000 mcg/L, and is a candidate for hematopoietic stem cell transplantation [1]. Chronically transfused patients should also be monitored for the complications of iron overload, such

as hepatic iron overload, iron overload of the heart (MRI T2* if available), thyroid function, diabetes mellitus, etc.

Platelet transfusions are usually limited to patients with severe thrombocytopenia ($\leq 10 \times 10^9$/L) or patients with active bleeding or otherwise at high risk of bleeding (e.g., concomitant infection). Patients should avoid drugs that can negatively affect platelet function (e.g., aspirin, certain NSAIDs).

11 Conclusion

The myelodysplastic syndromes form a heterogeneous group of disorders that require considerable expertise in terms of its diagnosis and management. As a general recommendation, these patients should be managed in referral centers with experience in managing these conditions.

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Acute Leukemia

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Acute myeloid (AML) and lymphoblastic (ALL) leukemias are clonal proliferations of hematopoietic progenitors that usually impair normal hematopoiesis. AML and ALL differ in their demographics and therapeutic strategy. In all countries, ALL is the most common cancer in childhood. In North America and most Western Europe countries, the management of children ALL is one of the greatest therapeutic successes in the field of cancer, with 90 % of patients alive at 5 years [1]. In the last decade, the development of pediatric-inspired protocols in adults younger than 60 years with ALL has improved 5-year survival rates to about 50 % of patients [2]. In AML, progresses have been less impressive, except in acute promyelocytic leukemia (APL), where the vast majority of patients with standard-risk disease benefit from the combination of retinoic acid (ATRA) and arsenic trioxide (ATO) and can now be cured without chemotherapy [3–5]. Outcomes in acute leukemias (ALs) depend on the use of effective combinations of mostly inexpensive, decade-old chemotherapeutical drugs but also from risk-adapted supportive care that has turned out to be the resource-limiting part of global care in these patients. Limited access to supportive care, presence of comorbidities, but also delayed diagnosis and low adherence to therapy have been identified as the main causes of treatment failure in middle- (MIC) and low-income (LIC) countries [6].

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1 Diagnosis and Risk Stratification

1.1 Morphology and Cytochemistry

The diagnosis of AL requires a bone marrow aspiration. Bone marrow smears should be examined by light microscopy after either May-Grünwald-Giemsa or Wright-Giemsa staining, according to local procedures. In the large majority of cases, standard morphology is sufficient for the diagnosis of AML. In immature AL, and in the absence of flow cytometry, cytochemistry for myeloperoxidase or Sudan black B and nonspecific esterase is recommended to distinguish ALL from AML. The diagnosis of APL can be done on morphology but staining for PML may help to confirm the diagnosis [7]. Bone marrow biopsy remains an optional procedure in AL diagnosis but should be performed in case of aspiration failure (dry tap).

1.2 Flow Cytometry

Immunophenotype of leukemic cells is required for accurate diagnosis of AL, to distinguish ALL from AML, and to decide risk-adapted therapy. Immunophenotyping using 2- or 3-color flow cytometry is relatively widely available and can be done on peripheral blood or bone marrow samples. The minimum panel of markers includes CD19, CD22, and cytoplasmic CD79a for B-cell precursor ALL, surface or CD7 and cytoplasmic CD3 for T-cell ALL, and cytoplasmic MPO for AML [8]. Detection of additional markers may be required to establish the diagnosis of AML with minimal differentiation, acute megakaryoblastic leukemia, and AL of ambiguous lineage [3]. Multiparameter flow cytometry may also be used to quantify early minimal residual disease (MRD) that is now considered as the most powerful prognostic factor in ALL [9].

1.3 Cytogenetics

Cytogenetic abnormalities are highly correlated to prognosis in AML and ALL [10]. The favorable prognosis of hyperdiploidy in childhood ALL is less clear in adult ALL. A t(12;21) translocation is detected in 25 % of children with ALL and is also associated with a favorable outcome but is very infrequent in adults. A t(4;11) translocation involving the *MLL* oncogene and associated with a dismal prognosis is present in 70 % of infant ALL but in less than 5 % of older children and adult ALL. Finally, the most common translocation in adult ALL is the t(9;22) "Philadelphia chromosome" (Ph1), resulting in *BCR-ABL1* gene fusion. In Ph1-positive ALL, combining chemotherapy and tyrosine kinase inhibitors has been shown to improve complete remission rate and survival. AML can also be

categorized into three cytogenetic risk groups (favorable, intermediate, and adverse), the favorable subgroup being composed of t(15;17) in APL, t(8;21) and inv(16)/t(16;16) in core-binding factor (CBF-AML) [11]. Fluorescence in situ hybridization, when available, may be helpful to identify recurrent chromosome translocations and numerical abnormalities [12].

1.4 Molecular Genetics

Molecular screening for recurrent oncogene fusion transcripts may be a valuable alternative to conventional cytogenetics. In ALL, reverse transcription PCR is recommended to identify *BCR-ABL1*, *MLL-AFF1* (*MLL-AF4*), and *ETV6-RUNX1* (*TEL-AML1*) fusion genes. In AML, molecular diagnosis should focus on the three favorable-risk gene fusions, namely, *PML-RARA* in APL and *RUNX1-RUNX1T1* or *CBFB-MYH11* in CBF-AML. In cytogenetically normal AML (CN-AML), identification of *NPM1*, *FLT3*, and *CEBPA* gene mutations has significantly helped to refine the prognosis and risk stratification [13]. *NPM1* mutations that are considered to be associated with a favorable outcome in the absence of *FLT3* internal tandem duplication can also be detected by immunohistochemistry on trephine biopsy [14]. Quantification of MRD by monitoring fusion transcripts or specific immunoglobulin heavy chain or T-cell receptor rearrangements can be done in centralized referral labs of countries with the highest resources.

2 Acute Lymphoblastic Leukemia Therapy

Risk stratification on age, patient, and disease characteristics, and early response to therapy are now routinely used in high-income countries (HICs). In LICs, risk-adapted strategy is of limited impact if treatment intensification options are not available. In this context, risk can however be evaluated with few clinical and biological parameters including age, baseline white blood cell count, peripheral blood response at day 8, and/or bone marrow response at D15/21 of induction therapy. If screening for both Ph1/*BCR-ABL1* transcript both and tyrosine kinase inhibitors (TKIs) are available, Ph1-positive ALL may benefit from specific targeted strategies.

2.1 Ph1-Negative ALL

A wide spectrum of income-adapted strategies has been reported mostly for children with ALL. In countries with poor access to chemotherapy and low training in the management of patients with AL, administration of myelosuppressive drugs is not

Table 1 Proposed protocol for children and adults patients with acute lymphoblastic leukemia in countries with limited resources

Induction (two-drug), for 1 month
Vincristine 1.5 mg/m^2 per dose[a], days 1, 8, 15, and 22
Prednisolone 40–60 mg/m^2 per day, for 28 days
L-asparaginase (if available) 6,000 U/m^2 per dose, days 4, 6, 8, 11, 13, and 15
Intrathecal methotrexate, days 8, 15, and 22
Interim maintenance (part 1), for 8 weeks
6-mercaptopurine 37.5–50 mg/m^2 per night (before bedtime)
Oral methotrexate 15–20 mg/m^2 per dose, weeks 2, 4, 6, and 8
Intrathecal methotrexate, weeks 1, 3, 5, and 7
Delayed intensification (part 1), for 4 weeks
Vincristine 1.5 mg/m^2 per dose[a], days 1, 8, 15, and 22
Dexamethasone 4–6 mg/m^2 per day, for 28 days
Intrathecal methotrexate, days 1 and 15
Interim maintenance (part 2), for 8 weeks
Same as interim maintenance part 1
Delayed intensification (part 2), for 4 weeks
Same as delayed intensification part 1
Maintenance, 4-week block, repeated until 2 years
6-mercaptopurine 37.5–50 mg/m^2 per night (before bedtime), for 4 weeks
Oral methotrexate 15–20 mg/m^2 per week, for 4 weeks
Dexamethasone 4–6 mg/m^2 per day, for 5 days during week 3
Vincristine 1.5 mg/m^2 per dose[a], week 3

Adapted from Yeoh et al. [6]
[a]Vincristine total dose should be capped to 2 mg

recommended. As proposed by the St. Jude Children's Research Hospital, a complete remission can be achieved in children and adult patients with a 2-drug induction regimen including prednisolone and vincristine (Tables 1 and 2) [6]. The treatment or prophylaxis of central nervous system (CNS) involvement can be achieved by repeated intrathecal methotrexate injections. If available, asparaginase may be added three times a week for 2 or 3 weeks in children or adolescents and young adults up to 25 years old. In older patients, hepatitis and pancreatitis may be limiting toxicities for using asparaginase. Once complete remission is achieved, patients should receive an interim maintenance with continuous 6-mercaptopurine, oral methotrexate, and intrathecal methotrexate injections. Two delayed intensification with weekly vincristine, dexamethasone, and intrathecal methotrexate should be given, separated by a second interim maintenance. After second delayed intensification completion, a 4-week block maintenance with 6-mercaptopurine, oral methotrexate, vincristine, and dexamethasone is recommended until 2 years of treatment. According to available resources, the use of additional drugs and reinforced strategies in high-risk

Table 2 Proposed protocol for children and adult patients with acute myeloid leukemia in countries with limited resources

AML (*non-APL*)	Cytarabine 20 mg/m^2 twice daily, for 10–15 days, monthly courses
APL	Induction
	ATO 0.15 mg/kg per day (2H IV), until CR (max 60 days) ATRA 45 mg/m^2 per day in 2 doses, until CR (max 60 days)
	Consolidation
	ATO 0.15 mg/kg per day (2H IV), 5 days per week, 4 weeks every 8 weeks, 4 cycles ATRA 45 mg/m^2 per day in 2 doses, 2 weeks every 4 weeks, 7 cycles

Adapted from Burnett et al. [20] and Lo-Coco et al. [5]
ATO arsenic trioxide, *ATRA* all-trans retinoid acid

patients have been proposed but should be adapted to available supportive care in order to limit treatment-related mortality (TRM) [6]. In adult patients, UKALL XII or hyper-CVAD are dose-intensive protocols that have been widely used [15, 16].

2.2 Ph1-Positive ALL

The outcome of Ph1-positive ALL has been dramatically improved by the use of ABL1 tyrosine kinase inhibitors in children and in adults. Addition of a TKI such as imatinib or dasatinib to conventional chemotherapy increased remission rates to more than 90 %. In adults, minimal induction approaches combining TKI and prednisone have shown that a CR can be reached in almost all patients with limited toxicities [17]. In spite of this improvement, allogeneic stem cell transplantation remains recommended in adults patients in HIC. If TKIs are available, combining continuous TKI administration with chemotherapy is recommended.

3 Acute Myeloid Leukemia Therapy

In resource-limited settings, emphasis should be set on the treatment of APL, which is highly curable without chemotherapy, and in other favorable-risk AML, which can be cured in a significant proportion of patients with intensive chemotherapy but without stem cell transplantation, provided adequate supportive care is available to limit TRM. In other patients, best supportive care and management of hyperleukocytosis with cytoreductive therapy can only prolong survival for a few weeks or months following diagnosis.

3.1 Acute Promyelocytic Leukemia (APL)

Despite its excellent long-term outcome with modern therapy, APL is still characterized by an important rate early death (ED) related to coagulopathy contrasting with favorable outcome once differentiation therapy has been introduced. ED rates are in the 5–10 % range in HIC but rise up to 30 % in MIC, resulting in long-term overall survival (OS) below 60 % [18]. Distance to treatment center and delay in diagnosis are key determinants of ED [7]. As soon as a diagnosis of APL is suspected, coagulopathy should be managed with immediate onset of oral all-trans retinoic acid (ATRA) and aggressive transfusion support (frozen plasma and platelets). The use of chemo-free, arsenic-based regimens to cure APL was pioneered in MIC, where intravenous arsenic trioxide (ATO) as single agent provided a CR rate of 86 % with 65 % overall survival at 5 years [19]. ATO has little hematologic toxicity and thus spares supportive care resources compared to chemotherapy. The main toxicity is cardiac, with QTc prolongation exposing to the risk of ventricular arrhythmias. Patients treated with ATO should thus avoid QTc-prolonging medications and their EKG be monitored on a regular basis.

In low-/intermediate-risk APL (WBC $< 10 \times 10^9$/L), combination of IV ATO and oral ATRA continued for a median of 35 days until achievement of CR and followed by consolidation therapy based on sequential ATO and ATRA courses is recommended [5]. Hyperleukocytosis can be managed with cytoreduction by hydroxyurea (HY). ATO-ATRA combination may lead to a life-threatening "differentiation syndrome" (DS) manifesting as weight gain, bilateral pulmonary infiltrates, pleural or pericardic effusions, and fever. DS requires steroids and/or transient tapering or discontinuation of ATO. It is likely that IV ATO can be safely substituted by oral ATO or oral tetra-arsenic tetra-sulfide (AS_4S_4), thus limiting patient's visits. Oral ATO may also have a better safety profile than IV ATO, with less frequent QTc prolongation. In high-risk APL (WBC $> 10 \times 10^9$/L), accumulated data suggest that some form of chemotherapy, e.g., an anthracycline, has to be added to an ATO-ATRA regimen to minimize the risk of relapse. Because APL is highly curable, limited blood derivative resources should prioritize APL. The experience from an international consortium has demonstrated that it is possible to improve the outcome of APL in MIC when drugs and blood derivatives are available, provided a prompt diagnosis of APL can be performed by a hematology laboratory with access to basic microscopy [7, 18].

3.2 Non-acute Promyelocytic AML

In children and young adults, other forms of AML are currently treated with several intensive chemotherapy courses as induction and consolidation therapy, followed by allogeneic stem cell transplantation in intermediate- or high-risk AML [3]. Best CR and survival rates are obtained by myelosuppressive regimen based on cytarabine

and anthracycline (7 + 3). These regimens typically result in prolonged neutropenia, requiring hospitalization, broad-spectrum antibiotics, and regular transfusion support. If limited transfusion and antibiotic resources are available, younger patients with favorable-risk CBF-AML should be prioritized. These patients can be cured in up to 60 % of cases with a "7 + 3" induction course, resulting in very high CR rates, followed by at least two high-dose cytarabine (HDAC) courses, each including 6 boluses of 1–3 g/m^2 cytarabine.

When transfusion support is not easily available, non-intensive options can be envisaged. Low-dose subcutaneous cytarabine can achieve CR in 30–40 % patients with CN-AML, but not in patients with abnormal cytogenetics. These CR are reached after a median of 3 months of therapy and thus LDAC should not be withheld after a single course, except in case of overt AML progression. Median disease-free duration after reaching CR is around 8 months with LDAC. Because LDAC does not increase resource consumption compared to oral HY, it should be favored in patients with CN-AML [20]. In other instances, patients should receive only available supportive care, with oral HY introduced in case of hyperleukocytosis. The median survival of such patients is around 3 months, even in developed countries with broad access to supportive care [20].

4 Supportive Care

4.1 Hyperleukocytosis and Tumor Lysis Syndrome

Hyperleukocytosis in AML should be managed with HY until WBCs are <10–20 × 10^9/L, with limited red blood cell (RBC) transfusions to avoid hyperviscosity. It has been proposed that leukostasis manifesting as bilateral pulmonary infiltrates, especially in AML with monocytic differentiation, could be managed with steroids until the WBC is controlled [21]. Tumor lysis syndrome (TLS) should be prevented with abundant saline hydration and allopurinol [22]. Rasburicase is highly effective in preventing TLS in high-risk patients but is expensive and risky in male of Mediterranean or African origin, who are more frequently glucose-6 phosphate dehydrogenase deficient.

4.2 Transfusion

At the initial phase of ALL and AML therapy, transfusion of platelets and RBC may be mandatory to avoid bleeding or hypoxia-induced organ failure. In countries with limited resources and/or in the absence of voluntary blood donation, family donors may be asked for donation. The antifibrinolytic tranexamic acid may be used to reduce bleeding episodes and platelet transfusions. Menstrual suppression should be considered in premenopausal women at risk of bleeding due to

thrombocytopenia. Local guidelines should be developed taking patient age and benefit/risk balance into account.

4.3 Pain and Nausea Management

Pain is not a common symptom at diagnosis in AL. However some patients may present with bone pain, painful infection, or organ enlargement that require appropriate pain control. Bone marrow aspiration and biopsy or lumbar puncture are both source of anxiety and pain that should be anticipated by appropriate local analgesia (lidocaine) and sedation. The WHO pain relief ladder should guide oral administration of drugs. Aspirin and nonsteroidal anti-inflammatory should be avoided in the context of thrombocytopenia. Nausea is more frequent in the treatment of AML than ALL. Setrons are very effective to prevent nausea and vomiting but are also expensive. In ALL, non-setron antiemetic drugs can be alternatively proposed including dopamine antagonists (metoclopramide, domperidone), antihistamines (diphenhydramine), benzodiazepines, and cannabinoids. Dexamethasone, proposed in AL protocols, is also an effective antiemetic. Appropriate pain relief and antiemetic strategies should be integrated to AL treatment program and would enhance adherence to therapy.

4.4 Infections

Prevention and curative treatment of infection is one of the most important budget items in AL treatment programs. A prophylaxis of disseminated strongyloidiasis by ivermectin or albendazole should be done in endemic areas. A combination of trimethoprim and sulfamethoxazole should be given in ALL patients to prevent *Pneumocystis jirovecii* pneumonitis. The risk of tuberculosis (TB) reactivation after ALL induction is high in uncompromised patients and has been reported in both ALL and AML. In children with ALL, the incidence of TB has been reported to be 22 times higher than in children from a similar background [23]. In endemic areas, a systematic detection for TB by a tuberculin skin test and chest X-ray is recommended at diagnosis. TB therapy can be safely conducted without delaying chemotherapy. If testing is available, HIV and HBV infections should be detected at diagnosis. Chronic hepatitis B infection can be reactivated by chemotherapy [24]. Vaccination for hepatitis B can reduce transfusion-acquired infection during therapy. If available, HBV therapies can be delivered along with AL treatments. The association of highly active antiretroviral therapy (HAART) and chemotherapy is feasible but requires a cautious evaluation of drug interactions [25]. At diagnosis and during therapy, fever that can be masked by steroids may be the first sign of bacterial infection. Local protocols should be settled for rapid antibiotic decisions

in neutropenic patients [26]. Prophylaxis of bacterial infections should insist on hygiene, with education on dental care using mouthwash and hand washing.

4.5 Psychosocial Support

One of the major causes of treatment failure in cancer is treatment discontinuation [27]. The high cost of treatment that includes the price of hospitalization, of drugs and investigations, and of additional charges including travels to medical centers often worsened by the loss of income for the patients or their parents is a major cause of poor adherence to treatment procedures. The global price of the treatment should be announced to the patient and his or her family at diagnosis. Social support may help patients and/or parents to pay for these additional costs. Palliative care program should be developed to reduce suffering and to improve survival by the development of specialized training and access to opioids [28].

5 Conclusion

Similarly to maximum resource area, treatment of AL in countries with limited resources requires a multidisciplinary approach to provide appropriate diagnosis, infectious disease diagnosis and treatment, transfusion, and psychosocial support. The training of medical and nursing staff should be one of the first steps of collaborative programs that aim to develop AL care for children and/or adult patients. Local recommendations inspired from attitudes developed in developed countries should be adapted to local income level and progressively enhanced together with expertise and resources.

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Part IV
Cancers

Breast Cancer

Temidayo Ogundiran and Clement Adebamowo

1 Introduction

Breast cancer is the commonest cancer in Africa. Though less common than in developed countries, its incidence has been rising in recent decades. There is significant variation in incidence rates across the different geographical locations within the continent. In the year 2012, the IARC estimated age-standardised incidence rates per 100,000 women were the highest in West Africa (35.1), followed by North (34.4) and Central Africa (24.9), respectively. The lowest rate of 19.6 occurred in East Africa [1].

Reviews based on hospital series of breast cancer patients, which were prevalent in the absence of good population-based data, have highlighted the young age at presentation of African patients and confounded this for age incidence and biological relevance. Population-based cancer registry data does not support substantial difference in age incidence of African breast cancer patients compared to other populations [2].

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2 Risk Factors for Breast Cancer in African Women

The risk factors for breast cancer in Africans are similar to those in other populations. The protective effects of lower lifetime endogenous oestrogen levels due to late menarche, early menopause, early childbirth, multiparity and prolonged lactation have been well established from studies in African women. Moreover, postmenopausal obesity, central adiposity, increasing height, positive family history of breast cancer, history of benign breast disease, alcohol consumption and reduced physical activity are positively correlated to the risk of breast cancer in African women [3–10].

Genetic epidemiological studies have identified a diverse spectrum of protein-truncating and non-truncating BRCA 1 and 2 mutations in unselected African breast cancer patients. Some of these genetic mutations were novel and occurred at sites that were previously unreported in people of African descent [11–15]. Genome-wide association studies (GWAS) scan the genome for low-risk alleles that contribute to genetic basis for cancer aetiology. Currently, GWAS for breast cancer risk variants in African women are limited in number and scope. However, emerging reports from such studies provide evidence of discovery of novel breast cancer susceptibility variants in women of African ancestry [16–18]. Altogether, findings from these studies lend support to the role of both high- and low-penetrance genetic alterations in the aetiology of breast cancer in a proportion of black women within and outside Africa.

3 Clinicopathological Features

In the absence of screening programmes, breast cancer and other cancers in Africa present with advanced disease and in the case of breast cancer with palpable tumours, axillary node involvement and distant metastases. This is due to interrelated sociocultural, political, economic and health system factors, as well as low levels of general and health professional education. The demographic pattern of African countries largely explains the young age and premenopausal status of most of breast cancer patients in Africa as well as the relatively high proportion of pregnancy-related breast cancer [19, 20].

Diagnosis is based on clinical assessment and investigations. Many patients are diagnosed with either locally advanced (UICC stage III) or metastatic breast cancer (UICC stage IV) [21, 22]. The minimum imaging modalities should include plain chest radiograph and abdominopelvic ultrasound scanning. Facilities for skeletal scintigraphy are sparsely available in Africa while access to computed tomography and magnetic resonance imaging facilities, where available, is limited by logistics and cost. Pathology services are available in many tertiary centres in Africa. Regionalisation of services will, however, improve access to advanced techniques like immunohistochemistry. See Table 1.

Table 1 Suggested paradigm for breast cancer diagnosis in Africa

Triple test: clinical, USS, Trucut/FNAC
One-day, one-stop triple diagnosis
Incision/excision biopsy as indicated
Mandatory pathology and IHC testing
Staging: CXR, abdominal USS, bone scintigraphy

USS ultrasound scanning, *FNAC* fine-needle aspiration cytology, *IHC* immunohistochemistry, *CXR* chest X-ray

4 Management of Breast Cancer in Africa

4.1 Locoregional Treatment

4.1.1 Surgery

Surgery is the mainstay for primary treatment of breast cancer in Africa. Because of stage at presentation, level of infrastructure, cost of more complex treatments and availability of adjuvant therapies, modified radical mastectomy remains the standard of care for patients with early and locally advanced breast cancer, as well as advanced breast cancer that has been sufficiently downstaged by neoadjuvant treatment. Post-mastectomy reconstruction is not widely practised and patients use external breast prosthesis. Breast conservation treatment may be suitable for a small proportion of women but needs to be used with care so that patients do not receive suboptimal management. Patients with advanced disease are treated symptomatically according to the affected systems of the body.

Fungating ulcerated malignant breast tumours with purulent, malodorous and sloughy floor are common and can be treated with honey dressing and topical application of metronidazole solution (Fig. 1). If they bleed, this can be controlled by radiotherapy or topical application of formalin solution [23].

4.1.2 Radiotherapy

There is paucity of radiotherapy services in Africa. A preponderance of locally advanced cancer and the lack of modern radiotherapy technology limit available services to mainly palliative radiotherapy [24]. Where available, its uses include adjuvant treatment of early and locally advanced tumours, neoadjuvant treatment of advanced cases and treatment of bone and brain metastases. Urgent irradiation of localised metastases in the spine or long bones that are threatening to collapse or fracture may predate systemic chemotherapy in stage IV disease. Radiation therapy is also indicated in selected cases for pain control and for securing haemostasis for intractable bleeding from malignant ulcers.

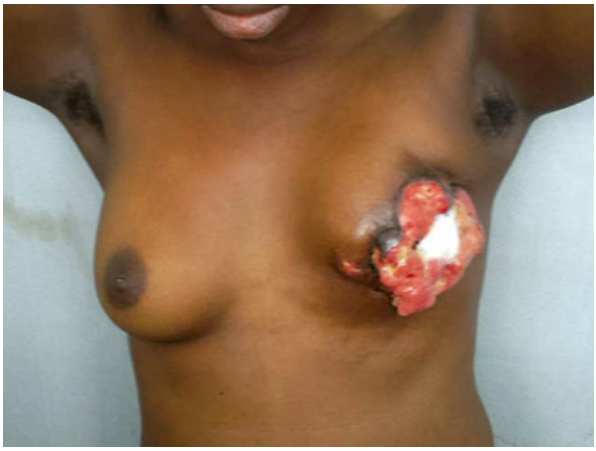

Fig. 1 A young lady with ulcerated fungating malignant ulcer of the left breast

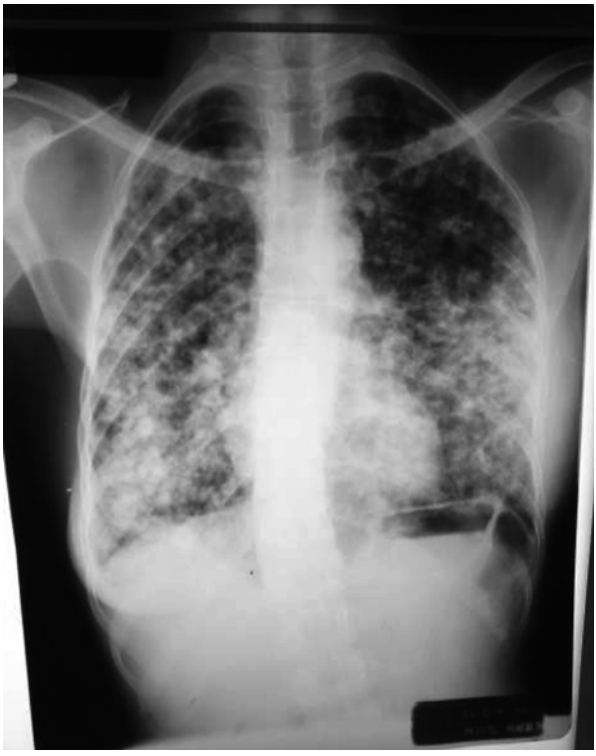

Fig. 2 Plain chest radiograph showing widespread lung parenchyma metastasis from breast cancer

4.2 Systemic Treatment

4.2.1 Chemotherapy

Anthracycline-containing combination regimens are recommended as the first-line adjuvant or neoadjuvant treatment of breast cancer. Taxane-containing combinations, e.g. capecitabine and docetaxel or gemcitabine and paclitaxel, are effective second-line options. They are also recommended for use in patients with extensive or progressing visceral metastases and who have good performance status. Capecitabine monotherapy may be advisable in some elderly patients and in patients who may not require more intensive chemotherapy [25]. In advanced diseases, objective tumour response should be assessed every two or three cycles and treatment changed or discontinued as required. Supportive treatment for complications of chemotherapy, including anti-emetics, should be available.

4.2.2 Endocrine Therapy

Controversy about prevalence of hormone receptor-poor tumours in African breast cancer patients are now largely resolved with carefully controlled studies showing that there is no substantial difference with other populations and majority of patients have receptor-positive tumours. This should increase use of hormone treatments including in cases where tumour receptor status is unknown [26, 27].

For premenopausal women, tamoxifen tablets for a minimum of 5 years are treatment of choice. Ovarian ablation with tamoxifen can be used in those who experience disease progression following previous tamoxifen treatment. Tamoxifen for 5 years or for 2–3 years, followed by aromatase inhibitors, is recommended in hormone receptor-positive postmenopausal women. Continuous aromatase inhibitors for 5 years are advised for postmenopausal women with no prior history of endocrine therapy [28, 29]. Chemotherapy and endocrine therapy should be administered sequentially and not concurrently. As neoadjuvant treatment, endocrine therapy should be the choice in elderly patients with locally advanced or widely metastatic hormone receptor-positive breast cancer.

4.3 Other Adjunct Therapies

Biological therapy with trastuzumab and lapatinib targeted at HER-2 receptors, which are over-expressed in about 20 % of breast tumours where it causes tumour cell proliferation and metastasis, is recommended in HER-2-positive breast cancer. Trastuzumab is indicated in both adjuvant and metastatic settings and is readily available in Africa. However, costs and logistics limit its use in many patients with HER-2-positive breast cancer. Tumour responses in clinical trials of many anti-angiogenic drugs have been highly variable and these drugs are not currently standard of care [30].

4.4 Management of Complications of Breast Cancer

Most African women with breast cancer present in the hospital with either locally advanced or metastatic disease. In many instances, patients present in the hospital for the first time with complications arising from distant metastasis, and these sometimes require emergency surgical intervention. In Table 2 is an annotation of common complications and their management which should be pursued together with the appropriate systemic anti-neoplastic treatment.

4.5 Socioeconomic and Cultural Challenges of Breast Cancer in Africa

Awareness of breast cancer is generally low among the general population and healthcare providers in Africa. The high prevalence of alternative belief models contributes to disdain of "Western" medicine, late presentation and poor outcome. Lack of healthcare financing models for complex diseases imposes heavy out-of-pocket costs on patients and their families. Treatment of cancers drives patients into poverty and the outcome is still unsatisfactory, leading to disillusionment, which feeds further distrust of medical establishment. The woman's pivotal role as the family rallying point is also compromised, with consequent adverse effects on family routines and cohesion. Invariably, some family relationships collapse, leaving behind it a trail of significant social, psychological and emotional morbidity [19].

High levels of stigmatisation and discrimination against cancer patients breed fear and non-disclosure of cancer status even to close family members. This complicates early presentation and compliance with complicated treatment regimens. Late presentation and its inevitable poor outcome reinforce community beliefs about incurability of cancer and the need to seek alternative treatments. Moreover, sub-Saharan Africa still faces major challenges from communicable diseases, malnutrition, infant/childhood illnesses, road traffic accidents and other competing healthcare threats. In spite of these, however, healthcare resources and funding are poor, there are inadequate facilities for diagnosis and treatment, and there are inadequate numbers and distribution of qualified cancer professionals [11].

4.6 Recommendations to Improve Breast Cancer Services and Outcome in Africa

The multimodality management of breast cancer is best provided by an interdisciplinary team of specialists in a designated breast oncology service. However most African countries do not have the resources and are not likely to have relevant

Table 2 Common complications of metastatic breast cancer and their management

Pleural effusion and/or widespread lung parenchyma disease (Fig. 2)
Drainage of effusion by thoracocentesis under aseptic conditions
Closed thoracostomy tube drainage (CTTD) followed with tetracycline-induced pleurodesis
Respiratory support with bronchodilators, antibiotics, steroids, supplemental oxygen and opioid analgesics
Fungating malignant ulcers
Topical metronidazole and honey dressing
Topical dressing with formalin-soaked gauze for multiple-site bleeding
Antibiotics, if there is evidence of systemic infection
Upper limb lymphoedema
Arm elevation
Mild diuretics in early phases
Multilayer bandaging or elastic garments
Pneumatic compression and massage
Control of co-morbidities like hypertension and diabetes mellitus
Meticulous skin care and prevention of infection
Brain metastasis
Steroids to reduce cerebral oedema
Anticonvulsants if indicated
Whole-brain radiation therapy
Surgical excision of resectable solitary tumours in select patients with good performance index and no widespread metastatic disease. This should be followed with whole-brain irradiation
Spinal metastasis
Steroids to reduce inflammatory oedema
Immobilisation if spinal collapse is imminent
Urgent radiation therapy if collapse is imminent
Urgent or emergency surgical decompression if spinal cord compression is imminent or has occurred, followed with radiation therapy
Attention to sphincteric (urinary and faecal) function
Long bone metastasis and pathological fracture
Analgesics
Orthopaedic stabilisation and fixation
Radiotherapy
Pain
Analgesic ladder
Antidepressants
Anxiolytics
Bisphosphonates
Radiotherapy
Involve palliative care team early

resources for decades to come. There is therefore an urgent need to develop care paradigms that take advantage of existing resources and utilise them in innovative ways to provide resource-level-appropriate cancer care. Uncoordinated provision of care by non-specialists at low-volume centres leads to poor outcome and poor utilisation of health resources. African countries need to develop training programmes in oncology that can produce the specialists that would be needed in the near future for the expected increase in cancer cases.

Breast cancer research in Africa lags far behind the rest of the world and has been dominated by single-institution case series. Training, personnel and infrastructure for multisite studies and clinical trials are sorely lacking and these need to be developed.

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Cervical Cancer

Matthys H. Botha

1 Epidemiology

Even though breast cancer is more common in many countries, cervical cancer remains the leading cause of death from cancer amongst women in less developed countries, where it is estimated to cause about 230,158 deaths each year [1]. The highest risk areas are in Central and South America, Southern and Eastern Africa and the Caribbean, where average incidence rates reach 40 per 100,000 women per year [2].

Reasons for the high incidence and mortality in certain geographical areas are linked to poorly developed primary health systems in many areas where uptake of cancer screening with cytology (or other methods) is generally poor. Reasons for the high cervical cancer rate and poor outcome of treatment include the low number of health-care workers per capita, high rates of concomitant HIV infections and competing health-care needs like infectious disease including tuberculosis and malaria. A general lack of patient knowledge and political empowerment leads to a low degree of health-seeking behaviour. Even where cytology screening is available and in those women identified with abnormal cytology, there is often a significant loss to follow-up and failure to receive treatment after the initial abnormal screening test.

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2 Aetiology

2.1 Natural History

Persistent HPV infection with an oncogenic strain of HPV is necessary for the development of invasive cervical cancer [3]. The most important oncogenic viruses seem to be similar in almost all geographical areas. High-risk strains of HPV may integrate viral DNA into the human genome. The onco-proteins E6 and E7 deactivate important processes associated with tumour suppressor genes like p53 and pRb gene functions. HPV is highly infectious and 'most sexually active people will get HPV at some time in their lives' [4].

After first exposure, there is an incubation period of between 1 and 8 months after which the first HPV-related lesions might appear. There is active growth of the virus for a period of between 3 and 6 months, but usually, there are host-immune responses that will, in most cases, clear the infection by about 9 months. The majority of the population will have sustained clinical remission, but a small proportion will develop resistant or recurrent infection and remain HPV-DNA positive on repeated testing [5]. These are the individuals at highest risk for the development of premalignant conditions and later invasive cancer (for more information, see chapter on HPV).

2.2 Anatomy of the Cervix

The outer surface of the cervix is covered with squamous epithelium which is constantly renewed by developing cells forming at the basement membrane. Whilst maturing, the cells move to the surface where they shed and where they can be sampled with a cytology smear. The development of new cells by cell division and the maturation are according to a preprogrammed pattern laid down in the genetic code. When cancer-producing agents like HPV disturb the genetic coding, abnormal cells develop which, after some time, can form a malignant tumour. If abnormal cells are found only within the epithelium, the condition is called a precancerous lesion. Once malignant cells penetrate through the basement membrane into the deeper tissue, the condition is called invasive cervical cancer.

The ectocervical *squamous* epithelium and the endocervical *columnar* epithelium join at the original squamocolumnar junction. In young women, a portion of the exposed part of the endocervical epithelium is replaced by squamous cells in a process called metaplasia. This is a normal physiological process, and usually metaplastic cells are benign. The area of metaplasia is now known as the transformation zone (TZ). Due to the high rate of genetic activity, the TZ is sensitive to exposure to one or more carcinogens which may lead to the process of dysplasia. In such cases, cervical carcinogenesis has started, a process which over time may lead to invasive carcinoma.

Screening for cervical precancer is possible due the time window from the initial HPV infection which may be followed by the appearance of abnormal cells from the TZ.

2.3 Prevention of Cervical Cancer

2.3.1 Primary Prevention

Primary prevention aims to reduce the risk of an individual getting a particular disease by reducing exposure to disease-causing agents from the environment. The most important aetiological factor for the development of premalignant and malignant cervical disease is persistent infection with oncogenic types of HPV infection. Measures like education about safe sexual practices, including mutual monogamy, and barrier contraceptive use (although this is not fully protective against HPV infection) have some role, but behaviour-change programmes have had relatively limited success. Vaccines against HPV infection are available and are the most promising form of primary prevention.

At the time of writing, there are two HPV vaccines available commercially: the bivalent vaccine Cervarix, containing VLP (virus-like particles) antigens for HPV types 16 and 18, and the quadrivalent vaccine Gardasil, containing VLP antigens for HPV types 16 and 18, as well as non-oncogenic HPV types 6 and 11. VLPs are combined with an immune stimulant, called an adjuvant, which leads to an improved immune response.

Both vaccines have been studied in large populations and have been found to be safe and well tolerated [6, 7]. Injection-site reactions such as pain, swelling and redness may occur and are short lived. Systemic adverse events could include fever, nausea, dizziness, fatigue, headache and muscle pain. The HPV vaccines are also well tolerated in boys. It is safe to co-administer the HPV vaccines with other paediatric and adolescent vaccines.

Cost-effectiveness studies have shown universal, female-only, HPV vaccination before exposure, to be an effective and economically viable option in developed countries. There is increasing emphasis on the inclusion of low- and middle-income countries in the drive to reduce the global cancer burden. In order for HPV vaccines to be effective, it must be given before exposure, which is before sexual contact. Studies have shown that the peak incidence of HPV infection occurs in most populations within 5–10 years of first sexual experience. There may be some differences between countries, but in general, most authorities agree that girls around age 11–12, just before leaving primary school, are the most suitable candidates for mass vaccination. High vaccine coverage is needed if significant improvement of cervical cancer rates is to be achieved. Gavi is an international organisation, a global vaccine alliance, which is committed to the provision of vaccines to the poorest nations of the world. Gavi has set the aim to support the immunisation of more than 30 million girls from low-income countries with HPV vaccines by 2020.

Smoking is associated with an increased risk for the development of squamous carcinomas of the cervix and other anatomical sites. Antismoking campaigns like the programme introduced in South Africa is highly effective in reducing many smoking-related diseases including cervical cancer.

2.3.2 Secondary Prevention

Secondary prevention of cervical cancer involves screening for early diagnosis and treatment of precancerous lesions.

Cervical Cytology

George Papanicolaou initially described the examination of posterior vaginal fornix cells to detect precursors for cervical cancer in 1928. Ayre, in 1947, introduced the wooden spatula. Cervical cytology (Pap test) remains a highly effective and trusted screening tool for cervical cancer. Regular cytology smears, combined with treatment of premalignant lesions, can reduce the incidence of cervical cancer drastically if it is used on a high proportion of the entire population. *Opportunistic* screening may be effective in certain populations where patient education and motivation are high, but for a programme to work efficiently, *population-based* screening policy is more suitable. Opportunistic screening tends to over-screen some subpopulations, whilst many others do not take part. In addition, the main target groups are often not well represented.

Liquid-based cytology is a similar technique, where the collected cells are transported in liquid to the laboratory. This method of preparation of cervical cytology may decrease the false-negative rate of standard Pap smears. Liquid-based cytology uses the same principle as the Pap smear, but the technique allows for additional tests, including HPV testing, on the same sample.

In order for cytology to work effectively, a fairly complex health infrastructure is necessary including laboratory services, colposcopy and recall systems. All the steps in the process should be carefully audited on a regular basis. Many authors conclude that this is not achievable in most middle- and low-income countries.

Human Papillomavirus Testing

Technology for the testing of specific human papillomavirus types has improved dramatically. The newest generation of HPV tests is very accurate and will detect low numbers of virus particles in any given sample. Broadly, there are two types of HPV tests, the first being a test for a ‘basket’ of high-risk viruses (hrHPV) (usually 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The other type of HPV test is called genotyping and tests for individual types of HPV. The modern tests use polymerase chain reaction (PCR) and are often completely automated. Genotyping HPV tests are relatively expensive. The first type, the so-called basket test, usually gives a simple yes/no answers for the positivity of high-grade HPV types. HPV

genotyping however is reported on a strip where the different HPV types will create a colour development reaction if present in the sample. It is therefore possible to detect the exact types of HPV present in the sample, even at very, very low concentrations. Some tests now offer partial genotyping for types 16 and 18 due to their high risk.

HPV testing generally has high sensitivity for the detection of premalignant lesions. Even if the specificity is lower than that of cytology, it has an excellent negative predictive value, and the test can be done on dry or wet samples. It is possible that a client self-collects samples for hrHPV in the form of a self-administered vaginal swab or even a tampon.

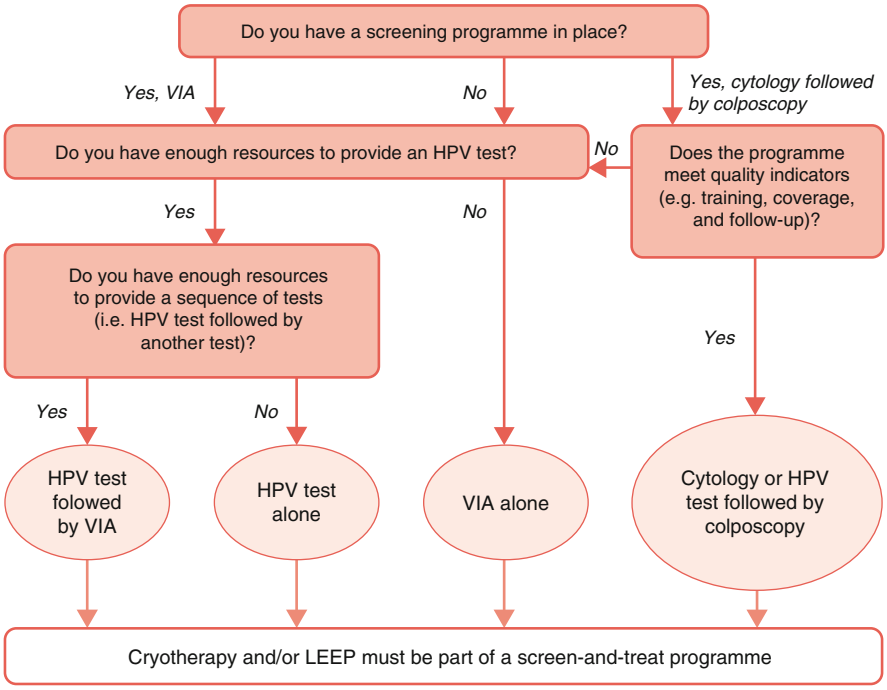
If HPV testing is to be used as a screening tool, it may be more useful after the age of about 30–35 years. If younger women are tested, the incidence of *transient* HPV infection could be high, and the detection rate for true histological abnormalities will be disappointingly low. If, however, older women test positive for HPV, the chances are that they have *persistent* infection with concomitant cytological abnormalities. This will likely become the screening test of choice in a vaccinated population.

Visual Inspection with Acetic Acid (VIA)

Visual inspection (of the cervix) with application of acetic acid can be used to identify early invasive cancers or premalignant conditions. The cervix is visualised during a speculum examination, and a weak solution of acetic acid is applied to stain abnormal epithelial lesions white. Alternative staining methods include Lugol's iodine (visual inspection with Lugol's iodine, VILI). VIA may result in 'downstaging' (detecting the invasive disease at an earlier stage) where simpler forms of treatment may still be given successfully.

VIA is often combined with immediate treatment of the precancer lesions when certain criteria are met. VIA may be used in combination with cryotherapy, and this 'see-and-treat' approach remains a popular option in many lesser developed regions of the world. VIA and treatment with cryotherapy were tested in a large study from India, and it was shown that it can reduce the mortality rate due to cervical cancer by approximately 35 %. This one-stop service eliminates additional clinic visits – an important factor in improving patient compliance as well as in keeping clinic loads manageable.

The World Health Organization (WHO) guidelines for screening and treatment of precancerous lesions for cervical cancer prevention recommend alternative strategies for countries with different resources and health infrastructure [8]. In many countries, VIA on its own or in combination with HPV testing may be the most cost-effective and reasonable strategy for cervical cancer screening.



Manage High-Risk Groups

Another strategy for secondary prevention is to identify *high-risk groups* and to manage them very carefully with regular clinical examination and special investigations. An example of a high-risk group are those patients who are HIV positive. In a study from South Africa, it was found that patients with cervix carcinoma and HIV infection presented 15 years earlier than their HIV-negative counterparts. From other studies, it is clear that patients with HIV infection are at increased risk for the development of intra-epithelial lesions and also have a higher risk for progression towards cancer. HIV-infected women should therefore be followed more closely with regular screening.

2.4 Premalignant Disease

2.4.1 Colposcopy and Conisation

Because cytology, VIA and hrHPV detection are screening tests, the definitive histological diagnosis of premalignant lesions is made on cervical biopsy. The use of the colposcopy allows the clinician to examine the cervix under magnification, and in cases with satisfactory colposcopy, the predictive value of directed biopsies as to

the final histological diagnosis is usually high. If colposcopy is unsatisfactory, biopsies may not be reliable, and diagnostic cone biopsy is often indicated.

Colposcopy is not an exact science and continuous training; audit and review cycles are necessary to keep standards high. Colposcopy is therefore often omitted from programmes in favour of 'see-and-treat' approach. This is a reasonable approach where histopathology is not readily available and where the health infrastructure is limited. Treatment should preferably be loop excision of the transformation zone or, if criteria are met, with ablative therapy of which cryotherapy is the most popular, safe and reliable.

With cold-knife conisation, the TZ and part of the endocervical canal are excised with a surgical knife as a cone-shaped tissue specimen. This procedure was very common a decade or two ago, but should be replaced by LLETZ (large-loop excision of the transformation zone) biopsy which can be performed under local anaesthesia. It is quick, is safe, removes the TZ, allows for healing and has a success rate of 95 % or more in immune-competent persons. In contrast to LLETZ, which only removes superficial tissue, cold-knife conisation may contribute to infertility due to destruction of major portions of the cervix or to later cervical stenosis or incompetence. It is associated with significantly higher rates of post-procedure bleeding.

For patients who have completed their families, for those with other gynaecologic pathology such as fibroids or abnormal uterine bleeding and for patients in whom follow-up will be problematic, vaginal or total abdominal hysterectomy can be offered as definitive therapy for high-grade lesions.

3 Invasive Cancer

3.1 Clinical Presentation

3.1.1 Symptoms

Precancerous changes of the cervix do not cause any symptoms and are not detected unless a woman undergoes a screening test. *Invasive cancer* presents with a wide variety of symptoms that may include offensive vaginal discharge, abnormal menstrual bleeding, postmenopausal bleeding or most commonly post-coital bleeding. Other complications may include recto- and/or vesicovaginal fistulae or it may be simply completely asymptomatic. Significant symptoms usually do not appear until there is deeply invasive disease.

3.1.2 Patterns of Spread

Cervical cancer has local effects and may invade and damage adjacent organs. The parametrial tissues and the rectum and/or the bladder are often involved at time of diagnosis in advanced disease. Metastatic spread to pelvic lymph nodes, bone and lungs usually (but not always) progresses in a stepwise fashion.

3.2 Diagnosis and Staging

Histological diagnosis is mandatory. Ulceration of the cervix may be due to other diseases including tuberculosis, Bilharzia, condylomata accuminata and even rare conditions like tularaemia.

Cervical carcinoma is staged clinically according to the rules of the International Federation of Obstetrics and Gynaecology (FIGO) [9]. Limited investigations are required to assist in clinical staging. Advanced imaging modalities such as X-ray-computed tomography (CT) and magnetic resonance imaging (MRI) scans have improved the ability to detect lymphadenopathy and better delineate local spread. Positron emission tomography-computed tomography (PET-CT) furthermore allows better determination of lymphadenopathy in cervical cancer, but these modalities have not been incorporated into the FIGO staging guidelines as they are not routinely available in developing countries where the burden of this disease falls. Although such tests may be used to plan therapy for individual patients, they are not used to assign the FIGO stage, since they are not universally available and are subject to differences in interpretation. The value of staging is that it directs treatment and suggests prognosis (Table 1).

3.2.1 Histology

The majority of primary cervical cancers are squamous cell carcinomas. Adenocarcinomas often occur higher in the endocervical canal but has similar prognosis and management is the same.

4 Treatment for Cervical Cancer

The decision about treatment for invasive cancer is best decided by multidisciplinary teams represented by gynaecologists, oncologists and radiologists. It is good practice to review histology of selected cases with a dedicated pathologist at a multidisciplinary meeting.

4.1 Surgery

Early invasive cervix carcinoma (up to FIGO stage IIa) may be treated with surgery. The aim of surgery is to preserve normal function and also to ensure complete removal of the tumour with adequate margins. New developments in the surgical management of cervix carcinoma include less radical surgery that may preserve fertility in young patients such as a cold-knife cone biopsy in very early lesions or more complex operations like radical trachelectomy, which entails removal of the cervix whilst maintaining the uterine body, in selected patients. The standard surgery for macroscopic, early cervical carcinoma is a radical hysterectomy with pelvic lymph node dissection. These patients should undergo surgery at a tertiary

Table 1 Carcinoma of the cervix uteri – staging

FIGO stages		TNM categories
	Primary tumour cannot be assessed	TX
	No evidence of primary tumour	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)	T1
IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are stage IB/T1b	T1a
IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread	T1a1
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less[a]	T1a2
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2/T1a2	T1b
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	T1b1
IB2	Clinically visible lesion more than 4 cm in greatest dimension	T1b2
II	Tumour invades beyond the uterus but not to pelvic wall or to lower third of the vagina	T2
IIA	Without parametrial invasion	T2a
IIB	With parametrial invasion	T2b
III	Tumour extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney	T3
IIIA	Tumour involves lower third of vagina, no extension to pelvic wall	T3a
IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney	T3b
IVA	Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis[b]	T4
IVB	Distant metastasis	M1

[a]Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification

[b]Note: The presence of bullous oedema is not sufficient to classify a tumour as T4

referral centre. Inappropriate surgical management may necessitate postoperative radiotherapy and thus increase the risk of associated complications.

4.2 Radiotherapy (RT)

More advanced cancers (stages IIb or greater) are treated by means of radiotherapy, often with concomitant chemotherapy for sensitisation. Radical radiotherapy lasting 6–7 weeks is appropriate for the large majority with 5-year survival after treatment of 35–65 %, depending on stage at presentation.

In more advanced stage 3b patients with bulky disease, bilateral hydronephrosis or impaired renal function, it may be reasonable to offer palliation with a shorter course of radiotherapy. Stage 4a and 4b are generally considered to be incurable, and the aim of palliative RT is to control symptoms such as bleeding or pain. Patients who present with or subsequently develop fistulae (to bowel or bladder) are best palliated by means of surgical bypass procedures if their functional status allows.

Conformal three-dimensional radiotherapy using CT-based planning allows accurate delineation of the tumour and normal tissues. This is available in modern treatment facilities. Intensity-modulated radiotherapy is another technique allowing accurate dosing to tumour whilst limiting dose to normal structures. Unfortunately, these techniques are not standard therapy in developing countries. However, simple techniques can be utilised in a 4- or 2-field arrangement. The target volume should consist of the primary tumour and uterus, parametria and vagina and the regional nodal drainage areas. This requires the whole pelvis to be treated. The dose which can be delivered is determined by the tolerance of the small bowel, bladder and rectum.

Multiple studies have demonstrated an absolute improvement in survival of around 12 % with chemosensitisation when administered concomitantly with radiotherapy compared to radiotherapy alone. Controversy exists as to the magnitude of the benefit in locally advanced disease as the majority of the patients accrued to these trials in the developed world represented surgically staged patients with earlier disease. A reasonable approach in the developing world is weekly cisplatin administration which is inexpensive and easily administered on an outpatient basis.

Intracavitary radium treatment had long been used in the treatment of cervical cancer. The techniques have evolved over time, but improvements have largely occurred as a result of our understanding of fractionation and radiobiology. The applicators available are still similar to the initial applicators used by the pioneers of this technique allowing the radioactive source to be introduced into the uterine canal and vaginal fornices with rapid dose fall-off sparing surrounding normal structures. The use of new, safer radioisotopes is standard. Obtaining sources and maintaining brachytherapy equipment is often a tremendous challenge in lower-income countries, and brachytherapy may not be available. A higher dose of external beam radiation to the centre of tumour may be a reasonable alternative.

In advanced disease where symptom control (e.g. bleeding or severe pain not responding to medical therapy) is required, treatment by large single fractions can bring rapid and long-term relief.

Radiotherapy remains an extremely scarce resource in many regions of the world. Only 23 out of 52 African countries offered external beam radiotherapy in 2010, and brachytherapy resources (high-dose rate [HDR] or low- dose rate [LDR]) were only available in 20 of the 52 [10]. In these circumstances, shorter courses of radiotherapy (with larger fractions) may be justifiable.

4.3 Cancer in Pregnancy

Treatment for premalignant disease can often be delayed to after confinement. Where invasive cancer is suspected, a biopsy is necessary but there is a significant risk for abnormal bleeding. Small-cone biopsies (avoiding the membranes) can be performed, and a haemostatic cerclage is often necessary to control bleeding.

When locally advanced invasive cancer is present, a conservative approach is reasonable if there is a firm desire to continue the pregnancy. Radical caesarean section hysterectomy can be performed after viability. Neoadjuvant chemotherapy may be an option to allow the pregnancy to progress to viability (around 30–32 weeks). Caesarean section is the delivery route of choice with bulky tumours.

4.4 Incidental Cancer Diagnosed During Hysterectomy

In places where routine screening is not available, patients are often diagnosed with invasive cervical carcinoma during or after simple hysterectomy. Where micro-invasive carcinoma (stage 1a) is detected, no further management is necessary. For all other patients, postoperative chemoradiation is indicated.

4.5 Pyometra

In bulky or recurrent tumours, blood (haematometra), mucus (mucometra) or pus (pyometra) may accumulate in the uterine cavity. This could be drained by dilatation of the cervix, which may be repeated if necessary. Antibiotics may also alleviate symptoms.

4.6 Acute Haemorrhage

Cervical tumours often bleed profusely, especially in cases with large and infected lesions. Packing with gauze may help in the acute situation. The gauze may be impregnated with saline, acriflavine or tranexamic acid solution, but none of these solutions have been shown to be superior. Caustic agents like acids, formaldehyde or trichloroacetic acid should be avoided. Antibiotic cover often helps to address the associated infection and the pack may be replaced after 24–48 h. After packing, pelvic radiotherapy should be started as an emergency procedure. Control of the bleeding can usually be obtained within days.

Other emergency measures such as pelvic vascular ligation and arterial embolisation can be used if the above management is not successful and the expertise is available.

4.7 Severely Offensive Discharge

The necrotic nature of a large tumour often leads to very pronounced offensive vaginal secretions. In combination with fistulae, the discomfort to the patient and her immediate caretakers and family can be overwhelming. Chronic low-dose administration of antibiotics (e.g. doxycycline 100 mg daily) may suppress the bacterial activity somewhat and lead to some improvement. If a patient is cared for in an enclosed space, a saucer with vanilla essence on the windowsill is a good way to mask some of the unpleasant odours.

4.8 Palliative Care

See chapter on palliative care for advice on pain control.

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Cancer of the Oesophagus

Joseph Brown Kigula-Mugambe and Awusi Kavuma

1 Introduction

The oesophagus extends from the cricoid cartilage (C6 level) to the stomach. It is about 25–40 cm long (from the incisors) and is divided into the upper third (C6–T5), middle (T5–T10) and lower third (T10 to the stomach). The malignancy may originate in the squamous cells or the columnar cells of the oesophageal mucosa. The lymphatic drainage follows arterial supply: upper third to the deep cervical nodes, middle third to the posterior mediastinal and lower third to the left gastric and coeliac nodes. Treatment modalities include surgery, radiotherapy, chemotherapy or some combination of these; however, long-term survival remains poor regardless of method of treatment with 5-year-average survival rate of only 17 %.

2 Epidemiology and Aetiology

According to the 2012 world cancer statistics, oesophageal cancer is the eighth most common cancer, accounting for nearly 460,000 (3 %) new cancer cases globally, and 80 % of these occur in less developed countries [1–4]. It mainly affects people over 60 years, with the average age at diagnosis being 72 [3]. The male-to-female ratio is 2.4:1 [4]. Several risk factors have been identified including heavy consumption of alcohol and tobacco usage over a long period of time, which independently

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increases the risk of oesophageal squamous cell carcinoma (SCC). A combination of these two factors upsurges the risk even further. Barrett's oesophagus where chronic gastroesophageal reflux disease (GERD) damages the oesophageal mucosa is the primary risk factor for adenocarcinoma (ADC) [5]. Evidence of an association between environment and diet with oesophageal cancers comes from the profound differences in incidence observed in various parts of the world, much higher in Asian countries like China, Japan and Middle East countries where the incidence is 22/100,000 [1, 6] compared to the USA where it is 4/100,000, raising to rates 20–30 times higher in China compared to the USA [3, 4].

3 Clinical Presentation

Early oesophageal cancer rarely causes any symptoms. Symptoms start to develop only when oesophageal lumen is reduced to a critical size. Symptoms and signs include the following:

- Dysphagia which is the cardinal presenting symptom, initially for solids progressing to fluids.
- Regurgitation and vomiting may follow.
- Weight loss occurs in more than 50 % of patients due to malnutrition and dehydration.
- Epigastric and chest pain as a result of disease spread may follow.
- Hoarseness of the voice caused by laryngeal nerve invasion is a late sign.
- Persistent non-productive and irritative cough or haemoptysis should prompt an investigation.
- Internal bleeding from the tumour may occur.

4 Investigations

A clinical evaluation including history, examination, baseline blood tests like complete blood count, renal/liver function tests and performance status assessment helps in deciding to manage the patient with curative or palliative intent. Recommended investigations include the following [7, 8]:

1. Upper gastrointestinal endoscopy and biopsy provide direct visualisation of the oesophageal mucosa, evaluation of extent of gross disease and allow biopsy of any suspicious areas. Abnormalities to note include hyperaemia, mucosal irregularity, ulceration and/or a frank mass with constriction of the oesophageal lumen. Balloon cytology, where no mucosal irregularities are identified, allows mucosal samples to be taken.
2. CT scans of the thorax and upper abdomen offer initial adequate metastatic workup and can be used to assess the local tumour invasion and node involvement

for the TNM staging. CT scan of the pelvis or brain may be done if there is clinical indication.
3. Endoluminal ultrasound (EUS) offers the best information on the depth of invasion and lymph node involvement which is also useful for the TNM staging.
4. Panendoscopy to exclude spread to adjacent structures may also be done. A PET and MRI imaging of the abdomen may offer additional information in the metastatic workup.
5. In low resource setting where a CT scan and EUS may not be easily accessible, the following line-up is useful:
   (a) Barium swallow (where an endoscope is unable to pass) will establish tumour site, length and degree of narrowing of the lumen and may demonstrate fistula formation.
   (b) Chest radiograph to exclude lung metastases and mediastinal widening.
   (c) Abdominal ultrasound to exclude liver metastases, lymph node involvement and ascites.
   (d) If the above tests indicate local regional disease, a chest CT scan and EUS may then be done for a more detailed TNM staging.

5 Pathology

The two predominant histological types are SCC and ADC. Other rare tumours include adenoid cystic, mucoepidermoid, adenosquamous and undifferentiated carcinomas contributing to less than 1 %. The histological classification has rapidly changed over the past 2–3 decades in the West. Previously, SCCs were making up to 90 % and the ADC 10 %. ADC now contributes 40–70 % in the USA and Western Europe with most of them located at the esophagogastric junction (EGJ). The biopsy/resection report should include degree of dysplasia, histological subtype, tumour grade, depth of penetration and involvement of adjacent structures, lymph node involvement and resection margins [7–9]. The TNM staging (AJCC 7th edition, 2010) [10] and Clinical Stage Grouping/Prognostic Group are shown in the Tables 1 and 2, respectively.

6 Treatment

The management decision should be taken by a multidisciplinary team consisting of surgical oncologists, gastroenterologists, radiation and medical oncologists, palliative care physicians, radiologists and pathologists after staging, performance status evaluation and patient's consent. The treatment options include surgery or external beam radiotherapy (EBRT) or chemotherapy alone, concurrent chemoradiotherapy (CRT), pre- or postoperative CRT, adjuvant chemotherapy and best supportive care. Surgery alone is an option for small tumours but is contraindicated in many patients

Table 1 TNM staging (AJCC 7th edition, 2010) [10]

T – tumour		N – node		M – metastases	
Tx	Primary tumour cannot be assessed	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis		
Tis	Carcinoma in situ/high-grade dysplasia	N1	1–2 regional lymph nodes (N1 is site dependent)	M1	Distant metastasis
T1	Lamina propria or submucosa	N2	3–6 regional lymph nodes		
T1a	Lamina propria or muscularis mucosae	N3	More than 6 regional lymph nodes		
T1b	Submucosa				
T2	Muscularis propria				
T3	Adventitia				
T4	Adjacent structures				
T4a	Pleura, pericardium, diaphragm or adjacent peritoneum (resectable tumour)				
T4b	Other adjacent structures (e.g. aorta, vertebral body, trachea) – unresectable tumour				

Table 2 Clinical stage grouping/prognostic group

	Squamous cell carcinoma					Adenocarcinoma			
Stage	T	N	M	Grade	Location	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X	Any	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1, X	Any	T1	N0	M0	1–2, X
1B	T1	N0	M0	2–3	Any	T1	N0	M0	3
	T2-T3	N0	M0	1, X	Lower, X	T2	N0	M0	1–2
IIA	T2-3	N0	M0	1, X	Upper, middle	T2	N0	M0	3
	T2-3	N0	M0	2–3	Lower, X	–	–	–	–
IIB	T2-3	N0	M0	2–3	Upper, middle	T3	N0	M0	Any
	T1-2	N1	M0	Any	Any	T1-2	N1	M0	Any
IIIA	TI-2	N2	M0	Any	Any	T1-2	N2	M0	Any
	T3	N1	M0	Any	Any	T3	N1	M0	Any
	T4a	N0	M0	Any	Any	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any	Any	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any	Any	T4a	N1-2	M0	Any
	T4b	Any	M0	Any	Any	T4b	Any	M0	Any
	Any	N3	MO	Any	Any	Any	N3	M0	Any
IV	Any	Any	M1	Any	Any	Any	Any	M1	Any

Histologic grades: *X* grade cannot be assessed – stage grouping as G1, *G1* well differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *G4* undifferentiated, stage grouping as G3 SCC

because of severe comorbidities (e.g. cardiovascular/respiratory disease), mediastinal and adjacent structure invasion (e.g. nodes, recurrent laryngeal nerve, tracheobronchial tree, aorta, pericardium), inaccessible lesions, lesions longer than 3–5 cm and distant metastases. Radiotherapy is mainly indicated for SCC of the cervical, upper and mid-thirds, while surgery is indicated for the lower third where ADC is predominant. For medically fit patients, CRT is followed by surgery. Tumours at the EGJ are sometimes treated with chemotherapy (without EBRT) followed by surgery. Patients are classified into those who are fit for surgery, unfit for surgery (or those who decline surgery) but fit for CRT and those unfit for both surgery and CRT. The RTOG 8501 randomised trial demonstrated a significant benefit of concurrent cisplatin and 5FU compared to RT alone, indicating a 5-year survival rate of 26 % versus 0 %, respectively [11]. Surgery results in 5-year survival rates of up to 30 %. The 5-year-average survival rate for different stages and treatment modalities is only 5–17 % [4, 12].

Oesophagectomy (minimally invasive or transhiatal/thoracic oesophagectomy) and lymphadenectomy should be considered for patients with localised, thoracic and EGJ cancers. Tis and T1aN0I tumours can be treated by endoscopic therapy (mucosal resection or submucosal dissection) utilising EUS. Oesophagectomy is recommended for T1b and T2. This may be followed by CRT depending on histological types, resection margins and nodal status. For stages II–III, CRT is followed by surgery (trimodality therapy), or definitive CRT is done. For stage IV, palliative chemotherapy or radiotherapy and best supportive care are the options.

Chemoradiotherapy: This may be neoadjuvant therapy, definitive CRT or sometimes postoperative CRT. CRT is the first option for cervical cancers. EBRT alone should be reserved for palliation or patients who cannot tolerate CRT. The RT dose ranges are 41.4–50.4 Gy for preoperative, 45.0–50.4 Gy for postoperative and 50.0–50.4 Gy for definitive RT, delivered at rates of 1.8–2.0 Gy per day. Doses of more than 60–70 Gy in 7 weeks have been given with no improvement in overall survival. The use of 3D conformal radiotherapy that utilises CT simulation is the standard treatment planning procedure. IMRT and IGRT have been used; however, their benefits over 3D conformal radiotherapy are better in target conformity and sparing of surrounding normal tissues [12, 13]. The GTV includes the primary tumour and involved regional nodes; the CTV includes microscopic disease and elective lymph nodes (e.g. coeliac), while the PTV includes the primary tumour plus 5 cm proximal and distal margins and a radial margin of 1.5–2.0 cm. Where 3D conformal radiotherapy is unavailable, 2D conventional simulator planning with a barium swallow can be used. Critical organs and their respective tolerance doses include spinal cord (45 Gy), lungs (20 Gy to 20 %), liver (30 Gy), heart (50 Gy to 30 %) and kidneys (20 Gy to one kidney) [14, 15].

The standard chemotherapy combination is 5FU and cisplatin. Cisplatin is administered with a dosage of 75–100 mg/m^2, IV over 4 h with pre- and post-hydration on day 1 and day 29. 5FU is administered with a dosage of 1 g/m^2 on day 1–4 and day 29–32, continuous infusion over 24 h (if possible) or IV bolus. The first two cycles are given with EBRT and the other two cycles after RT. Other combinations include oxaliplatin and 5FU, cisplatin and capecitabine, oxaliplatin and capecitabine or

taxane-based combinations, etc. In a metastatic setting, targeted therapies with trastuzumab (if the cancer is HER2 positive) and taxanes can be considered.

Late presentation is common even in the West where only 30 % of patients are fit for curative resection, and approximately 70–80 % of these would have involved lymph nodes which are associated with poor prognosis. The late presentation problem is even worse in the less resourced countries where more patients present with advanced disease, only fit for best supportive care, including palliative radiotherapy, stenting, chemotherapy and laser therapy.

7 Palliative Management

For patients with advanced disease where cure is deemed impossible, palliation is the main objective. Symptoms requiring palliation are dysphagia, pain, drooling of saliva, nausea, vomiting and bleeding [15–19].

Dysphagia: Interventions aimed at allowing swallowing of food include bougie dilatation alone or prior to stenting, stenting with expandable metal mesh or plastic stent, palliative external beam RT, brachytherapy and pharmacological measures. Many patients develop reflux symptoms after stenting and are advised as follows: eat small frequent meals; remain upright for about 1 h after eating; elevate the bed when sleeping; avoid heavy physical work; cook food until soft, mashed or mixed with soup; and eat slowly and take sips of water between mouthfuls. Distal migration of the tube and tumour ingrowth/overgrowth are complications of stenting. Aspiration of oesophageal contents can lead to choking and possibly aspiration pneumonia. Insertion of an enterogastrostomy or a percutaneous enterogastrostomy (PEG) tube can assist in feeding and strengthen the patient prior to more intensive treatment such as surgery or CRT. Where surgery is anticipated, an enterostomy tube is preferred to a gastrostomy tube as this may interfere with gastric mobility. Helpful drugs include dexamethasone (4–12 mg in the morning), with either nystatin 100,000 units/ml, 1–2 ml tds, or ketoconazole 200 mg daily for 7 days. Palliative radiotherapy is delivered with either EBRT or brachytherapy. The dose and fractionation depends on the performance status, prognosis and field length to be irradiated. The dose ranges from 8 Gy/1 fraction, 20 Gy/5 fractions, 30 Gy/10 fractions, etc. A recent retrospective review of 114 patients in a single institution did not show any significant difference in palliation of dysphagia between the above three regimens [19]. Doses of brachytherapy are either 16 Gy/2 fractions or 18 Gy/3 fractions [12, 15].

Painful swallowing (*odynophagia*): Discomfort or pain ranging from mild to severe may be felt retrosternally, in the neck or between the shoulder blades. The WHO analgesic ladder for somatic pain and above options for dysphagia may be helpful.

Anorexia: To improve appetite, low-dose steroids, e.g. dexamethasone 2 mg orally od or prednisolone 10 mg orally od and multivitamins, can be helpful.

Drooling of saliva, choking sensation and vomiting: Anticholinergic drugs can relieve excessive salivation or drooling. Hyoscine butylbromide SC 10–20 mg bd–tds;

amitriptyline 12.5 mg od or bd orally; antihistaminic antiemetics, e.g. cyclizine 50 mg tds subcutaneously or orally; and oral morphine 2.5–5 mg/2.5–5 ml 4 h may also be used.

Bleeding: Palliative radiotherapy or endoscopic (laser, cautery) management may be useful.

Psychosocial aspects: In addition to physical symptoms, psychological, social and spiritual issues of patients and their families have to be addressed. These include anxiety, low self-esteem and spiritual issues like fear of death and what happens after death. The patient and family may find comfort in prayer and counselling from their religious leaders.

8 Conclusion

Most of the patients presenting in low resource settings present with advanced disease and are unfit for curative treatment of a combined surgery and CRT which offers long-term survival in some patients. These patients may however have an improved quality of life from well-planned palliative interventions that provide symptomatic relief resulting in a sensation of well-being, improved nutritional status and sometimes prolongation of life.

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Gastric Carcinoma in Developing Countries

Oludolapo O. Afuwape

Background: Gastric cancer is one of the commonest causes of cancer-related death even in developing countries. The challenges associated with the treatment of gastric cancer are related to factors such as late presentation, reduced access to appropriate investigative tools and lack of funds for treatment. Surgery remains the most feasible treatment modality in developing countries. The outcome is dismal. Early detection, adequate treatment and proper follow-up will improve treatment outcome.

I. Gastric cancer ranks as the fourth most common malignancy in the world [1]. Although the incidence is highest in developing countries, current data suggests a decline in the incidence in developed countries [2, 3] with relative increase in the incidence in developing countries with Africa inclusive. Approximately 60–72 % of new cases occur in developing countries [4]. There is relatively lower prevalence in sub-Saharan Africa compared to countries like Uganda, Congo and Rwanda [5–7]. There is a strong association with low socioeconomic state and gastric cancer.

II. Aetiology

Gastric carcinogenesis is complex multifactorial sequence. Although poverty is not a risk factor, it is surrogate for many other conditions such as nutrition, inadequate food preservation and smoked foods which are factors prevalent in developing countries. Alcohol and smoking have been implicated among other risk factors. While *Helicobacter pylori* colonisation of the gastric mucosa has been implicated as a risk factor for gastric cancer, this relationship is modified by exposure and interaction with other factors.

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1 Clinical Symptoms and Signs

Patients in low-income countries with dyspeptic symptoms are often managed solely based on clinical examination because access to radiological and basic endoscopic facilities is not readily available. Consequently, these patients present later with advanced gastric cancer. Frequent symptoms at presentation are epigastric mass, obstructive symptoms (vomiting) and weight loss on a background history of recent onset of dyspeptic symptoms, anaemia and ascites.

The challenge and limitations of gastric cancer management in developing countries emanate from a combination of factors. These are:

I. The lack of screening programmes for early diagnosis
II. Late presentation
III. Limited access to investigative facilities and subsequent inability for curative rather than palliative surgery [8]

2 Diagnosis

There is no routine screening programme for gastric cancer currently. However, upper gastrointestinal endoscopy (UGIE) and double-contrast barium meal may be routinely performed in asymptomatic patients with dyspepsia of recent onset though the yield may be low in early gastric cancer.

UGIE is not as readily in many secondary centres, and often by the time patients go up the referral pathway, reasonable time is lost before diagnosis. Other ancillary endoscopic diagnostic tools such as narrowband imaging, chromocytography and endoscopic ultrasonography are rare thus reducing the yield in early gastric cancer. Nevertheless, UGIE provides direct visualisation of gastric mucosa, allows biopsy of suspicious areas and evaluation of anatomical extent of gross disease and assists in planning.

3 Double-Contrast Barium Meal

Barium meals are useful in the diagnosis of structural and motility abnormalities. Masses and mucosa defects are outlined, while infiltrative lesions are suggested by narrowing and rigidity of the stomach; however, these features may overlap.

4 Other Staging Investigations

The routine use of diagnostic laparoscopy, computerised tomogram (CT) scan, magnetic resonance imaging (MRI) and bone scans (skeletal scintigraphy) when available assists in staging and planning surgery. Patients require a full blood count,

urea and electrolytes, liver function tests, abdominopelvic ultrasound in the absence of a CT and baseline chest x-ray prior to surgery.

5 Pathology

In various publications, the commonest histological subtype is adenocarcinoma which accounts for 80 % and above [9]. Other histological types such as leiomyosarcoma, lymphoma, gastrointestinal stoma tumours (GIST), etc. all constitute about ten percent of the histological diagnosis. Eighty percent of the tumour is in the antrum. The high prevalent rates of *Helicobacter* in Nigeria are not reflected as a causative factor in the relatively low incidence of gastric cancer in Africa. However, more than 50 % of the subtypes are of the intestinal type.

Factors which affect treatment modalities are:

I. The anatomical site, stage and size of the disease
II. The overall status and performance index of the patient [8]

6 Symptoms at Presentation

Gastric cancer is difficult to diagnose early because there is usually a time lag between the onset of the disease and the manifestation of symptoms. The commonest symptoms are easy satiety, vomiting, weight loss and epigastric mass. Others are haematemesis, tiredness and weakness and epigastric pain of recent onset [9, 10]. Broadly, patients may be grouped into two categories, i.e. early and late, for the purpose of planning treatment.

7 Treatment

Cancer of the stomach is difficult to cure unless it is diagnosed at the early stage. The optimal appropriate treatment for early gastric cancer is not clear. Unfortunately, as early stomach cancer causes few symptoms, the appropriate diagnosis is usually at the advanced stage. Consequently, surgery (palliative) plays the dominant role in the treatment with adjuvant combination chemotherapy. Although there is an increasing incidence of proximal gastric carcinoma, antral tumours are still the commonest location necessitating partial or subtotal gastrectomy. Total gastrectomy may be considered in exceptional cases [11]. The response to chemotherapy is suboptimal. Responses to chemotherapy have been reported in up to 60 % of patients in phase II trials; however, drug resistance developed within few months with median survival of treated patients usually ranging from 7 to 9 months. Despite these findings, chemotherapy should be offered to all patients with metastatic gastric cancer in good general conditions. There is potential benefit of chemoradiation schedule

after palliative and curative resection. Although targeted therapy has been successful in breast cancer treatment, the same outcome is not reproducible in gastric cancer. This is because of the low prevalence of HER-2/Neu and other epidermal growth factors in gastric carcinoma [12]. Monoclonal antibodies have only demonstrated very modest improvement in outcome. They are not readily available in developing countries.

8 Outcome

The overall survival rates vary. However, the average 1-year and 5-year survival figures for patients who present early enough to have gastrectomy done are 70.1 % and 21.8 %, respectively [13]. This may be explained by the predominance of the intestinal over the diffuse type.

9 Conclusion

Prevention and early diagnosis seem to be the most effective tools in improving outcome in gastric cancer. The location of appropriate diagnostic tools only in the metropolis combined with the high cost of these procedures hinders early diagnosis.

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Colorectal Cancer

David O. Irabor and Olufunsho A. Adedeji

1 Introduction

The effective treatment of colorectal cancer (CRC) in developing countries is hampered by the frequent advanced state of the disease when the patient presents to a tertiary hospital [1]. Whether this is as a result of unusually aggressive tumours, late presentation or both factors are yet to be conclusively determined. The quality of colorectal cancer incidence and outcome data is very variable worldwide [2] (Ferlay et al.), and this limits the accuracy of epidemiological data from developing countries especially sub-Saharan Africa.

2 Incidence

Incidence in sub-Saharan Africa is estimated at 4.04 per 100,000 population with males slightly more affected than females (4.38 for men and 3.69 for women) [3]. In Asia, the incidence rate in males varies from 4.3 per 100,000 (3.4 for females) in India to 19.1 per 100,000 (15.6 for females) in Indonesia [4], uniformly low in all South Asian countries and high in developed Asian countries. In Brazil, this is estimated at 15 per 100,000 in males and 16 in women [5]. In Nigeria, the age range is 11–94 years with an average age between 43 and 46 years; a significant proportion, 23–48 %, is below the age of 30 years [6]. The average age is similar to that of 47 years in India

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where up to 38 % of the patients are younger than 45 years [7]. In direct comparison, Nigerian patients (52 years) were younger than Americans (59 years) [8].

3 Geographic Incidence

Similar to the geographical variation of CRC seen in the USA [9], there seem to be differences in the incidence of reported cases in the various regions of Nigeria with rates higher in metropolitan cities like Lagos and Ibadan in the southwest and much lower as one moves eastwards (ethnic Igbo), south-south (Rivers/Bayelsa states) and northwards (ethnic Hausa/Fulani) [10]. However, in the absence of population-based registries, it is difficult to know if these differences are real or as a result of sociocultural or economic factors, unlike India where the intracountry variation is not significant for CRC but is striking for other malignancies like stomach and gall bladder cancer which have significant North-South differences [4].

4 Aetiology

It is most likely sporadic in Nigeria where there is a rarity of inflammatory bowel diseases, polyps and inherited syndromes [11, 12] unlike other developing countries like India and Brazil where polyps and inherited syndromes may account for up to 6 % of all CRC. Lifestyle and dietary causes may be responsible for over 66 % of CRC in the developing countries [4, 13]. In view of a significant proportion of young black patients with CRC, it seems CRC in young patients may likely develop through the accumulation of mutations, probably via mismatch repair deficiency or promoter methylation [14]. In Nigeria, the effect of dietary heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) cannot be ruled out because of widespread smoking and deep-frying of meat and fish, due to lack of refrigeration from poor electricity generation [15] and the bad practice of singeing cattle hides with used engine oil, plastics or tyres at many abattoirs in the country [16].

5 Clinical Features

Colon cancer patients present with abdominal pain and abdominal mass (70 %), while rectal cancer patients present with rectal bleeding (100 %), tenesmus (73.5 %) and a palpable mass (80 %) during digital rectal examination [17, 18]. The ratio of rectal cancer to colon cancer is roughly 1.5:1 [6]. This means that more rectal operations are to be expected [4, 6, 7].

6 Making the Diagnosis

This is not much of a diagnostic as much as a therapeutic challenge. By the time a history of abdominal pain, abdominal mass, weight loss and easy fatigability (for colon cancer) or post-defecation bleeding and tenesmus (for rectal cancer) is obtained, you have a fairly certain diagnosis. Specific investigations available include colonoscopy or barium enema (each procedure is roughly the equivalent of $200; majority of Nigerians (70 %) exist on less than $2 a day) [19]. For those who present for surgery, preoperative investigations like full blood count (FBC), cross-matching of blood, chest X-ray, E&U and an ultrasound scan (USS) for liver secondaries, presence of ascites, etc. are also done. Carcinoembryonic antigen (CEA) assay is done occasionally when reagents are available at the labs; however, its usefulness is probably academic and maybe for follow-up. National CRC screening programmes are not yet established in many developing countries.

7 Preoperation Workup

It is useful for a 'double-informed consent' to be obtained before embarking on an abdominoperineal excision of the rectum (APER). This simply means the patient and his/her spouse (or any other significant person in the family preferably senior in the hierarchy) have to be fully aware of the permanence of the colostomy and any other significant sequelae of the operation. (Marriages have broken where the other spouse does not fully comprehend the result of APER.)

The patient is admitted and bowel preparation (with enema saponis as integral component) is instituted, usually a 3-day preparation. Mechanical washouts are still used in our practice.

Those with anaemia (PCV < 30 %) will undergo blood transfusion. Nutritional status is assessed although this seldom stops or delays operative procedures.

For patients with rectal cancer, a biopsy is taken. Rectal biopsy is important in patients with suspected rectal cancers to exclude benign causes like amoebic granulomata, lymphogranuloma venereum, schistosomiasis and tuberculosis although these are rare. However, the time waiting for biopsy results usually delays treatment (see turnaround time (TAT) of pathology department below), so this is better done as an outpatient procedure. The patient is admitted when the histopathology report has been seen and options of surgery discussed and accepted.

8 Operation Findings

Once the surgeon is within the peritoneal cavity, the sites where lesions are likely to be encountered are in the caecum, sigmoid colon and the rectum.

Studies have shown the percentage of lesions located in the caecum to be from 6.9 to 21.5 %, ascending colon 2.8–10.3 %, hepatic flexure 2.5–10.3 %, transverse

colon 2.2–6 %, splenic flexure 2.1–3.9 %, descending colon 2.5–6.3 %, sigmoid colon 3.6–40.9 % and the rectum 27.6–66.7 % [1, 6].

Many of these tumours will be advanced with published reports showing that 50–81.5 % will fall in to Duke's C and D [11, 20, 21]. Thus, it is reasonable to assume that most of the patients you will operate on have metastatic disease.

9 Treatment: Emergency or Elective

Some colon cancer patients may present with large bowel obstruction (3–33 %) [6]. For such patients, investigations are limited to plain abdominal X-ray, FBC, E&U and sufficient resuscitation to get them ready for an emergency exploratory laparotomy.

The colonic tumours that obstruct are usually left sided; thus, any resection performed usually will include a colostomy (Devine or Hartmann's).

Rarely, patients with rectal carcinoma may present with large bowel obstruction. Such patients benefit from emergency sigmoid loop colostomy. Options of APER or sphincter-saving resections (SSR) will be contemplated after the patient recovers from the acute episode and is re-evaluated.

For patients with colon cancer which is not obstructed, it is acceptable to perform an exploratory laparotomy without any imaging (i.e. ultrasound scan, colonoscopy or barium enema) once an abdominal mass is palpable. In a resource-challenged setting, you kill three birds with one stone (laparotomy); the resected specimen provides histopathological information, exploration confirms or excludes synchronous tumours, and the liver is palpated directly for metastases. The occurrence of synchronous tumours is rare [11, 22].

Majority of patients (69–80 %) have the rectal malignancies in the middle and distal thirds [7, 15, 17]. This means general surgeons in sub-Saharan Africa and India have to be skilled in APER.

Do not expect that all the patients diagnosed with rectal cancer will turn up for APER; indeed, the attrition rate is up to 60 % [1]. Be prepared to accept refusals for APER from many patients (10–30 % [7, 18]).

10 Available Options of Treatment

- Synchronous combined APER (Miles operation). Probably the most frequent of operations done for rectal cancer [4, 6, 7, 18]. In a few advanced cases, this is facilitated by neoadjuvant chemoradiation. It presents problems of a permanent colostomy and also postoperative erectile impotence. A few patients have benefitted from sphincter-saving resections (SSRs) like low-anterior resection using stapling devices [23]. The obstacle to its frequent employment is that it adds approximately $1,000 to the operation costs and thus cannot be accessible to the majority.
- Colonic tumours are resected as published in standard-operating textbooks. Laparoscopic resections of the colon are not yet established.

- Low-anterior resection for proximal and middle thirds rectal lesions. Surgeons should be adept at performing hand-sewn anastomosis for low-anterior resection deep inside the pelvis; this is usually a one-layered sigmoidorectal anastomosis using 2–0 Vicryl by the parachute method [24].
- In selected patients with rectal cancer who have complete clinical response after neoadjuvant chemoradiation, a 'watch-and-wait' approach has been encouraged in Brazil where studies have shown that up to 50 % have sustained remission after 12 months [25]. Hopefully, this may encourage Nigerian patients to show up for treatment.

11 Intra-Hospital Obstacles

The turnaround time (TAT) of the pathology department, i.e. the time interval between submitting the specimen (whether biopsy or operative) and obtaining a pathology report, an average of 15 days, is too long in our institution [1]. This delays commencement of surgery or adjuvant treatment. Getting the patient on the radiotherapy (RTH) table on time may be difficult because of frequent machine breakdowns from oversubscription by patients from all over Nigeria. It is on record that due to the dearth of radiotherapy centres in Nigeria, one megavoltage machine serves a population of 19.4 million people [26].

12 Adjuvant Treatment

Combination chemotherapy with FOLFOX or FOLFIRI is now recommended. In the recent past, 5-FU with oral levamisole was instituted. Probably less than 50 % of patients start chemotherapy [27]. The additional costs of adjuvant cytotoxic chemotherapy may lead to some delay in commencement of the treatment after surgery [28]. Starts and stops occur frequently in consonance with the present financial status of the patient.

13 Targeted Therapy?

In developed countries, therapies targeted against epidermal growth factor receptor (EGFR) using monoclonal antibodies are said to increase survival in patients with metastatic CRC. Unfortunately, few studies on the molecular biology of Nigerian CRC are available. A study by Abdulkareem et al. in 2012 showed that KRAS mutation was demonstrated in 20.5 % and BRAF (V600E) mutation in 4.5 % suggesting that Nigerian patients may actually benefit more than Caucasian populations from cetuximab (an anti-EGFR monoclonal antibody) [29]. Cetuximab costs up to

$30,000 for 8 weeks of treatment per patient which certainly ensures that it is out of reach of the majority of Nigerian patients.

14 Follow-Up

Abdominal USS, CEA levels and colonoscopy are useful for follow-up, however, greater than 75 % of operated patients are 'lost to follow-up' [12]; thus, survival rates and disease-free intervals are impossible to document [1].

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Hepatocellular Carcinoma

Michael C. Kew

1 Introduction

Of the three regions – sub-Saharan Africa, Malaysia and the Philippines – for which an association between a tropical environment and the occurrence of hepatocellular carcinoma (HCC) has been mentioned, sub-Saharan Africa alone has a parallel between the two conditions being considered and then only indirectly. We, therefore, confine our analysis to HCC as it occurs in sub-Saharan Africa.

2 Incidence

A large percentage of the Black population of sub-Saharan Africa, but only a relatively small proportion of the far smaller Caucasian population, lives in rural areas located in tropical or subtropical regions of the subcontinent. HCC is known to occur commonly in the rural, and less often in the urban, Black populations of sub-Saharan Africa, although information about its occurrence in these populations is neither complete nor always accurate, as anyone who has ever tried to obtain accurate estimates of cancer incidences in the subcontinent will attest [1, 2]. Certainly, estimates of the occurrence of HCC in the Black population living in rural areas grossly underestimate the true incidence of the tumour, but this occurs to a far lesser extent in the Black population living in urban areas. In spite of these inaccuracies, HCC is clearly one of the three most common malignant tumours in the Black African population

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of sub-Saharan Africa [3, 4]. With the exception of Mozambique in Southeast Africa, which has the highest recorded incidence of HCC in the subcontinent, the highest incidences of the tumour occur in Central and West African countries.

In contrast with the high incidence of HCC in the Black population of sub-Saharan Africa, the tumour occurs rarely in the Caucasian populations of the subcontinent, accounting for less than 1 % of all malignant diseases. The great majority of the Caucasian populations live in urban areas, where they benefit from the superior diagnostic and treatment facilities that are available in these areas. Even so, the treatment of HCC available in the urban areas of sub-Saharan Africa is not yet of the same high standard as, and the results obtained are less gratifying than, those now being achieved in many of the resource-rich countries of the world.

Medical facilities located in the rural areas of sub-Saharan Africa are, with rare exceptions, few and far between, and it has long been known that attendance at the local country clinic or hospital decreases with the increasing distance from the patient's home [5]. Furthermore, the paucity of doctors practising in rural areas, as well as the often scarce and inferior quality of the diagnostic facilities available in these areas, may preclude the correct diagnosis being made and hence the appropriate treatment administered. These shortcomings in rural areas may be compounded by a nihilistic attitude in some of the medical personnel to making a definitive diagnosis of HCC, engendered by the usually inoperable stage of the tumour when the patient is first seen, as well as the disappointing results of treatment by other means, and the dismal prognosis of the patients [4, 6].

Equally, or even more, important in this context is that many Black Africans living in rural areas prefer, or choose for other reasons, to rely on the diagnostic and treatment methods of traditional healers ("witch doctors"), such as they are, rather than those of conventional medical practitioners [4, 6]. At the very least, this prevents or delays the correct diagnosis of HCC being made and appropriate treatment being administered timeously.

In addition to the often longer interval before the rural patient receives appropriate medical attention and treatment, and hence the more advanced stage of the tumour at that time, the optimal management of HCC requires resources and skills that are seldom available in rural, and not always in urban, sub-Saharan Africa.

For all of these reasons, and because very few, if any, Black African countries have reliable cancer registries, HCC is both under-diagnosed and under-reported in the rural areas of sub-Saharan Africa, and an accurate incidence of the tumour in Black Africans residing in these regions is consequently not known.

As a result, the frequency and importance of HCC in the Black population of sub-Saharan Africa, especially in rural dwellers, have not received the attention it urgently requires. Nevertheless, it is clearly evident that the tumour occurs with a high incidence in the rural Black population and, to a lesser extent, in Black urban dwellers. In support of this conclusion, 46,000 new cases of the tumour have been recorded in recent times to be diagnosed annually in sub-Saharan Africa [1, 2, 7], and the vast majority of these have been Black Africans.

The age-standardized incidence rates of HCC in most sub-Saharan Black African populations range between 19.2 and 28.4 per 100,000 persons per year, and the tumour accounts for approximately 20 % of all malignant diseases in the inhabitants [6].

Exceptions to this incidence of HCC are Mozambique, where the incidence recorded some years ago was 101.7 per 100,000 males and 31.4 per 100,000 females per annum and the tumour accounted for 65.5 % of all malignant diseases in males and 31 % in females [6], and Senegal, where HCC accounted for 42 % of all malignant tumours [8]. At that time it was estimated that HCC was 500 times more likely to develop in a Mozambican Shangaan male than in a Caucasian male of the same age living in Europe. HCC occurs far more often in rural Black than in urban Black dwellers in sub-Saharan Africa (ratio 4.4:1.0) [4, 6], although many urban dwellers were born and spent the early part of their lives in a rural area.

Accurate registration of cancers depends upon identifying every patient with the tumour, which can only be achieved if all patients have ready access to appropriate health services, a privilege not currently enjoyed by many rural sub-Saharan Black Africans. Little accurate information is thus available on possible changes in the incidence of HCC over time in different parts of sub-Saharan Africa.

3 Age

The mean age of rural Black Africans with HCC is 34.7 years, and that of their urban counterparts 51.0 years [9, 10]. Those patients who were born in a rural area but migrated to the city (usually in early adulthood) have a mean age of 50.9 years [9]. By contrast, HCC in the populations of industrialized countries occurs almost exclusively in the seventh to ninth decades of life. HCC occurs in Black African children, although with a far lower incidence than in adults. The numbers are, however, significantly greater than those in Caucasian children living in sub-Saharan Africa.

4 Sex

Black African men have a higher incidence of HCC than Black African women do (mean sex ratio 3.5:1.0, range 2.1:1.0–5.7:1.0) [1, 10]. Male predominance is more striking in young patients: 8.1:1.0 in patients less than 30 years of age, compared with 4.2:1.0 in those over 40 years of age [1, 10]. In populations elsewhere in the world with low incidences of HCC, male predominance is less striking: 1.1:1.0–3.5:1.0 [1].

5 Cirrhosis

Although cirrhosis is present far less often in Black Africans with HCC (between 30 and 60 % in different reported series [11]) than in patients with this tumour in other parts of the world (80 % or more [12]), the presence or absence of cirrhosis must still be taken into account when considering the treatment of individual Black African patients with the tumour.

6 Clinical Presentation

Rural Black African patients with HCC often consult a doctor only when the tumour has reached an advanced stage. Despite this, the duration of symptoms admitted to by the patients is usually surprisingly short: 30 % admit to symptoms of less than 2 weeks' duration, and another two-thirds to symptoms of less than 4 weeks' duration.

Unremitting upper abdominal pain, often severe, is an almost invariable complaint, and this is frequently accompanied by weakness and loss of weight. The pain invariably becomes more severe as the tumour increases in size. Jaundice is a rare presenting complaint in patients with HCC, as is "acute abdomen" (acute haemoperitoneum) as a result of rupture of the tumour [4, 6, 12].

On examination, the liver is invariably found to be enlarged, often massively so [4, 6, 12]. Weight loss is almost always evident. About 25 % of the patients are jaundiced. The tumourous liver is always firm and may be stony hard; it is invariably tender. An arterial bruit may be heard over the tumour in approximately one-quarter of the patients [6]. Ascites is present in about 50 % of the patients [4, 6, 12].

7 Course and Prognosis

The prognosis of Black patients with HCC in sub-Saharan Africa is especially grave, with the usual time from the onset of symptoms to death being approximately 11 weeks and that from diagnosis to death approximately 6 weeks [4, 6, 12]. The often fulminant course of HCC in this population is related, at least in part, to the rapid growth rate of the tumour, with doubling times as short as 30 days [4, 6, 12]. Rapidly progressive deterioration in the patient's condition is usual. Tumour rupture may be the terminal event [4, 6, 12]. Survival times in Black Africans with HCC are not influenced by the presence or absence of the associated cirrhosis.

Improving on the present-day highly unsatisfactory prognosis for Black Africans with HCC will be difficult as long as late presentation or delayed diagnosis of the tumour remains the norm.

8 Diagnosis

8.1 Biochemical Tests

Serum α-fetoprotein levels are useful in the diagnosis of HCC in the Black African population, approximately 75 % of the patients having a diagnostically raised level (above 500 ng/ml) at the time that they are first seen [13]. The raised serum levels are

age-related: 89.3 % of Black African patients less than 30 years of age compared with 59.7 % of those more than 30 years of age have a diagnostically raised level of the tumour marker [13]. The serum levels of α-fetoprotein also differ, albeit to a lesser extent, between rural (raised in 89.7 %) and urban patients (raised in 76.9 %) [13]. Other biochemical tests are not useful in the diagnosis of HCC in sub-Saharan Black Africans [13].

8.2 Chest Radiographs

Pulmonary metastases are radiologically evident in 19.8 % of Black African patients with HCC when they are first seen and become apparent in a further 5.3 % of the patients before death [14]. The metastases are almost always multiple. In 30 % of the patients with HCC, the right hemidiaphragm is seen radiologically to be significantly raised [14]. The raised hemidiaphragm is almost always generalized, but it occasionally takes the form of a localized bulge. The left hemidiaphragm is rarely elevated. A right basal pleural effusion is occasionally present [14]. Accurate visualization of the tumour in rural regions is hampered by a lack of the sophisticated imaging equipment that is currently available only in large cities in developed countries.

9 Pathology

The tumourous liver at autopsy in Black African patients with HCC is often of a very large size, weighing between 3,045 and 3,914 g (the highest recorded weight in this population is 8,780 g) in comparison with weights of between 2,036 and 2,615 g in low-incidence populations with the tumour [12, 15]. Invasion of surrounding organs or structures by the tumour occurs significantly more often in Black African patients than in patients in other populations.

The histological features of HCC per se do not differ from those in other populations [12], although the frequency with which a number of features are present does differ: the expanding (massive) type of tumour is present in 30–36 % of Black African patients, which is significantly more often than that in populations with low incidences of the tumour, for example, in 17 % in North American patients [12]. The degree of differentiation of the tumour also differs from that in other populations, the tumour being poorly or moderately differentiated in 87 % of the patients [12]. In most populations other than Black Africans, HCC frequently arises in a cirrhotic liver (±80 %). This association occurs significantly less often in Black African patients (in 30–60 % in different series of patients [12]).

10 Aetiology

Despite the reasons for the under-diagnosis of HCC in sub-Saharan Black Africans, considerable progress has been made in identifying the risk factors responsible for the high incidences of the tumour in this population. The major risk factor is chronic hepatitis B virus infection. Chronic hepatitis C virus infection plays a lesser, but still significant, role in the aetiology of the tumour in these regions. Hepatitis B and C virus infections are dealt with in another section of this book and will not be considered further here. Other major risk factors for HCC in sub-Saharan Black Africans are dietary exposure to the fungal toxin, aflatoxin B_1, dietary iron overload in the Black African and membranous obstruction of the inferior vena cava.

10.1 Aflatoxins

Aflatoxins are difuranocoumarin metabolites of the fungi, *Aspergillus flavus* and *A. parasiticus* [16]. These fungi are mutagenic and carcinogenic in humans and animals. They contaminate a number of staple crops, particularly maize, ground nuts and fermented soy beans, in subsistence farming communities in tropical and subtropical countries in sub-Saharan Africa with warm, humid climates. Between 4.5 and 5.5 billion of the world's population are exposed to aflatoxins [16]. Contamination occurs both during growth of the crops and as a result of their improper storage. Exposure begins *in utero,* continues during breast-feeding and is lifelong.

The innocuous parent molecule of the fungus is converted by members of the cytochrome p450 family into mutagenic and carcinogenic intermediates [16]. Aflatoxin B_1 is the aflatoxin most often found in contaminated human foodstuffs and is the most potent liver carcinogen known to man – no animal model tested so far has developed HCC on being exposed to the toxin! The liver carcinogenic effects of AFB_1 and chronic HBV infection are synergistic, with a multiplicative relative risk of HCC resulting.

10.2 Dietary Iron Overload in the Black Africans

Many rural-dwelling Black Africans in sub-Saharan countries consume large volumes of home-made beer that they brew in iron drums or pots. During the process of fermentation, the pH of the ferment decreases to very low levels, resulting in the iron in the wall of the container being leached from the container into the beer [17]. As a consequence the beer has very high iron content. Because the alcohol content of the beer is low, large volumes of the beer must be consumed in order to achieve its desired effects. The end result of drinking large volumes of iron-rich beer over a period of time is a heavy deposition of iron in the liver, which may, over time, be complicated by the development of HCC. The incidence of HCC may be as high as 23.5 % [17].

10.3 Membranous Obstruction of the Inferior Vena Cava

Membranous obstruction of the inferior vena cava is an occlusive lesion of the inferior vena cava close to its entry into the right atrium or just below the level of the diaphragm [18]. The obstruction is usually caused by a membrane or a fibrotic lesion of variable length, each of which is thought to be either a congenital anomaly or the end result of an organized thrombus in the hepatic portion of the inferior vena cava [18]. The condition is rare in most countries but occurs more frequently in Nepal, Southern Africa, China and Taiwan. Membranous obstruction of the inferior vena cava may be complicated by the development of HCC [18]. The lesion is present in 3.7 % of Southern African Blacks and 43 % of these develop HCC [18].

11 Management

In the past, treatment of HCC has been largely unrewarding in patients in all populations, and in rural Black Africans, who almost invariably seek medical advice only when the tumour is already at a very advanced stage, is virtually completely unrewarding. For example, only 8 % of Ugandan [19] and 1 % of rural Southern African Blacks [20] proved to have resectable tumours, compared with resectability rates of up to 37 % in some countries with low or intermediate incidences of HCC [21]. In the latter countries implementation of surveillance programmes has made early tumour diagnosis possible, but such programmes are rarely in use in sub-Saharan African countries.

There are a number of reasons for the late presentation and low resectability rates of HCC. Because of the large size of the liver, the tumour must reach an appreciable size before it can be felt or before it invades adjacent structures. In addition, the considerable functional reserves of the liver ensure that jaundice and other evidence of hepatic dysfunction appear only when a large part of the organ has been replaced by tumour. Consequently, the tumour is often not amenable to resection at the time that the patient is first seen. HCCs in Black African patients frequently reach a very large size. This makes resection of the tumour even more difficult and therefore less likely.

A further reason for the low resectability rate of HCC in the sub-Saharan Black African population is the frequency of dissemination of the tumour beyond the liver at the time the patient is first seen (e.g. the high incidence (19.8 %) of pulmonary metastases [14]). In addition, although the association of HCC with cirrhosis is less close in Black Africans than it is in resource-rich countries, its presence in the non-tumourous liver is an additional consideration when assessing suitability for surgical resection of the tumour. Furthermore, the presence of cirrhosis precludes postoperative regeneration of the remaining liver tissue.

The management of patients with HCC with all but terminal illness should be in the hands of surgeons, physicians and radiotherapists experienced in the management

of such patients in hospitals equipped with the necessary sophisticated up-to-date equipment to allow for the assessment of the extent of the tumour in respect to its size and spread beyond the liver. These members of staff will be working in hospitals in the large cities. Surveillance programmes in developed countries have in recent years resulted in early tumour diagnosis and an increased number of curative treatments, achieving 5-year survival rates of as much as 75 % [22–24].

Doctors working in rural areas of sub-Saharan African hospitals should have a high index of suspicion for the presence of HCC in Black African patients, with knowledge of its symptoms, physical signs, x-ray findings and serum α-fetoprotein levels. The risk of disseminating malignant hepatic cells into the bloodstream, thereby enhancing the risk of spread of the tumour beyond the liver, by performing percutaneous liver biopsy has been raised. Using highly sensitive reverse transcriptase polymerase chain reaction assays, it is possible to detect malignant cells in the circulation [25]. Using this technique hepatocytes have been shown to be disseminated into the circulation with a high frequency after percutaneous biopsy [25]. However, the available evidence suggests that only a very small proportion (0.01 %) of circulating malignant cells is capable of initiating a metastasis [26]. Percutaneous biopsies should therefore be performed if necessary. The rural doctor should arrange, without delay, for the patient to be transferred to the nearest urban hospital where he or she will be cared for by a team of surgeons, physicians and radiologists experienced in the investigation and management of such patients. These doctors will in turn assess the patient as to the best way to manage the tumour, with a choice that includes resection, transplantation and locoregional and systemic treatments, and then to take the necessary steps to set the chosen treatment in motion.

With patients in rural hospitals, obviously in the terminal stages of what is known or believed to be incurable HCC, the local doctor may or may not need to confirm the diagnosis by performing a percutaneous liver biopsy. When the diagnosis is certain, the necessary medication for pain should be administered and the patient kept as comfortable as possible and any other requirements seen to during the short time that he or she will live.

12 Assessment and Management of Patients with Hepatocellular Carcinoma after Referral to the City Hospital

12.1 Tumour Resection

On the positive side, during recent years great strides have been made in First World countries in increasing the number of patients in whom resection of the cancerous portion of the liver is possible. Liver resection is now widely accepted as first-line treatment of patients with early-stage HCC and preserved liver function, giving an expected 5-year survival rate of 33–75 % depending upon the stage of the

tumour [22–24, 27]. The main prognostic indicators are liver function, number of tumours, presence of satellite lesions and vascular invasion [27]. Perioperative mortality has decreased to 3–5 % in the majority of large referral centres and to <1 % in some centres [28]. Unfortunately, in practice less than 30 % of patients are currently suitable for liver resection [22–24], and this figure is considerably lower in Black African patients. Moreover, recurrence of the original tumour or development of a *de novo* tumour after approximately 5 years is reported to be as frequent as 70 % [22]. With recurrence of HCC after initial resection, repeat resection, if possible, is the treatment of choice [28]. In the case of virally induced HCC, antiviral therapy reduces the chances of post-transplant tumour recurrence [29]. The growing disparity between the number of liver transplant candidates and the supply of donor organs during recent years has activated the development of living donor transplants [28]. The number of hepatic resections for HCC performed in sub-Saharan Africa has increased in recent years, but not to a great extent and not in many countries.

12.2 Liver Transplantation

If surgical resection is not possible, the next step is to consider the possibility of performing liver transplantation. In the past, hospitals in sub-Saharan Africa able to undertake this form of therapy were few and far between.

However, this shortcoming has recently been partly corrected. Local spread of the tumour to surrounding structures may or may not influence the suitability for liver transplantation. Clearly, for a transplant operation to be considered, the tumour must not have spread beyond the liver by way of metastases. A compatible donor liver must then be found, a not easy undertaking. The results of liver transplant operations for HCC have improved appreciably during recent years. Patients undergoing successful liver transplantation for HCC can expect to have a 5-year recurrence-free survival rate [22–24]. However, thereafter the possibility of tumour recurrence needs to be borne in mind, and at this stage curative treatments remain unclear. Very little has yet been published about the results of liver transplantation in Black African patients.

12.3 Photons Beam Radiation Therapy

Sophisticated new photon beam radio-therapeutic techniques in the form of 3-dimensional high-dose radiotherapy or stereotactic radiotherapy can accurately direct its rays to the tumour tissue, sparing adjacent liver tissue and achieving far superior results than were hitherto possible with radiotherapy [30]. These forms of treatment are, however, unlikely to be available in sub-Saharan African hospitals at the present time.

12.4 Treatment of Unresectable Tumours

For unresectable tumours, a variety of treatments have been used. These include transarterial chemoembolization (TACE) [30]. The results obtained when treating inoperable tumours with oral multikinase inhibitors such as sorafenib improved survival in comparison with that obtained with the drugs used in the recent past. Unfortunately, the response has not been persistent. Moreover, little information, if any, is available on their use in Black Africans.

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Cholangiocarcinoma

Miral Sadaria Grandhi and Timothy M. Pawlik

Cholangiocarcinoma (CCA) is a rare malignancy arising from the biliary epithelium. Based on the tumor's anatomic origin, CCA can be classified as intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA). While each of these may have various presentations and behave uniquely in comparison to one another, CCA has a poor prognosis. Moreover, diagnosis and surgical resection of CCA can often be technically difficult. In particular, for patients with resectable disease, the operative intervention can be extensive and, depending on the location of the CCA, its extent may involve a liver resection, resection of the extrahepatic biliary tree, or a pancreaticoduodenectomy. Thus, diagnosing and treating CCA in a tropical area with limited resources is quite challenging.

1 Epidemiology

Hepatobiliary malignancies account for 13 % of all cancer-related deaths annually worldwide, with CCA accounting for 10–20 % of deaths from hepatobiliary malignancies [1]. Furthermore, CCA, particularly iCCA, is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC) [2]. However, the worldwide incidence of CCA varies significantly based on geographic location with an incidence of 85 per 100,000 people in northeast Thailand compared with 0.43 per 100,000 in Canada [3]. Most patients present with CCA at a median age greater than 65 years old; younger patients in the age range of 40–50 years can develop CCA, with these patients typically having associated primary sclerosing cholangitis (PSC) [1]. A slight male predominance exists for CCA [1].

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2 Aetiology

Recently, progress has been made in understanding the mechanisms of the pathogenesis of CCA. Traditionally, CCA has been thought to be derived from a chronically inflamed biliary epithelium as a result of various inflammatory processes, such as hepatolithiasis, congenital hepatic fibrosis, choledochal cysts, PSC, and biliary flukes *Clonorchis sinensis* and *Opisthorchis viverrini* endemic to East Asia [1, 2]. These chronic inflammatory insults may result in malignant transformation of cholangiocytes [1]. However, recent evidence indicates that CCA may directly originate from hepatic transdifferentiation of hepatocytes [4, 5]. Supporting this hypothesis, various risk factors associated with iCCA are similar to those for HCC, such as cirrhosis, chronic hepatitis B and C, obesity, diabetes, and alcohol [6]. Cholangiocarcinogenesis is likely a multifactorial process, however, and the majority of CCA cases are sporadic without any of these suspected risk factors present [2].

3 Diagnosis

The majority of CCA cases are clinically silent with symptoms developing only at an advanced stage. However, once symptomatic, clinical presentation is primarily dependent upon tumor location. Given the scant resources in a tropical setting, the clinical presentation is particularly useful as a potential indicator whether the tumor may be a dCCA, pCCA, or iCCA. For instance, painless jaundice is the most common presenting symptom (90 %) in patients with dCCA with 10 % presenting with cholangitis [7]. pCCA can cause unilobar biliary obstruction and ipsilateral vascular compromise resulting in atrophy of the affected hepatic lobe. As a result, the unaffected hepatic lobe often hypertrophies in response [8]. Patients with pCCA typically present with jaundice also, as well as possible constitutional symptoms. Finally, in the case of iCCA, presenting symptoms are typically more constitutional in nature, with patients complaining of abdominal pain, weight loss, night sweats, and generalized fatigue; a palpable mass and jaundice may also be associated with iCCA and typically denotes very advanced disease [1].

Prior to becoming symptomatic, an elevated bilirubin level may be the first indication that the patient may have a biliary obstruction/malignancy. In the setting of abnormal liver function tests or signs and symptoms concerning for a biliary or hepatic lesion, further workup should be initiated with serum tumor markers as well as imaging. While tumor markers such as carbohydrate antigen (CA) 19–9, carcinoembryonic antigen (CEA), and CA-125 are often utilized in the workup of CCA, tumor markers tend to have variable sensitivity and specificity [1, 2, 9]. For instance, CEA and CA-125 can be fairly nonspecific tumor markers that can be elevated in various other gastrointestinal or gynecologic malignancies [1]. CA 19–9 is the most common tumor marker used to detect the presence of CCA. However, CA 19–9 is a more specific, than sensitive, tumor marker for CCA. For instance, a high CA 19–9 may be strongly associated with the diagnosis of CCA and have prognostic significance; in contrast, a low or normal CA 19–9 cannot be used definitively to rule out the diagnosis of CCA [10, 11].

4 Imaging Techniques

While imaging is useful for both diagnosing CCA and determining the resectability of CCA, limited resources in a tropical area may make obtaining advanced imaging difficult. Ultrasound and computed tomography (CT) scan may be the best available imaging modalities for CCA. In the case of preoperative ultrasound, the accuracy of detecting CCA is dependent upon the tumor type, quality of the equipment, and experience of the person performing the ultrasound, making ultrasound fairly nonspecific with low sensitivity for detecting CCA [12, 13]. More useful than ultrasound, CT scan allows for much better delineation of the level of biliary obstruction, potential lymph node involvement, and the tumor's relationship to the vasculature, especially in the arterial and portal venous enhancement phases of the scan [13]. CT scan can also be particularly useful in distinguishing iCCA from HCC as well as distinguishing the various subtypes of CCA. While findings of dCCA and pCCA predominantly are characterized by biliary dilation in the presence or absence of a mass, iCCA characteristically appears as a hepatic mass with irregular borders, peripheral enhancement in the arterial phase, and progressive contrast filling on delayed imaging, attributable to fibrosis enhancement [14]. Magnetic resonance imaging (MRI) can also be very helpful, especially for pCCA; however its availability may be limited in a tropical setting. While ultrasound and cross-sectional imaging are critical in helping to assess resectability of CCA in that they can assist in detecting metastatic disease, vascular involvement, and lymph node involvement, as well as aid in preoperative planning, cholangiography is also typically desirable [13]. Cholangiography in the form of endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or percutaneous transhepatic cholangiography (PTC) is an important and useful diagnostic modality to assess tumor location and the intraductal extent of CCA among patients with dCCA and, in particular, pCCA [15]. Unfortunately, cholangiography may or may not be readily available in the tropical setting with scant resources.

With limited imaging resources as well as limited resources to obtain a pathological diagnosis of malignancy, a low threshold for surgical intervention and operative exploration should exist. The goals of surgery should be curative intent surgical resection consisting of microscopically negative margins (R0 resection). For those patients with pCCA who require a liver resection, consideration of leaving an adequate future liver remnant is also required. In fact, for patients with pCCA and iCCA, surgical resection can be quite complex requiring extensive hepatic resection as well as biliary resection and reconstruction [2, 16]. In the setting of dCCA, pancreaticoduodenectomy is typically required if the lesion is resectable, which also can be technically difficult. While liver transplantation is not an option for patients with iCCA or dCCA, a subset of patients with unresectable pCCA or primary sclerosing cholangitis-associated pCCA may be candidates for liver transplantation; however, liver transplantation for pCCA may not be an option for patients in a tropical setting with limited resources [17–19].

5 Surgery: Curative Intent

In terms of the technical aspects of surgical resection, the surgeon should be comfortable with hepatopancreaticobiliary anatomy as well as dissecting out the portal structures to proceed forward with abdominal exploration and plan for curative surgical resection in CCA, regardless of subtype. In the operating room, the first step is operative exploration. If the patient is noted to have frankly metastatic disease, biopsies should be taken in the operating room for a pathological diagnosis. When no metastatic disease is present and the surgeon plans to proceed with a curative intent operation, intraoperative ultrasound should be utilized to further define the lesion and its proximity to the major vasculature for intraoperative planning purposes [20]. If the patient appears to be resectable in the operating room and partial hepatectomy is required as in the case of pCCA and iCCA, the portal structures should be dissected out to perform a Pringle maneuver as needed during resection. While dividing the liver parenchyma can be done using various techniques, a crush clamp technique to crush the liver parenchyma thus exposing the vessels and bile ducts for ligation is the most applicable approach in the tropical setting with limited resources. The Pringle maneuver should be implemented as indicated for hemostasis during the resection, and final hemostasis should be obtained with bipolar cautery. For patients with pCCA, in addition to a liver resection, removal of the extrahepatic biliary tree and a hepaticojejunostomy are typically required. For those patients with a dCCA, pancreaticoduodenectomy with removal of the head of the pancreas, duodenum, and distal biliary tree is required.

6 Palliative Surgery

If the patient is unfortunately not amenable to surgical resection, a surgical palliative bypass should be considered and is dependent upon the subtype of CCA present. In general, a minimum of 30 % of the liver parenchyma or two liver segments must be drained for relief of cholestasis and pruritus [21]. In the case of unresectable dCCA, a hepaticojejunostomy can be performed to alleviate biliary obstruction of the entire liver. In the case of a patient with unresectable pCCA, a proximal hepaticojejunostomy may not be feasible due to the location of the tumor. As such, for unresectable pCCA a segment III cholangiojejunostomy or side-to-side biliary enteric anastomosis at the base of segment IV can be performed intraoperatively for biliary drainage – especially when PTC or ERCP with biliary stent placement is not an available option in a remote tropical setting (Fig. 1) [21–23]. Unfortunately, surgical biliary bypass is not of benefit in the setting of iCCA and patients with massive iCCA causing biliary obstruction an abysmal prognosis.

For patients with advanced disease, systemic therapy should be considered either as definitive therapy (i.e., for patients with unresectable disease) or as adjuvant therapy (i.e., for patients with resected disease and adverse pathological features such as lymph node metastasis). Unfortunately, chemotherapy has minimally proven benefit in CCA and likely would not be administered in a remote tropical area [1]. In addition, radiation or other intra-arterial therapies are not curative in nature, and these therapies are unlikely to be feasible in a remote tropical setting [2].

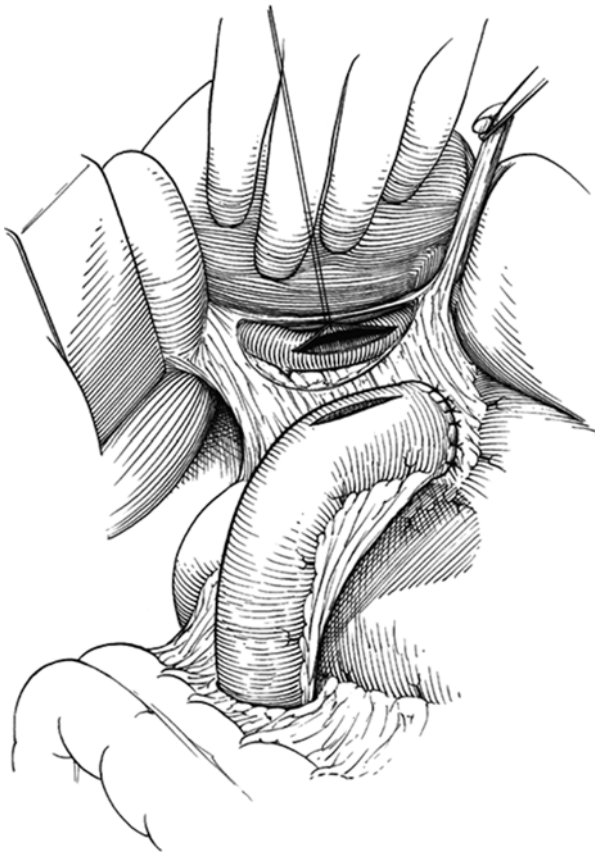

Fig. 1 By incising Glisson's capsule at the base of segment IV, the origin of the main hepatic duct, the bifurcation, and the left main hepatic duct are exposed. By retracting segment IV cephalad and incising the overlying tissue, the proximal extrahepatic biliary system and more specifically the extrahepatic portion of the left main hepatic duct are exposed. A side-to-side biliary enteric anastomosis can be performed at this time for biliary drainage in the setting of unresectable pCCA (Drawing by D. Factor, Mayo Clinic, Rochester, Minnesota, copyright 1995). Used with permission

While cholangiocarcinoma can be managed with scant resources, transferring a patient with a possible diagnosis of CCA to an area with more available resources may be appropriate. In addition, transferring the patient for appropriate surgical resection is also appropriate if the surgeon in the remote setting is not comfortable with the complexity of surgical resection associated with CCA. CCA traditionally requires extensive workup and complex surgical management. As such, both the diagnosis and surgical management of CCA in a tropical setting with limited resources can be quite challenging.

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Pancreatic Cancer

Christelle de la Fouchardière and Béatrice Cenciu

1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most frequent cause of tumor-related death in the Western world [24, 25]. Few data are published concerning PDAC frequency in tropical countries, but it may be less frequent than in more developed countries [1, 10, 15]. However, its incidence is increasing worldwide, and PDAC will become by 2020 the second leading cause of cancer-related mortality [16]. Median survival is 5–8 months and median 5-year survival is less than 5 % [23]. Majority of the patients are diagnosed with metastases and are candidates for palliative treatment.

2 Risk Factors

PDAC is usually sporadic but may be familial, needing attentive care to familial history.

Sporadic PDAC development is the result of a combination of different causes including somatic genomic, genetic, and epigenetic alterations and environmental factors, especially cigarette smoking and alcohol. Long-standing type 2 diabetes mellitus is also associated with an increased risk of pancreatic cancer [13]. Tropical calcific pancreatitis (TCP) has been described as a form of chronic nonalcoholic pancreatitis and is associated with a 4 % lifetime risk of developing cancer [19]. The

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typical clinical phenotype of TCP includes an onset at less than 30 years of age, a body mass index (BMI) less than 18 kg/m^2, absence of any other cause of pancreatitis, and presence of diabetes [5].

Hereditary basis of PDAC is traditionally found in 5–10 % of patients [20]. Subsets of familial pancreatic cancer involve germ line cationic trypsinogen or PRSS1 mutations (hereditary pancreatitis), BRCA mutations (usually in association with hereditary breast–ovarian cancer syndrome), CDKN2 mutations (familial atypical mole and multiple melanoma), or DNA repair gene mutations (e.g., ATM and PALB2, apart from those in BRCA) [29].

3 Diagnosis

Histological diagnosis should be obtained when nonsurgical treatment is considered, because 10 % of malignant tumors of the pancreas aren't exocrine and all pancreatic tumors are not malignant. If the tumor is resectable, a biopsy is not recommended/mandatory in order to avoid gesture's morbidity and theoretical risk of tumor seeding along the needle tract [6]. In case of diagnostic doubt (nodule of pancreatitis or a pseudotumor pancreatitis) and unresectable or metastatic tumor, a fine-needle cytology or tumor biopsy needs to be achieved. When endoscopic ultrasonography (EUS) is available, fine-needle aspiration may be EUS-guided (EUS-FNA). EUS may be also useful to detect vascular invasion and to treat pain through celiac plexus block and obstructive jaundice through biliary drainage [11]. If EUS is not available, ascites or hepatic metastases may be sampled under radiological guidance (ultrasound or CT scan).

A contrast-enhanced computed tomography of the chest, abdomen, and pelvis is the primary and easily available modality for both diagnosing and staging [2]. It is typically a multiphase thin-section imaging technique showing the primary tumor at the earlier phase, while the latter phase best demonstrates tumor involvement of venous structures and liver metastases [4]. Pancreatic magnetic resonance (MR) imaging may be useful but is not mandatory [21]. Likewise, 18FDG PET/CT also offers no benefit over CT scan in diagnosing pancreatic cancer [22].

The staging system for pancreatic exocrine cancer is defined by the 7th edition of the American Joint Committee on Cancer (AJCC)/TNM classification [9].

4 Treatment of Resectable Tumors

Resectable tumors include AJCC stages I and II. It concerns only 10–20 % of the patients. The surgical procedure for the pancreatic head's tumors is a pancreaticoduodenectomy or Whipple procedure involving the removal of the distal half of the stomach, gallbladder, distal portion of the common bile duct, as well as the head of the pancreas, duodenum, proximal jejunum, and lymph nodes. Three anastomoses are

required for reconstruction, namely, pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy. As morbidity and mortality can be high following surgery, patients need to be addressed in high-volume centers [30]. Recurrences after initial surgery are frequent, and 5-year survival after surgical resection of PDAC is as poor as 18–27 % and correlates with resection margin status (R0 vs. R1) and lymph node metastases [14]. A 6-month adjuvant therapy with 5-FU or gemcitabine-based chemotherapy is recommended for all patients after pancreatic surgery, independently of the T and N stages [17, 18]. The median overall survival for patients with resected pancreatic cancer treated with adjuvant chemotherapy is approximately 2 years.

5 Treatment of Locally Advanced Unresectable Tumors

Locally advanced pancreatic cancers (stage III) are divided into borderline resectable or locally advanced unresectable tumors. They are separated according to the relationship of the tumor to the adjacent major vascular structures (superior mesenteric artery (SMA), celiac axis, and superior mesenteric and portal veins (SMV–PV)). Tumors without vessel involvement or with only focal involvement of the SMV–PV confluence are considered to be resectable, while patients whose cancers involve arteries or have more extensive involvement of the SMV–PV confluence are classified as having clinical stage III tumors. Their median survival in most historical studies ranges from 8 to 12 months. In this setting, treatment options include mostly chemotherapy (CT), chemoradiation (CRT), and surgery but strong evidences for therapeutic sequences are lacking. Controversies mainly exist about the place of radiation therapy, because the definition of locally advanced pancreatic cancers varies in published series, borderline resectable and unresectable tumors are both included in the same studies, and metastatic progression during or immediately after radiation is usual. Recently, the LAP 07 trial showed no benefit in survival for CRT after 4 months of gemcitabine-based induction CT over CT alone in locally advanced unresectable tumors. Despite these results, chemoradiation is not abandoned and remains investigated after more aggressive neoadjuvant CT (like FOLFIRINOX or nab-paclitaxel–gemcitabine). At least, due to the high rates of metastatic progression, it is recommended to use first induction CT which may subselect the proportion of patients who may benefit from subsequent CRT. In borderline resectable pancreatic cancer, the role of CRT remains less controversial and will be answered in future prospective phase III trials.

6 Metastatic Disease

Cytotoxic chemotherapy is the standard treatment option for stage IV pancreatic cancer patients. Between 1997 and 2011, gemcitabine monotherapy remained the standard treatment for metastatic patients with a median survival of 5–6 months in

the study by Burris et al. [8]. Since gemcitabine, two CT combinations demonstrated their superiority to gemcitabine alone. First, in 2011, Conroy et al. published the efficacy and safety results of the FOLFIRINOX combination CT regimen in the ACCORD 11 randomized phase III trial (Conroy et al.). FOLFIRINOX (leucovorin at 400 mg/m^2, fluorouracil at 400 mg/m^2, irinotecan at 180 mg/m^2, and oxaliplatin at 85 mg/m^2 given as a bolus, followed by 2,400 mg/m^2 given as a 46-h continuous infusion, every 2 weeks) demonstrated its superiority in comparison to gemcitabine alone in 342 chemotherapy-naive patients with metastatic pancreatic cancer with an ECOG PS of 0 or 1 and a serum bilirubin level < 1.5 times the upper limit of normal. The median overall survival, progression-free survival (PFS), and objective response rate were significantly higher with FOLFIRINOX (median overall survival, 11.1 vs. 6.8 months; PFS, 6.4 vs. 3.3 months; objective response rate, 32 % vs. 9 %). However, treatment-related toxicity was also significantly higher with FOLFIRINOX, including grade 3/4 neutropenia (46 % vs. 21 %), febrile neutropenia (5.4 % vs. 1.2 %), thrombocytopenia (9.1 % vs. 3.6 %), sensory neuropathy (9 % vs. 0 %), vomiting (15 % vs. 8 %), fatigue (23 % vs. 18 %), and diarrhea (13 % vs. 2 %). The same efficacy and safety results were obtained later in an Indian phase III trial, confirming the substantial activity of FOLFIRINOX in non-European populations [26].

Much recent progress in metastatic PDAC was obtained with the association of nab-paclitaxel and gemcitabine, whose superiority over gemcitabine monotherapy was shown in the multinational phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT). This study included 861 patients with previously untreated metastatic pancreatic adenocarcinoma [28]. Combination therapy was associated with a significantly higher objective response rate (23 % vs. 7 %) and significantly longer median overall survival (8.5 vs. 6.7 months) and PFS (5.5 vs. 3.7 months) compared with gemcitabine alone. Grade 3/4 adverse events occurred more often with combination therapy. They included neutropenia (38 % vs. 27 %), febrile neutropenia (3 % vs. 1 %), fatigue (17 % vs. 7 %), diarrhea (6 % vs. 1 %), and neuropathy (17 % vs. 1 %). In September 2013, nab-paclitaxel in combination with gemcitabine was approved by the FDA for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

As no phase III study has compared the efficacy of FOLFIRINOX and gemcitabine plus nab-paclitaxel in first-line metastatic setting, they both are reasonable choices for first-line therapy in patients with good performance status (ECOG PS 0 or 1). However, recent Canadian cost and quality-of-life data suggest that FOLFIRINOX may be more cost-effective than gemcitabine or gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer [3, 12].

7 Palliative Care

Palliative care is very important in PDAC because 80–90 % of newly diagnosed tumors are not resectable or with distant metastases. The most common symptoms of PDAC are obstructive jaundice, gastric outlet obstruction, pain, weight loss, and

anorexia. About 90 % of the patients are diagnosed with obstructive jaundice. Biliary drainage can be achieved surgically (biliary bypass) or by endoscopic/percutaneous placement of stents with equivalent results [27]. Malignant gastric outlet obstruction can also be treated surgically with gastrojejunostomy or endoscopically with a self-expandable metallic stent. As pain incidence and severity tend to increase with disease progression, a good palliation is necessary. Opioid analgesics, radiation therapy, and celiac plexus neurolysis could be used, besides chemotherapy that has also a role in pain control. Even if weight loss has been found to have a prognostic effect on survival, few attentions are given to medical interventions that can prevent or reduce the progressive weight loss of the patients. Weight gain and higher daily total energy intake can be obtained with enteric-coated pancreatic enzyme supplements [7].

8 Conclusion

The treatment of PDAC combines, according to the disease stage, surgery and chemotherapy. The role of radiotherapy is not clearly established and should be reserved to clinical trials.

Palliative care should be introduced as early as possible because of the poor survival of the patients.

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Lung Cancer

Digamber Behera and V. Nagarjuna Maturu

1 Epidemiology

The global burden of cancer continues to increase largely because of an increasing adoption of cancer-causing behaviors, particularly adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and "westernized" diets in economically developing countries. Lung cancer has remained the most common cancer worldwide for several decades and represents 12.9 % of all new cancers [1]. It is also the most common type of cancer in men and remains the most common cause of cancer-related mortality in both sexes [2]. It accounts for one of every five cancer deaths. Most patients with lung cancer present with advanced disease [3]. Although the cancer incidence rates in India are lower than in the developed world, the relative mortality rates are higher, and this disparity results in a significant contribution to the world cancer deaths. Delay in diagnosis and inadequate, incorrect, or suboptimal treatment (due to lack of access to specialist care, financial constraints, or lack of awareness) are the chief factors leading to poor cancer survival in India. In women, the incidence rates are generally lower than in men, and the geographic pattern is somewhat different, depending on the uptake and consumption of tobacco.

Registration and notification of cancer in general and lung cancer in particular are poor in most of the low- and middle-income countries (LMICs) in Asia and in Pacific Island countries, so the true incidence may still be high and underestimated. A substantial proportion of the worldwide burden of cancer could be prevented

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through the application of existing cancer control knowledge and by implementing programs for tobacco control.

The major histological types of lung cancer include squamous cell carcinoma (SqCC), adenocarcinoma (ADC), and small cell lung cancer (SCLC). In the recent past, a relative increase in the incidence of ADC has been witnessed. In most of the countries, it has become the dominant histological type of lung cancer [4]. This histological shift (increase in the incidence of adenocarcinoma) has been linked to changes in the smoking behavior of the population in these regions as well as in the method of manufacturing (use of filtered cigarettes) and composition of cigarettes (higher levels of nitrates) being marketed therein [5].

2 Etiology

2.1 Smoking

Smoking is by far the most common cause of lung cancer. The lifetime risk of developing lung cancer varies widely (1–15 %) even among smokers [6]. The factors which modify this risk include (a) the duration of smoking (number of years smoked), (b) the age at initiation of smoking, (c) the intensity of smoking (number of cigarettes smoked per day), (d) the total exposure to smoke (smoking index or pack years), (e) the exposure to cocarcinogens (radon, asbestos, silica, etc.), (f) the genetic susceptibility and (g) the years since the cessation of smoking (for reformed smokers). A recent meta-analysis involving 287 studies observed that although RR estimates were markedly heterogeneous, it demonstrated a relationship of smoking with lung cancer risk and the relationship was as follows [7]:

- Ever smoking (random-effects RR 5.50, CI 5.07–5.96)
- Current smoking (8.43, CI 7.63–9.31)
- Ex smoking (4.30, CI 3.93–4.71)
- Pipe/cigar only smoking (2.92, CI 2.38–3.57)

In many of the developing countries, including India, a majority of smokers use indigenous forms of tobacco (bidi, chutta, khaini, hookah, and many more). These forms of smoking also predispose to the development of lung cancer. In fact, a review of eight studies from different parts of India has concluded that bidi smoking poses a higher risk for lung cancer than cigarette smoking [8].

2.2 Environmental Tobacco Smoke

Environmental tobacco smoke (ETS), also known as secondhand smoke (SHS), is also a known lung carcinogen. The chemical composition of the sidestream smoke is qualitatively similar to the mainstream smoke but quantitatively different, with certain carcinogenic agents such as aromatic amines being present at a higher concentration in the sidestream smoke. A meta-analysis of 41 studies showed that

environmental tobacco exposure carries a relative risk of developing lung cancer of 1.48 (1.13–1.92) in males and 1.2 in females (1.12–1.29), and this risk increases with increase in duration of exposure. Exposure to ETS before the age of 25 years is associated with a higher risk of developing lung cancer than exposure after the age of 25 years [9].

2.3 Indoor and Outdoor Air Pollution

Use of biomass fuels has been implicated as a causative agent for lung cancer. The International Agency for Research on Cancer (IARC) had identified coal as group 1 (known) pulmonary carcinogen and biomass fuels as group 2A (probable) pulmonary carcinogen [10]. A recent meta-analysis of 28 studies has shown that both coal and biomass fuels are associated with lung cancer, though the odds ratio was greater for coal (OR 1.82, 95 % CI 1.60–2.06) as compared to biomass fuels (OR 1.50, 95 % CI 1.17–1.94 [11]). The IARC also recently (in 2013) included the exposure to outdoor particulate matter and air pollution as a group 1 lung carcinogen. Though the risk associated with air pollution is much lesser than the risk associated with active smoking, as almost everyone is exposed to outdoor air pollution, the anticipated public health effect is quite large [12].

2.4 Other Causes

In addition to the abovementioned causes, several other factors have also been implicated in the development of lung cancer. These include occupational exposures to organic and inorganic dusts, radiation and exposure to radon, long-standing structural lung diseases, HIV infection, and genetic factors. It is beyond the scope of this chapter to discuss in detail the individual risk factors.

3 Clinical Presentation

Most patients with lung cancer present with symptoms related to the intrathoracic spread of the tumor. The most common presenting symptoms include cough, followed by dyspnea, chest pain, and hemoptysis. A majority of them would also have significant constitutional symptoms (loss of weight ad anorexia). In addition to these, the patients may have symptoms related to the underlying comorbidities (chronic obstructive airway disease and coronary artery disease). Symptoms which would increase the probability of a malignant etiology include mediastinal symptoms (superior vena cava syndrome, hoarseness of voice, dysphagia, and Horner's syndrome), metastatic symptoms (bony pains, lymph node swellings, and neurologic symptoms), or paraneoplastic syndromes. Less than 10 % of the lung cancer patients are asymptomatic at presentation.

4 Evaluation of a Patient with Lung Cancer

In addition to detailed clinical history and examination, appropriate investigations need to be performed to confirm the diagnosis of malignancy, accurately subtype the lung cancer, and determine the stage of the disease. It is of utmost importance to get a confident pathologic diagnosis of lung cancer before any therapeutic decisions are taken. Depending on the clinical presentation and the radiologic pattern, any one of the following techniques can be used to get a tissue sample for histological or cytological examination – endobronchial biopsy, transbronchial lung biopsy, bronchoalveolar lavage, sputum cytology, pleural fluid cytology, pleural biopsy, transthoracic needle aspiration/biopsy, transbronchial needle aspiration, and peripheral node biopsy. The clinicians should ensure that while procuring sample for tissue diagnosis, enough tissue is available for immunohistochemical/molecular testing as well. Once a tissue diagnosis of lung cancer is established, an accurate staging of the tumor has to be done as per the new TNM system (seventh edition) [13].

The T stage of the tumor is primarily assessed on the CT scan of the chest. However, a fused PET/CT scan is more accurate than chest CT in accurately determining the T stage (82 % vs. 68 %) [14], as it is more accurate in delineating the chest wall/pleural invasion and differentiating distal collapse from the mass per se. An accurate N staging is very important as tumors with N2 or N3 disease are generally considered unresectable. The noninvasive modalities for assessing the N staging (including the chest CT and PET scan) are inaccurate. In the developing world, the mere presence of nodes >1 cm on chest CT or the presence of an SUV of >2.5 does not necessarily imply nodal spread of disease as they can also be due to infections like tuberculosis which are endemic in these countries. It is always preferable to use invasive modalities to confirm the tumoral involvement of lymph nodes.

The invasive modalities of nodal staging can be further classified as surgical procedures (mediastinoscopy and mediastinal lymphadenectomy) or endosonographic procedures (endobronchial ultrasound (EBUS)- or endoscopic ultrasound (EUS)-guided TBNA). The procedure chosen would depend on the availability of the equipment, technical expertise, and patient preferences. Complete medical mediastinoscopy (EBUS + EUS-guided TBNA) has been shown to have sensitivity better than that of mediastinoscopy (85 % vs. 79 %) [15]. For determining the M stage of the disease, the ideal investigation is a whole-body PET scan. However, it needs to be performed to search for occult metastatic disease only in patients who are being treated with a curative intent. A brain MRI is however superior to PET scan for detecting metastases to the brain.

5 Treatment of Non-small Cell Lung Cancer (NSCLC)

The various modalities used for the treatment of patients with lung cancer include:

1. Surgery
2. Radiotherapy

3. Chemotherapy
4. Targeted therapy

These modalities are used in isolation or in combination. An ideal management of patients with lung cancer requires a multidisciplinary approach – pulmonary physician, radiologist, radiation therapist, thoracic surgeon, histopathologist, and medical social worker. The treatment of NSCLC depends on the stage of the disease.

5.1 Stage I NSCLC

Surgery is the mainstay of treatment for patients with stage I NSCLC. The optimal surgical procedure is lobectomy along with systematic lymph node dissection (SND). While performing an SND < all the mediastinal tissue containing the lymph nodes is dissected and removed. Sub-lobar resections (segmentectomy or a wedge dissection) have been shown to have outcomes similar to lobectomy in a subset of cancers which are <2 cm in diameter [16, 17]. Lobectomy using a video-assisted thoracoscopic surgery (VATS) is a promising alternative to open thoracotomy with similar five-year survival rates [18]. Patients with stage IB tumors where the tumor size is >4 cm may benefit from the addition of cisplatin-based adjuvant chemotherapy [19]. The role of adjuvant targeted agents following surgical resection is still being evaluated. For patients who have a resectable disease, but are medically inoperable, novel therapeutic options include stereotactic body radiation therapy (SBRT) which has been shown to have survival outcomes similar to surgical resection [20].

5.2 Stage II NSCLC

The standard of care for patients with stage II NSCLC is surgical resection followed by four cycles of cisplatin-based adjuvant chemotherapy. The surgical procedure recommended is lobectomy/pneumonectomy with SND. The lung adjuvant cisplatin evaluation (LACE) network meta-analysis of five RCTs has shown that adjuvant cisplatin-based chemotherapy improves the disease-free and overall survival by 3 % and 5 %, respectively [21]. Patients with positive resection margins (R1 or R2 status) will benefit from the addition of adjuvant radiotherapy.

5.3 Stage III NSCLC

Stage III NSCLC, also known as locally advanced NSCLC, is a heterogeneous disease, and the treatment decisions have to be individualized. Patients with stage IIIA disease who have non-bulky, discrete N2 disease may be considered for surgical resection. In such patients neoadjuvant chemotherapy may also be considered to

downstage the tumor before surgery [22]. The treatment of choice for patients with unresectable stage III NSCLC is a combination of chemotherapy and radiation (chemoradiation). Concurrent chemoradiation is superior to sequential chemoradiation as it improves the 2-, 3-, and 5-year survival and is to be preferred in patients with good PS (ECOG 0–1) [22].

5.4 Stage IV NSCLC

Palliative chemotherapy is the standard of care for patients with metastatic NSCLC. The first-line chemotherapy is usually a platinum-based chemotherapy doublet given for 4–6 cycles. Cisplatin is the preferred platinum compound (except in patients with nephropathy, neuropathy, or hearing loss) as it has been shown to have better response rates and overall survival as compared to carboplatin [23]. The choice of non-platinum agent would depend on the histology of the tumor. For patients with non-squamous NSCLC, pemetrexed is now the preferred agent as it has been shown to have better OS (12.6 months vs. 10.9 months) [24]. For squamous NSCLC, the options include gemcitabine, paclitaxel, docetaxel, or vinorelbine. The cost of the regimen also should be borne in mind while selecting the chemotherapy regimen as most of the patients come from an economically backward strata of the community.

Patients with nonprogressive disease after first-line chemotherapy may benefit from maintenance chemotherapy. This can be either switch maintenance (docetaxel, pemetrexed, and erlotinib) or continuation maintenance (gemcitabine and pemetrexed) [25]. Maintenance chemotherapy is given using a single non-platinum chemotherapy drug 3–4 weekly till disease progression/intolerance. Patients with relapsed/progressive disease may be considered for second-/third-line chemotherapy regimens.

6 Treatment of Small Cell Lung Cancer (SCLC)

SCLC, unlike NSCLC, is considered a systemic disease from onset, and the standard of care is chemotherapy with/without radiotherapy. In general, patients with limited disease (LD) are treated with chemoradiation, whereas those with extensive disease (ED) are treated with chemotherapy alone. The principles of chemotherapy for SCLC are similar to that of NSCLC. The choice of non-platinum compound is between irinotecan and etoposide. Irinotecan has been shown to have a better OS and ORR as compared to etoposide in ED (but not LD) patients [26]. Irinotecan causes more gastrointestinal upset and lesser hematologic toxicity (as compared to etoposide), and it has been shown to be better tolerated in the Asian/Japanese population as compared to Caucasians (because of genetic polymorphisms). Other drugs which have been tried include amrubicin and topotecan. As there is a high risk of CNS relapse in patients with SCLC, patients who achieve a complete/partial remission following initial therapy are to be given prophylactic cranial irradiation (PCI)

as this has been shown to increase the survival and decrease the CNS relapse rate [27]. There is also data to suggest that patients with stage I NSCLC may benefit from surgical resection [28]. In such patients adjuvant chemotherapy and PCI are to be given following surgery.

7 Evolving Role of Personalized Medicine in Lung Cancer

The discovery of oncogenic driver mutations (epidermal growth factor mutation (EGFR) and anaplastic lymphoma kinase (ALK)) and approval of targeted agents against these driver mutations have revolutionized the approach to the management of lung cancer patients. It is now recommended that all patients with advanced non-squamous NSCLC and select patients (nonsmokers/light smokers) with squamous NSCLC should be tested for the presence of these oncogenic driver mutations at the diagnosis. The treatment of such EGFR-mutated or ALK-rearranged tumors is first-line targeted agent instead of chemotherapy.

(a) *EGFR gene mutations*: EGFR is a family of genes which encodes transmembrane tyrosine kinase molecules. Most EGFR mutations occur in four exons–18, 19, 20, and 21. The two most common EGFR mutations are the exon 19 deletion and the exon 21 L858R point mutation. These EGFR mutations are more commonly seen in women, nonsmokers, East Asians, and patients with adenocarcinoma histology. The prevalence of EGFR-activating mutations varies according to the ethnicity and is highest in the East Asians (50–60 %) and least in the Caucasians (5–15 %). The prevalence in India is intermediate (20–35 %) [29]. Several EGFR tyrosine kinase inhibitors (TKI) have been approved for use as first-line, maintenance, and second-line agents in patients with advanced NSCLC. These can be classified as first-generation (reversible selective EGFR inhibitors – gefitinib, erlotinib, and icotinib), second-generation (irreversible pan-ErbB inhibitors – afatinib and dacomitinib), and third-generation agents (selective T790M inhibitors). The two most commonly used agents are oral erlotinib (150 mg/day) and gefitinib (250 mg/day). Several trials have shown erlotinib, gefitinib, and afatinib to be superior to chemotherapy (response rates and progression-free survival) in patients with EGFR-mutated lung cancers [30]. The group-specific adverse reactions because of these drugs include diarrhea, skin rash, transaminitis, and less commonly, interstitial lung disease.

(b) *ALK gene rearrangements*: ALK gene rearrangements on the short arm of chromosome 2 are seen in 3–5 % of the NSCLC. This translocation brings the exons of EML4 and ALK together leading to constitutional activation of ALK tyrosine kinase. These are more commonly seen in nonsmokers/light smokers and patients with adenocarcinoma histology and younger age. The presence of EGFR ALK, and KRAS mutations is mutually exclusive of one another. Crizotinib, an oral ALK inhibitor when given at a dose of 500 mg/day, has been shown to be superior to chemotherapy both in the first-line and second-line settings when used in

patients with this translocation [31, 32]. Several "next-generation ALK inhibitors" are also under development to overcome the problem of acquired resistance to crizotinib. Such compounds include ceritinib and alectinib.

(c) *ROS1 gene rearrangements*: ROS 1 gene rearrangements, seen in 1 % of the lung cancer patients is another targetable driver mutation. A recent study of crizotinib, which also blocks ROS1, has shown that the response rate was 72 % and the median PFs was 19 months when used in subset of patients with ROs 1 positive tumors [33].

(d) *Vascular endothelial growth factor (VEGF) inhibitors*: Though, in a true sense, these agents would not qualify for personalized medicine, discussion of these novel targetable agents would be incomplete without a mention of VEGF inhibitors. Bevacizumab, a humanized monoclonal antibody against VEGF, is approved for use in non-squamous NSCLC in combination with chemotherapy followed by continuation maintenance [34]. The most common adverse reactions include thromboembolism, pulmonary hemorrhage, hypertension, bleeding, and proteinuria. Several other small-molecule VEGF TKIs (nindetanib, vandetanib, and sorafenib) are also being evaluated for their role in managing NSCLC.

In conclusion, lung cancer remains the leading cause of cancer-related mortality in the developing world. Smoking is the most important preventable risk factor and strong public health efforts are needed to curtail this. Most patients with lung cancer have advanced disease at presentation; hence, the survival rates are poor. The role of screening low-dose CT for early detection of lung cancer has not been evaluated in the tropics and hence cannot be recommended in these areas. The standard of care for early-stage lung cancers remains surgical resection. The approach to and management of advanced NSCLC, however, has changed dramatically since the discovery of EGFR and ALK inhibitors.

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Head and Neck Cancers

Jérôme Fayette and Esma Kerboua

1 Introduction

Head and neck squamous cell carcinomas (HNSCC) account for 8 % of cancers worldwide. The incidence is weaker in Western countries and higher in tropical areas. Similarly, the rate of death is higher in tropical areas with more than 50 % of cases against less than 30 % in Western countries. The treatment of HNSCC is largely multidisciplinary with various associations of surgery, radiotherapy (RT), and chemotherapy. In tropical areas, radiotherapy is not always available, and we will explore the decrease of survival without radiotherapy and with approach could be then adopted. Similarly with chemotherapy, due to the cost of anti-EGFR (epidermal growth factor receptor), their nonuse leads to decreased survival.

2 Prevention, Diagnosis, and Objective of Treatment

HNSCC is clearly related to alcohol consumption and tobacco smoking. Primary prevention is probably the most efficient approach as demonstrated with a strong decrease in mortality in Western countries since 1970. For example, in France, the world standardized mortality decreased from 50 to 75 % since the 1970s. The risk of cancer decreases as soon as 1 year of tobacco cessation (−30 %) and reach the level of never smoker after 20 years [1].

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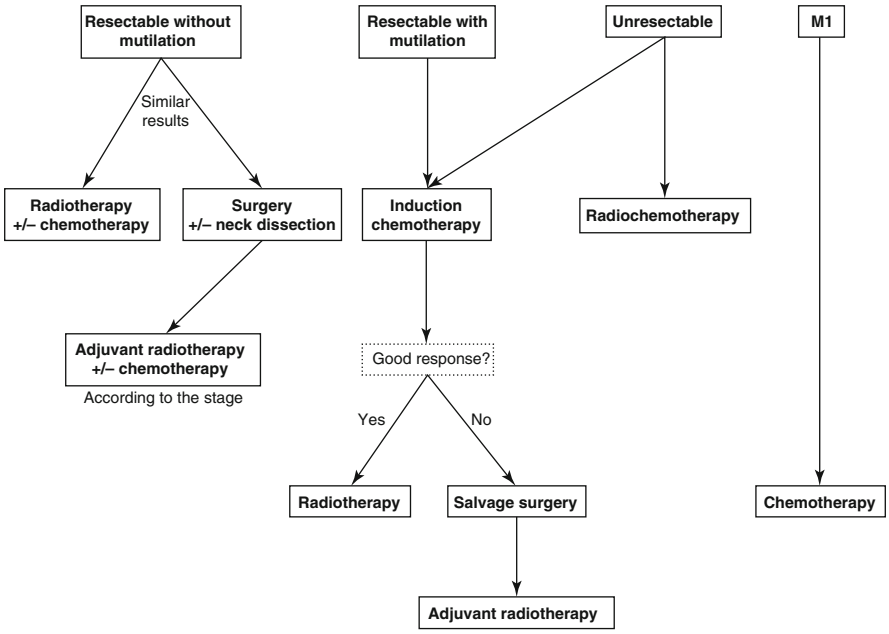

Fig. 1 Principles of treatment of HNSCC

For the diagnosis of HNSCC, the needed exams are a cervicothoracic CT scan and a panendoscopy for precise staging and search of a second synchronous tumor and a biopsy.

For head and neck cancer, the objective of treatment is double: to cure patient and preserve his/her function. Indeed, head and neck region is crucial for speaking, breathing, and eating. The global principles of treatment are summarized in Fig. 1, which combine, at various degrees, surgery, radiotherapy, and chemotherapy. We will analyze which impact can have the lack of all possibilities for treatment and how to obtain the best results with minimal financial and technical possibilities.

3 Treatment of Resectable Tumors

Despite no direct comparison, it seems that similar results are obtained with surgery or radiotherapy. So surgical approach should be considered in tropical areas.

The most efficient action for reducing recurrence is stopping tobacco. For example, for laryngeal cancer, a study demonstrated, after complete resection, 28.7 % and 55.26 % ($p = 0.0022$) recurrence for patients who stopped smoking versus patients who continued [2].

After complete surgery for tumors of stage III or IV, radiation therapy decreased the risk of disease. A study of 8795 patients within the Surveillance,

Epidemiology, and End Results (SEER) database showed that adjuvant RT improved the 5-year overall survival (43.2 % [95 % confidence interval (95 % CI), 41.9–44.4 %] for surgery + RT vs. 33.4 % [95 % CI, 30.7–36.0 %] for surgery alone; $P < .001$) and cancer-specific survival (50.9 % for surgery + RT vs. 42.1 % for surgery) on univariate analysis [3]. On multivariate analysis, adjuvant RT (hazard ratio [HR] of 0.78; 95 % CI, 0.71–0.86 [$P < .001$]) is a strong independent prognosis factor. For patients with high risk of relapse (marginal resection or capsular effraction of an involved node), addition of chemotherapy by three cycles of cisplatin at the dose of 100 mg/m^2 decreased again the level of recurrence. In a phase III study, 334 patients were randomized to radiotherapy alone (66 Gy over a period of 6 1/2 weeks) without or with cisplatin. The overall survival rate was also significantly higher in the combined-therapy group ($P = 0.02$ by the log-rank test; hazard ratio for death, 0.70; 95 % confidence interval, 0.52–0.95), with five-year Kaplan-Meier estimates of overall survival of 53 % and 40 %, respectively [4]. The estimated 5-year cumulative incidence of local or regional relapses (considering death from other causes as a competing risk) was 31 % after radiotherapy and 18 % after combined therapy.

So, for resectable disease, after surgery, radiotherapy clearly decreases the risk of relapse, but its benefit is inferior to this of smoking cessation, and in countries where radiotherapy is poorly available, it should be reserved to patients who stopped tobacco.

For operable disease but with a mutilating surgery, organ preservation could be tempted. Since it seems that results are similar between surgery and radiochemotherapy, if surgery is mutilating, radiotherapy should be preferred. Induction chemotherapy demonstrated its benefit. For laryngeal or hypopharyngeal cancer, if radiotherapy is available, patients should receive an induction chemotherapy by TPF (cisplatin 75 mg/m^2 D1, 5FU 750 mg/m^2/d D1 to D5, docetaxel 75 mg/m^2 D1) every 3 weeks. The response rate was 80 %, and these patients were irradiated (without potentiation) and could avoid surgery, and after a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3 % [5]. After induction chemotherapy, no study focused on the possibilities to avoid radiotherapy (i.e., exclusive chemotherapy in the case of complete response or the possibility of surgery of residual tumor after partial response).

4 Treatment of Unresectable Tumors

For non-resectable tumor, the pillar treatment is radiotherapy potentiated by based chemotherapy. In a large meta-analysis including 50 concomitant trials, the addition of concomitant cisplatin-based chemotherapy allowed a hazard ratio of 0.81 ($p < 0.0001$) with an absolute benefit of 6.5 % at 5 years in overall survival [6]. If radiotherapy is unavailable, we can propose an induction chemotherapy (the TPF regimen allowed a response rate of 68 % with 8.5 % of complete response) [7] followed by surgery if possible.

5 Type of Potentiation of the Radiotherapy

If radiotherapy is available, it should be largely used in HNSCC as adjuvant or exclusive setting. The standard chemotherapy for potentiation is cisplatin at the dose of 100 mg/m^2 every 3 weeks for three cycles. Cetuximab, an inhibitor of EGFR, demonstrated a benefit for inoperable disease in combination with radiotherapy. In the pivotal phase III study, the median overall survival was increased from 29 to 49 months [8], but the control arm was radiotherapy alone, without cisplatin. No direct comparison of the potentiation by cisplatin or cetuximab was done. A small study suggests that cisplatin could be better [9]. The costs of cetuximab being largely superior to that of cisplatin will be chosen. The addition of cetuximab to cisplatin in combination with radiotherapy brought more toxicity without clinical interest [10]. So the better type of chemotherapy for potentiation of the radiotherapy is the less expensive drug.

6 Recurrent or Metastatic Disease

In this situation, if locoregional treatment is not possible, we propose palliative chemotherapy. Five types of molecules showed clinical benefit: methotrexate, cisplatin, 5FU, taxanes, and EGFR inhibitors that give about 10–15 % of objective response in monotherapy and an overall survival of about 6–8 months [11]. The combination of cisplatin (100 mg/m^2) and 5FU (1,000 mg/m^2/d for 5 days) every 3 weeks is a good standard because with low cost, despite the overall survival not increased, the response rate is higher to about 25 %, and for these relapsing patients, often symptomatic, the increase of response rate brings a gain of quality of life [12]. The standard treatment is the triple combination of cisplatin, 5FU, and cetuximab (250 mg/m^2 every week): the response rate is increased from 26 to 36 %, and the median overall survival is significantly increased from 7.4 to 10.1 months [13]. Due to its costs, cetuximab is rarely available in tropical areas, and the median overall survival is minored for 2.5 months. Studies demonstrated that with sequential treatment with the five efficient drugs, long survival could be achieved [14].

7 Tumors Induced by Viruses

7.1 Papillomavirus (HPV)

In Western countries, despite a decrease of the incidence of HNSCC, there appeared an increase of incidence in never smoker, in younger, and in female patients. The cause of this increase was clearly attributed to the HPV infection that is correlated with specific sexual behaviors (multiple partners, oral sex, etc.) [15, 16]. The prognosis of the HPV-positive tumors is largely better, but today, the search of expression has no impact in clinical practice since we have no demonstration of any benefit of deintensification of treatment for these patients. Similarly, no information is available concerning the potential benefit of the vaccination against HPV for prevention of HNSCC.

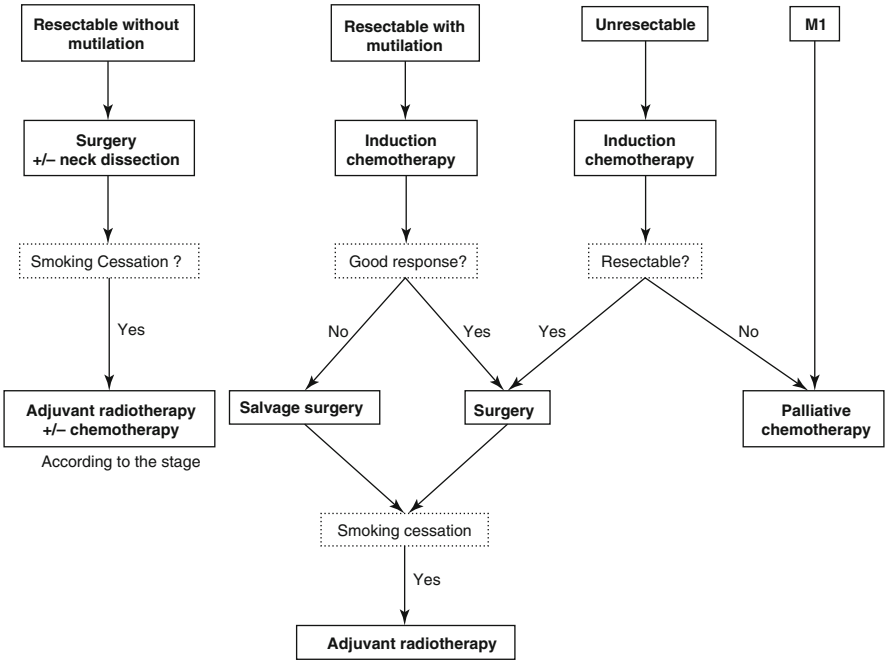

Fig. 2 Proposed approach for treatment of HNSCC if radiotherapy is unavailable or available only for a few patients

7.2 Epstein-Barr Virus (EBV)

The undifferentiated cancer of the cavum (UCNT) is related to EBV infection and food habits and is particularly frequent in South China, Southeast Asia, and North Africa. The only treatment is radiotherapy potentiated by weekly cisplatin at the dose of 40 mg/m^2 which gives a 5-year overall survival of 70 % [17]. Due to delay for onset of radiotherapy, neoadjuvant chemotherapy with TPF or the doublet cisplatin/docetaxel could be proposed, followed by chemoradiation. Furthermore, a study suggests that this approach could increase overall survival [18]. The prognosis is poor in the absence of radiotherapy. The surgical approach is not feasible because in this anatomic site, tumors are unresectable. Similar to HNSCC, effective drugs are cisplatin, 5FU, taxanes, methotrexate, and anthracyclines. But chemotherapy could be only palliative. No data are available with anti-EGFR treatments.

8 Conclusion

The treatment of HNSCC combines, at various degrees, surgery, radiotherapy, and chemotherapy. Prognosis is worse without radiotherapy which is not always available in tropical areas, and Fig. 2 summarizes the situation we can have in this scenario. Induction chemotherapy could be an optional approach with surgery of the

residual tumor, and only few patients can have radiotherapy; it should be reserved only for patients who stopped smoking. After recurrence, the nonuse of anti-EGFR decreases the overall survival of about 2.5 months. In very poor countries, we can propose only surgery or palliative chemotherapy with methotrexate.

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Bladder Cancer: A Perspective for Tropical Regions

André van der Merwe, Dedan Opondo, and Amir Zarrabi

1 Epidemiology of Bladder Cancer in Tropical Regions

With the increase of bladder cancer with age, one can expect a higher prevalence as the life expectancy in tropical areas increases [1]. The two most common types of bladder cancer worldwide are transitional cell carcinoma (TCC) and squamous cell carcinoma (SCC). Transitional cell carcinoma is less prevalent in rural areas in developing countries as compared to developed countries. Squamous cell carcinoma is more common in areas where schistosomiasis is endemic [2, 3].

Bladder cancer is a relative rare disease in the African tropics. In Burkitt's epic paper in 1966 where he described different diseases during his travel from the origin of the Nile river to the Nile delta, bladder cancer was not encountered in the tropical areas such as the origin prior to traversing the equator [4]. Cancer registries in the tropics are not common; however, a successful registry from Ghana serving much of West Africa exists. The findings on bladder cancer are very similar to Burkitt's findings in 1966 – bladder cancer is scarce in the tropical areas of West Africa [5]. The incident rates (per 100,000) for males and females are in Ghana (1.1, 1.2), Cote d'Ivoire (0.5, 0.2), Niger (1.6, 1.4), and Nigeria (1.1, 0.2) with male predominance in most cases. This might be due to smoking habits, occupational/agricultural exposure, or difficulties in data gathering. The crude total cancer incident rates (per 100,000) for these countries are for males and females, respectively, in Ghana (21.3, 37), Cote d'Ivoire (18.7, 23.3), Niger (32.5, 48.8), and Nigeria (32.6, 42.6) placing bladder cancer as a relative rare cancer. Bladder cancer appears also to be rare in other tropical areas such as South America and Tropical Asia [2].

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Ferguson, in 1911, linked the causal relationship between schistosomiases and bladder cancer in a description of 40 cases [6]. In North African countries like Egypt, with its southern part below the Tropic of Cancer, therefore in the tropics, SCC is common in men who perform agricultural work in the schistosomiasis-infested waters of the Nile. SCC presents on average 10–20 years younger than TCC and is usually more locally advanced [7, 8]. In Egypt, bladder cancer is as common as 12.7 % of all cancers in males. The crude incident rate (per 100,000 population) for all types of bladder cancer is 12.2 for Southern Egypt vs. 19 for Northern Egypt. The majority of these are SCC [9].

Risk factors for the development of TCC of the bladder include smoking, analgesic abuse, and industrial carcinogens. Risk factors for the development of SCC include exposure to chronic irritation, e.g., prolonged catheterization, and schistosomiasis. Exposure to schistosomiasis increases the risk of bladder cancer. Previous studies have shown that patients with TCC and SCC have similar outcomes of treatment if they are at a similar stage of the disease [7, 8, 10]. Late presentation is common in the tropics with 5-year survival of less than 22 % for bladder cancer in the Gambia and Uganda [11, 12].

Because of long-term survival and lifelong monitoring and treatment, the cost of care per patient from diagnosis to death is highest in bladder cancer than any other malignancy [6]. Cost of care is therefore an important impediment to optimal management of bladder cancer patients in low resource settings [2, 3].

2 Clinical Presentation and Special Investigations

Macroscopic hematuria remains an important finding. As patient with Bilharzia-associated bladder cancer often had macroscopic hematuria as a child, this is often not seen as an important sign to the patient until it is too late [11]. Dysuria and necroturia accompany the late presenting pathology in both SCC and TCC cases. Clinically, even in late presentation, there is very little difference between the different types of cancer except for the history mentioned above [3].

Bilharzia-associated bladder cancer presents with an earlier median age, more in males and less frequently with early disease (Ta, Tis, and T1). However, it presents with near-similar lymph node spread and distant metastases to non-Bilharzia-associated bladder cancer [3].

Should the facilities be available, bladder cancer in the tropics is investigated similar to other regions in the world. Note that patients might be malnourished and anemic due to late presentation. As chemotherapy is not always available, a simple metastatic workup (abdominal and chest X-rays, ultrasound of the abdomen) should be done prior to embarking on expensive computerized tomography (CT) scans. Once metastases are found, treatment should be palliative, not excluding a palliative cystectomy and diversion. With this sequence of investigations, much savings can be achieved in resource-poor environments. Cystoscopy and biopsy by resection remains the gold standard of making a diagnosis. However, in advanced cases, a Tru-Cut biopsy of the tumor via the rectum under antibiotic cover might save time and risks of an anesthetic.

3 Treatment Options in the Resource-Poor Tropical Areas

Early cancers are managed the same as elsewhere: either repeated resections and or intravesical immunotherapy if available. The problem lies with the urine diversion after the radical surgery.

3.1 Radical Cystectomy and Urinary Diversion

Urinary diversion after radical cystectomy is the gold standard treatment for patients with localized muscle-invasive bladder cancer (>T2). As mentioned above, it is also an option for high-risk patient with T1 disease. Ileal conduit and orthotropic neobladder are the two popular modalities of urine drainage after cystectomy. Both techniques are associated with metabolic complications. Ureterosigmoidostomy, which is rapidly becoming obsolete, is an alternative for continent urinary diversion. Its main disadvantages include recurrent UTI, anastomotic urocolonic cancers, and metabolic disturbances [13, 14]. The modified ureterosigmoidostomy (Mainz II) is a less morbid alternative, but still has problems. Nitkunan et al. report from a center of excellence that only 11 of 17 patients were continent with nocturnal incontinence being the biggest problem needing a diverting colostomy. Seven of these patients needed treatment for hyperchloremic acidosis. Only one patient suffered from recurrent upper tract urine infections. In the 4–8.6-year follow-up, no cancers were detected [15]. This type of surgery is a possibility, but still no panacea for urine diversion in tropical resource-poor areas, as, for example, might be difficult to treat electrolyte abnormalities. The author has seen an ingenious patient plan from Angola where a patient used four small Mopani tree sticks, two ropes, and a "disposable" amount of double shopping bags to make a near-perfect stoma bag. Desperate patients sometimes use condoms as disposable condom catheters if a neobladder leaks. Condoms are in some areas freely available for the fight against HIV.

Neobladder is a good option for SCC as there is no urethral involvement. The younger patients might develop long-term complications similar to above.

3.2 Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy should be considered where affordable and available to improve long-term survival in patients with MIBC [11]. The aim of neoadjuvant therapy is to eradicate micrometastases that are often not visible at the time of clinical staging but later result into recurrent disease. Unfortunately, identification of patients who are likely to respond to neoadjuvant chemotherapy still remains a challenge thus limiting this treatment approach. In addition, one must pay attention to the logistics of neoadjuvant therapy which may unduly delay the timing of radical cystectomy.

3.3 External Beam Radiotherapy (ERBT)

EBRT is a treatment alternative to patients with MIBC who are unfit for radical surgery – if available. This is a very scarce resource in central Africa. It is an option for patients who object to radical surgery. The overall survival after EBRT is reported to be lower than radical cystectomy [16].

3.4 Inoperable Bladder Cancer

Palliative care is the mainstay of treatment of patients with locally advanced bladder cancer (T4) with invasion to the pelvic or abdominal wall deemed too risky to even perform palliative radical cystectomy. These patients suffer from debilitating symptoms such as recurrent bleeding, severe pain, intractable dysuria, and urinary obstruction. Optimal palliative care includes direct treatment of the disease as well as functional, psychosocial, and spiritual support [17].

Treatment options for these symptoms include the following:

1. General supportive measures include adequate analgesia including opioid analgesia and blood transfusion.
2. Bladder irrigation with cold saline is often used to alleviate hematuria. A 10 % formalin solution used to irrigate the bladder for 5–30 min is an alternative. Alum instillation can also be used to reduce bleeding [18].
3. Bilateral nephrostomy or cutaneous ureterostomy may be considered for patients with obstructive uropathy who are not yet terminally ill. This is, at times, a difficult emotional decision-making process where the family should be in close communication with the patient and the caring physician.
4. Palliative cystectomy and urinary diversion that is done to alleviate intractable hematuria and severe LUTs which are refractory to conservative treatment.
5. Palliative radiation therapy is used to control pain and hematuria – if available [19].

4 Conclusions

Bladder cancer in the tropical areas is often not common, with clear exceptions such as in Egypt. However, if diagnosed, it is often in an advanced stage needing radical curative treatment if available. Internal diversions has its problems as stated above, but neobladder, if possible, is generally a reasonable alternative to external stoma appliances. As life expectancy in the tropics is increasing, the incidence of bladder cancer in the tropical areas will also increase.

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Prostate Cancer

Pascal Blanchet and Laurent Brureau

1 Epidemiology

1.1 Incidence

Prostate cancer is the most common cancer in industrialized countries. Advanced age, ethnogeographical origins and the presence of a family history of prostate cancer are the main risk factors clearly established.

The estimated incidence in Guadeloupe and Martinique for 2008–2010 was 180.0 and 163.7 per 100,000 respectively [1]. Considering Guadeloupe and Martinique not as French departments, but as full-fledged territories, prostate cancer incidence appears to be the highest in the world (Fig. 1). The incidence of prostate cancer in South America, sub-Saharan Africa and South East Asia is, respectively, 60.1, 27.9 and 11.2 per 100,000.

1.2 Mortality

Cancer mortality in the Caribbean is generally lower, except for prostate cancer with a mortality rate four times higher than metropolitan France (27.4 against 6.4 per 100,000 inhabitants) [1]. The rate of mortality of prostate cancer in South America, sub-Saharan Africa and South East Asia is, respectively, 16.6, 20.9 and 6.7 per 100,000.

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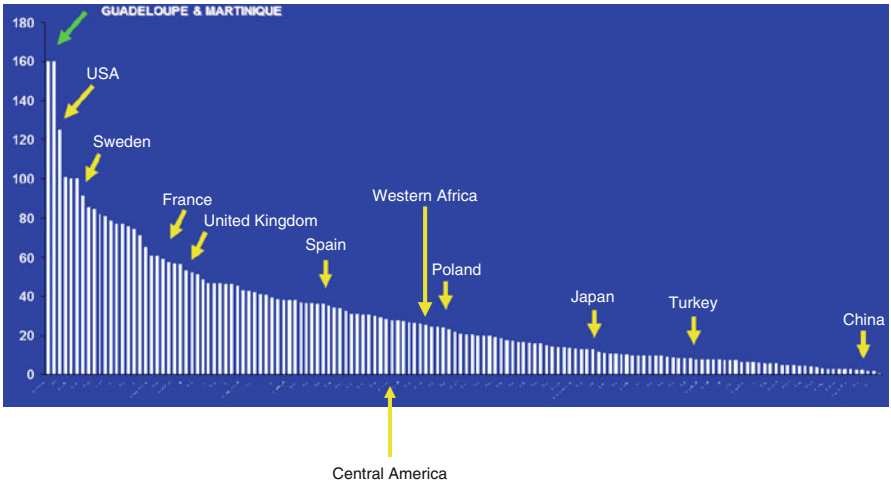

Fig. 1 Standardized incidences of prostate cancer in the different countries of the world and in Guadeloupe and Martinique

1.3 Risk Factors of Prostate Cancer

The high incidence of prostate cancer in the Caribbean area may be due to risks factors such as:

- An aging population with high life expectancy.
- African ethnogeographical origin (sub-Saharan) for the majority of the population (~90 %), a result of the slave trade and the deportation of people from West and Central Africa to the Caribbean.
- Development of individual early diagnosis of prostate cancer.
- Food. West Indies populations are characterized by a change (transition) in progressive eating behaviours, a traditional diet rich in fruits, vegetables and fish to the so-called Western alimentations rich in animal fats.
- Pesticides. Agricultural activities in the Caribbean, especially bananas, have led to intensive use of pesticides, to neutralize the development of parasitic nuisances favoured by the tropical climate, hot and humid. These uses have led to contamination of the population, especially to chlordecone [2].
- Genetic. Association studies have identified, at the end of the twentieth century, loci of susceptibility genes for prostate cancer. Several other loci for susceptibility genes in hereditary forms of prostate cancer have been demonstrated on other chromosomes (Table 1).
- Genes involved in androgen metabolism. The involvement of androgens in the development of the prostate as well as in the development of cancer of the prostate gland has been widely established [4]. The study of polymorphisms associated with the risk of the disease is carried on the key enzymes in androgen metabolism and its receptor (Fig. 2).

Table 1 Predisposing genes to prostate cancer [3]

Genes	Area	Mutations/variants
HPC1/RNASεL	1q24-25	Mutations: E265X, Met/1le, 471 del AAAG
		Variants: Arg462Gln, Glu541Asp
PCaP	1q42-43	Non-identified
HPCX	Xq27-28	Non-identified
CAPB	1p36	Non-identified
HPC20	20q13	Non-identified
HPC2/εLAC2	17p11.2	Mutations: Arg781His, 1641insG, Glu216stop
		Variants: Glu622Val, Ser217Leu, Ala541Thr
PG1/MSR1	8p 21-23	Mutations: Arg293X, Asp174Tyr, Pro36Ala, Ser41Tyr, Val113Ala, Gly369Ser, His441Arg
		Variants: Pro275Ala, PRO3, INDEL1, IVS5-59, INDEL7
BRCA2	13q12-13	6051delA (exon 11), 999del5, 6174del5

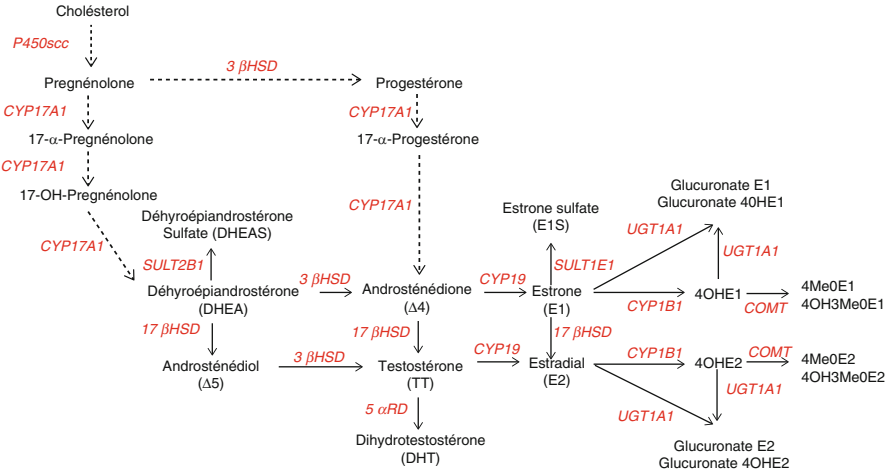

Fig. 2 Main metabolic pathways of androgens and oestrogens

- Multiple regions of the genome have been associated with the risk of prostate cancer in Caucasians, in particular several polymorphisms located at 8q24. Region 2 of 8q24 has been repeatedly found to be associated with the risk of prostate cancer among men of African descent [5].
- The epidemiological studies of Asian immigrants living in North America or European continents reported that the incidence and mortality rates of prostate cancer among these Asian immigrants are 50–80 % lower than those for non-Hispanic whites and African-Americans suggesting that in addition to environmental influences, genetic heterogeneity also contributes to prostate carcinogenesis. So far 77 single nucleotide polymorphisms (SNPs) associated with prostate cancer susceptibility have been identified, including two new risk loci, 9q31.2 and 19q13.4 [6].

2 Diagnostic

2.1 Histology

Prostate cancer is, in the vast majority (>95 %), an adenocarcinoma resulting from the malignant transformation of cells of the glandular epithelium. This transformation is the consequence of the loss of balance between proliferation, differentiation and apoptosis. The development of adenocarcinoma is from the stroma, extends throughout the prostate and prostatic capsuleprior to spread to lymphatic and heamtogenous pathway. Other forms of prostate cancer (<5 %) can be reported and include sarcomas and carcinomas and rhabdomyosarcoma of the child in which development depends on the anterior fibromuscular area.

2.2 Diagnostic Modality

Prostate cancer is usually asymptomatic. Nevertheless, it may result in voiding dysfunction or erection or painful ejaculation. In its very advanced forms, bone pain or weight loss may reflect the presence of metastases. In practice, this cancer is the most frequently diagnosed as the result of an abnormal rise in the value of serum PSA and/or an abnormal level of the consistency and/or volume of the prostate at the time of digital rectal examination. The "normal" value of serum PSA was often considered to be less than 4 ng/mL for the entire population (all ages combined).

Confirmation of the presence of prostate cancer is imperatively done by pathology. It is obtained by sampling prostate biopsies guided by transrectal ultrasound. In some cases, the pathological diagnosis may also be established in the examination of tissue removed during resection of the prostate.

Because of unequal access to health care in most of tropical countries, more than 20 % of patients have metastatic diseases at the opposite of those in industrialized countries (rate of advanced disease at diagnostic represent less than 10 %). Most patients in poor countries have a diagnostic with high rate of PSA and an aggressive disease with Gleason score ≥8. During diagnostic, they need bone scan to eliminate bone metastases and CT SCAN to eliminate visceral and lymph node metastases.

2.3 Screening

There is no scientific consensus to conclude the justification of systematic screening of prostate cancer organized nationally or in the subpopulation through the PSA. Important questions about the routine screening of prostate cancer remain, particularly its impact on survival, but also the risk of overdiagnosis and

overtreatment primarily for cancer diagnosed at a very early stage and slightly aggressive, especially in the elderly [7, 8]. Despite high incidence of prostate cancer in the Caribbean area, screening is recomended for men aged 45 years old.

3 Classification

3.1 TNM Classification

(7th American joint committee of cancer TNM staging system for prostate cancer, 2009)

The state of progress of the disease is established from an international classification, TNM classification according to the American Joint Committee on Cancer. This classification takes into account three factors:

- Size of the tumour (T for the original tumour)
- Presence or absence of cancer cells in the lymph nodes (N for the initial node)
- Presence or absence of metastases (M for initial metastasis)

There are two TNM classifications: one, cTNM (clinic c) which is based on clinical data prior to the completion of treatment and guide the choice of treatment; another, pTNM (pathology p) which takes into account the additional information provided by the surgical and histopathological examination of the surgical specimen.

3.2 D'Amico Classification

This is a classification of localized prostate cancer [9]. This classification established three subgroups of localized disease based on the risk of relapse or recurrence after local treatment, that is to say, three levels of risk of cancer progression: low risk, intermediate risk and high risk.

Three subgroups defined according to their clinical and biological characteristicsare:

Low risk: TNM ≤ T2a and Gleason score ≤ 6 and PSA (ng/ml) ≤ 10
Intermediate risk: TNM = T2b or Gleason score = 7 or PSA (ng/ml) between 10 and 20
High risk: TNM ≥ T2c or Gleason score ≥ 8 or PSA (ng/ml) > 20.

4 Evolution and Treatment

Prostate cancer is a tumour that progresses slowly in most cases. Active surveillance is a treatment option increasingly used in recent years. The aim is not to treat immediately cancer newly diagnosed prostate, if patient agrees and his

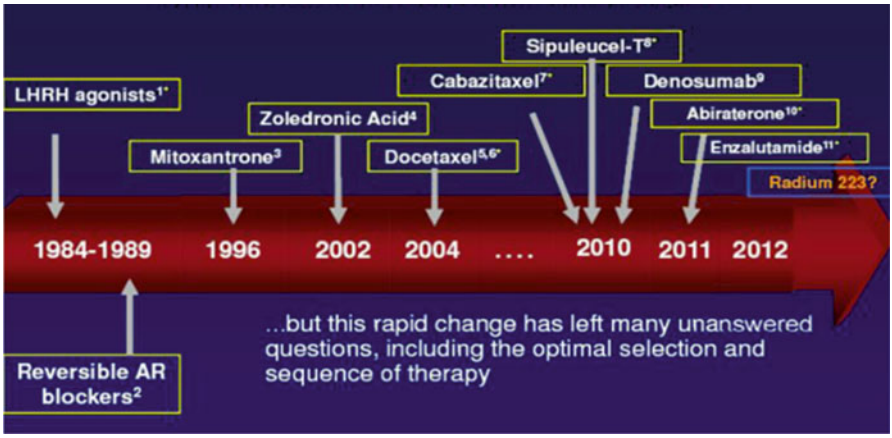

Fig. 3 History of systemic therapies in advanced prostate cancer

tumour is clinically localized, low risk of progression [10]. The patient is subject to regular monitoring, clinically, biologically and histologically by prostate biopsies. A classic treatment for cancer (radical prostatectomy, external radiotherapy or brachytherapy) is proposed in case of tumour progression or if the patient asks.

The choice of treatment depends on the characteristics of cancer (location, degree of extension, aggressiveness, etc.) and those of the patient (age, comorbidity, etc.).

For localized prostate cancer, whatever is the prognostic group, radical prostatectomy is the reference treatment. However, for patients with comorbidities and above 70 years old, radiotherapy is an option. Whatever is the choice of treatment, a follow-up is mandatory to prevent recurrence disease. The main aim is to control the primary site of cancer.

After these two treatments, the most common side effects are impotency and incontinence. In the following months after treatment, there is a possibility to recover up to 24 months.

During this time, physiotherapy could help to improve continence and intracavernous injection and vacuum pump are cheaper options to treat impotency.

For the most aggressive with metastases, androgen deprivation therapy is the first option. In case of resistance to castration, chemotherapy is attempted our new hormonotherapy like Abiraterone our Enzalutamide (Fig. 3).

In countries with low incomes, surgical castration seems to be a good option to control advanced diseases. At time to castration resistance, chemotherapy by docetaxel is an option in terms of price, because new hormone therapies are expensive.

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Renal Cancer

Fiona Mei Wen Wu and Edmund Chiong

1 Introduction

Renal cancer accounts for about 2–3 % of all adult cancers, and the majority (>90 %) are renal-cell carcinomas [1, 2]. In 2012, there were about 213,924 new cases with 90,802 deaths from kidney cancers worldwide (Globocan 2012) [3]. The increase in global kidney cancer incidence has been attributed to new imaging techniques, which in turn, leads to higher number of incidental cases detected [4]. Another possible reason is the greater prevalence of risk factors (e.g., obesity and cigarette smoking) associated with the disease. As most of the kidney cancers are renal-cell carcinoma, the discussion in this chapter will focus on renal-cell carcinomas. In 2012, the incidence of RCC for both sexes is higher in developed countries (199,991 cases) than in less developed countries (137,869 cases) [3], and this trend was previously noted by a kidney cancer working group [2].

With imaging performed for other purposes, kidney tumors are now increasingly found as small, asymptomatic, incidental renal masses [5, 6]. As a result of this cancer stage shift, treatment for localized RCC has also progressed in the last decade, with nephron-sparing surgery using minimally invasive techniques replacing open radical nephrectomies. This is possible as the disease-free survival (DFS) of small (<4 cm) localized RCC is high and current focus is on renal parenchymal preservation and quality-of-life outcomes.

Although RCC is now detected at an earlier stage, about 20–30 % of cases still present with metastatic disease at diagnosis, and about a third of patients undergoing nephrectomy for localized disease will eventually develop metastases [7]. In these cases, the main goals of systemic treatment will be for palliation of symptoms and disease control. The Memorial Sloan-Kettering Cancer Center (MSKCC) risk

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classification describes several factors which are used to classify patients treated with interferon-α into good, intermediate, or poor risk [8]. Prognosis is generally guarded for patients with metastatic renal-cell carcinoma, with median survival being 20 months in the good-risk group and 4 months in the poor-risk group [8]. Treatment for metastatic RCC has also undergone a paradigm shift, with the advent of administration of systemic therapies with cytoreductive nephrectomy and development of new targeted therapies [9]. Risk stratification and normograms can also help in treatment planning.

2 Resource-Stratified Consensus Framework

Guidelines for RCC are evidence based, but they do not take into consideration the differences in economies, available resources, and facilities between countries [9]. These issues are especially pressing in low and middle-income countries. With the increase in therapeutic options for RCC, there is a need for management strategies that improve cancer outcomes with minimal morbidity but, at the same time, take cost and resource availability into account [9]. Treatment guidelines are reviewed according to best clinical evidence, and management recommendations are based on resource availability. Resource levels are defined according to a four-tier system (basic, limited, enhanced, and maximum), which was previously described by the Breast Health Global Initiative [10].

3 Treatment of Localized Renal-Cell Carcinoma

Surgical resection remains an effective method for clinically localized RCC [11]. Radical nephrectomy (RN) has been the standard of care for many years, but recently, partial nephrectomy (PN), energy ablation therapies, and active surveillance have emerged as alternative options. To embark on these alternative therapies to prevent chronic kidney disease, we have to consider the skill level of health professionals, the health-care resource level, and the likelihood of follow-up compliance [9].

3.1 Radical Nephrectomy

Radical nephrectomy is the recommended standard for locally advanced RCC (T3-T4) [11]. Routine regional lymph-node dissection with RN is controversial because treatment benefits have not been shown. A randomized, prospective European Organisation for Research and Treatment of Cancer (EORTC 30881) trial failed to show a survival benefit, over a median follow-up of 12.6 years, for patients with localized RCC ($n=732$) who underwent limited regional lymph-node dissection [12]. Adrenalectomy with RN is usually performed if there is adrenal involvement or for

upper pole tumors [11]. For inferior vena cava (IVC) involvement, RN with resection of caval thrombus is performed [11]. Cardiopulmonary bypass (CPB) with hypothermia circulatory arrest may be necessary for thrombus above the hepatic level, where cardiovascular expertise will be required. If intrahepatic IVC is involved, hepatobiliary surgery expertise may be required to mobilize the liver to gain access to the IVC. Radical nephrectomy can also be performed laparoscopically if resources and trained personnel are available. Advanced centers may also perform robotic-assisted laparoscopic RN. A systematic review by MacLennan [13] showed that laparoscopic RN offered equivalent survival to open radical nephrectomy, and all laparoscopic approaches achieved equivalent survival for localized RCC.

3.2 Partial Nephrectomy

Partial nephrectomy is traditionally indicated for patients with a solitary kidney and bilateral renal tumors or those with preexisting medical conditions that may predispose to chronic kidney disease. However, in recent times, PN for small, localized renal masses (<4 cm) [14] is considered the standard of care even when the contralateral kidney is normal. The rationale for PN is to achieve equivalent oncological efficacy to RN, while avoiding overtreatment of small, possibly benign or indolent lesions and preserving renal function. Several single, multi-institutional, and population-based studies consistently showed similar cancer-specific survival rates for open partial nephrectomy and radical nephrectomy for T1b tumors despite the lack of randomized trials [15]. Van Poppel et al. [16] showed in an EORTC randomized trial that for solitary tumors <5 cm, there was no significant difference between RN versus PN in overall survival over 9.3 years of follow-up. For tumors >7 cm, PN can be considered an option for selected patients in experienced centers [14], but no recommendation can be made due to paucity of data on oncological efficacy. Laparoscopic and robotic partial nephrectomy can be performed at some experienced centers with skilled surgeons. Again, more data is required.

3.3 Energy Ablative Therapy

Energy ablative therapy, namely, cryotherapy and radiofrequency ablation (RFA), can be offered to patients with T1a (<4 cm) small renal masses as a minimally invasive nephron-sparing alternative. Percutaneous and laparoscopic approaches have been used, and the tumors should ideally be exophytic and not adjacent to the hilar vessels or collecting system. Issues with these methods are higher rate of local recurrence (RFA more than cryotherapy) when compared to PN [17], and posttreatment success is defined radiologically (lack of radiological enhancement) which is not ideal. Due to the paucity of evidence, energy ablative therapy is usually offered to elderly patients with multiple comorbidities who are poor surgical candidates.

3.4 Active Surveillance

This strategy is for the management of small renal masses (<4 cm) to avoid overtreatment in elderly patients with medical conditions in which surgical risks may outweigh its survival benefits. A meta-analysis by Chawla et al. [18] showed that these small, solid lesions grow slowly (increase of 0.28 cm/year), and only 1 % progress to metastatic disease. However, the studies are retrospective with short follow-up. As such, there is still risk of disease progression and metastasis, and this option is currently most suitable for surgically unfit, elderly patients with limited life expectancy.

3.5 Treatment Recommendations According to Resource Level

Our recommendation, based on resource availability, is summarized in Table 1. At the basic resource level, open surgery (RN or PN) should be offered if possible, depending on the level of surgical skill. At the limited resource level, laparoscopic RN can be attempted if there is appropriate equipment. Laparoscopic partial nephrectomy, which requires more sophisticated equipment and more trained personnel with higher skill level, should be offered at the enhanced resource level. In a maximum resource level center, robotic-assisted laparoscopic surgeries can be an option to laparoscopic nephrectomies. For renal tumors with IVC involvement (especially above the hepatic level), cardiovascular expertise with good postoperative intensive care is essential; therefore, surgery should be performed at the enhanced and maximum resource level centers. Energy ablative therapies require specific resources and skilled professionals, which should only be offered at enhanced/maximum levels. Active surveillance requires close follow-up with imaging modalities and may be more suitable for enhanced or maximum resource levels although it is an option at basic or limited resource levels if facilities and skilled personnel (i.e., radiologists) are available.

4 Treatment of Metastatic Renal-Cell Carcinoma

4.1 Role of Cytoreductive Nephrectomy

Two large randomized trials, SWOG 8949 [19] and EORTC 30947 [20], provided level 1 evidence for the role of cytoreductive nephrectomy in metastatic RCC patients with good ECOG (Eastern Cooperative Oncology Group) status. A combined analysis of these 2 trials showed an increase in median survival by 5.8 months (13.6 vs 7.8 months, $p=0.002$) of the group with cytoreductive surgery [19–21]. This has become the standard of care for patients with metastatic RCC before immunotherapy.

Table 1 Surgical treatment of renal-cell carcinoma according to health-care resource level

Resource level	Localized RCC				Metastatic RCC
	Radical nephrectomy	Partial nephrectomy	Energy ablation	Active surveillance	Cytoreductive nephrectomy for selected patients with metastatic RCC
Basic	Open surgery	Open surgery	No	No	Open surgery if systemic treatment available
Limited	Open or basic laparoscopic surgery	Open surgery	No	No unless imaging modalities and trained personnel available	Open or basic laparoscopic surgery
Enhanced	Open or advanced laparoscopic surgery. IVC thrombectomy with CBP. Liver mobilization for intrahepatic IVC involvement	Open or advanced laparoscopic surgery	Percutaneous or laparoscopic cryotherapy or RFA	Yes	Open or advanced laparoscopic surgery
Maximum	Open or advanced laparoscopic or robotic surgery. IVC thrombectomy with CBP/hypothermia arrest. Liver mobilization for intrahepatic IVC involvement	Open or advanced laparoscopic or robotic surgery	Percutaneous or laparoscopic cryotherapy or RFA	Yes	Open or advanced laparoscopic or robotic surgery

Adapted from Chiong et al. [9]
RFA radiofrequency ablation, *IVC* inferior vena cava, *CPB* cardiopulmonary bypass

The role of contemporary targeted therapy, sunitinib with cytoreductive nephrectomy, is being investigated in two large European trials now, CARMENA and SURTIME. The MSKCC risk stratification model [8] can be used to predict outcomes after cytoreduction, which is crucial for patient selection before surgery.

4.2 Systemic Treatment

Renal-cell carcinoma is considered to be both chemo- and radioresistant. As clear-cell RCC accounts for 75 % of RCC [22], the discussion will be confined to the treatment of this most common subtype. Before 2005, cytokine-based immunotherapy was the standard treatment for metastatic RCC. Interleukin-2 and interferon-α were the main treatments used. High-dose interleukin-2 is the only agent that was able to demonstrate complete, durable response in tumors [23]. It can be used in patients with good performance status, but due to its potentially serious side effects, patients will need to be observed in maximum resource level center with highly skilled personnel. Interferon-α and low-dose interleukin-2 are more commonly used because of their better side-effect profiles. Immunotherapy provides a response rate of 20 % and median progression-free survival of 5 months [24].

New agents have been developed in recent years, and they can be broadly classified into two groups, those that inhibit VEGF (tyrosine-kinase inhibitors, sorafenib, sunitinib, pazopanib, and axitinib, and VEGF monoclonal antibody, bevacizumab) and those that inhibit the mTOR (temsirolimus and everolimus) pathways. With adequate resources, these targeted therapies should be the standard of care.

First-line treatment options for patients with metastatic RCC with good or intermediate prognosis are sunitinib, bevacizumab with interferon-α or pazopanib. For poor-risk prognostic group, temsirolimus and sunitinib can be used. Second-line agents to be used after VEGFR are axitinib, sorafenib, and everolimus and after cytokine therapy are sorafenib, axitinib, and pazopanib [14]. There is a lack of data to guide treatment at third line and beyond. Systemic treatment should be initiated in symptomatic patients and side effects managed while on treatment.

Sunitinib, which is a TKI (tyrosine-kinase inhibitor) that inhibits VEGF receptors 2 and 3, PDGFR B (platelet-derived growth factor receptor B), FLT-3, and c-KIT, has been shown in a phase 3 trial by Motzer et al. [25] to be superior to interferon-α in terms of ORR (objective response rate, 31 % vs 6 %, $p<0.0001$), PFS (11 months vs 5 months, $p<0.001$), and OS (overall survival, 26.4 months vs 21.8 months, $p=0.049$), respectively.

Bevacizumab (monoclonal antibody against VEGF) with interferon-α has been shown in two large phase 3 trials, AVOREN [26] and CALGB 90206 [27], to have a higher response rate and improved PFS when compared to interferon-α alone in treatment-naïve patients with metastatic RCC. This is now approved as first-line treatment for metastatic RCC.

Sorafenib (TKI against VEGF receptors 1–3, PDGFR B A and B, FLT-3, c-KIT, and intracellular Raf kinase signaling) is used as a second-line agent after disease

Table 2 Systemic treatment of metastatic renal-cell carcinoma according to health-care resource level

Resource level	Systemic treatment		
	1st line	2nd line	3rd line
Basic	Best supportive care	–	–
Limited	Targeted therapy, interferon-α with financial assistance, clinical trials	Clinical trials	–
Enhanced	Most cost-effective and efficacious first-line therapy, clinical trials	Most cost-effective and efficacious second-line therapy, clinical trials	Clinical trials
Maximum	Any approved first-line therapy, clinical trials, high-dose interleukin-2 in patients with good performance status if facilities and skills available	Any approved second-line therapy, clinical trials	Clinical trials

Adapted from Chiong et al. [9]

progression on cytokines, interleukin-2, or interferon-α. Its use in prolonging PFS (median 5.5 months vs 2.8 months, $p<0.001$) and ORR (10 % vs 2 %) when compared to placebo was shown in a phase 3 trial by Escudier et al. [28].

Temsirolimus, a mTOR inhibitor, blocks PI3K/AKt/mTOR pathway. It is used as a first-line treatment for patients with metastatic clear-cell RCC with poor MSKCC prognostic risk as it showed benefit in terms of PFS and median overall survival when used as monotherapy [29]. Everolimus showed benefit as second-line therapy after disease progression on VEGF TKI therapy in the phase 3 RECORD-1 trial (PFS 4.0 months vs 1.9 months, $p<0.0001$) when compared to best supportive care [30], and it is recommended in the EAU guidelines [14].

4.3 Treatment Recommendations According to Resource Level

Patients' quality of life should be the goal for managing metastatic RCC together with prolonging life. Table 2 summarizes medical management of metastatic RCC based on resource level. Open cytoreductive nephrectomy can be offered at all levels. Options to this (e.g., laparoscopic or robot assisted) can be offered if resources and skills allow (see Table 1 for surgical management of RCC). Due to the lack of resources, for basic level of health-care resources, best supportive care is recommended even when targeted therapies are the standard of care for patients with metastatic RCC. First-line targeted therapies can be used if there are assistance programs to offset the costs of treatment at the limited resource level. Clinical trials and interferon-α are options. At enhanced level of resources, the most cost-effective and efficacious first- and second-line agents should be given. Clinical trials can also be considered. This is similar for maximum level of resources except that costs may be less of an issue. High-dose interferon-α can also be administered if there are facilities to monitor the adverse effects of the treatment. If patients with good performance status progress after recommended second-line treatment, clinical trials should be considered.

5 Conclusion

The emphasis is now on functional outcome and quality of life, together with oncological clearance, after treatment for localized RCC. Active surveillance, minimally invasive surgeries, and energy ablative treatments are emerging options in the last two decades for this disease. The agents available for systemic therapy for metastatic RCC are also increasing and improving. However, due to issues with access to these therapeutic modalities, patients may not benefit from these modern treatments. With these guidelines, treatment should be administered according to resource level availability.

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Cutaneous Cancers (Including Melanoma)

Pierre Couppié and Adama Traoré

1 Major Determinants of Skin Cancer Carcinogenesis and Their Management in Tropical Areas

Four main factors are associated with the epidemiological profile of skin cancer in the tropics: more intense ultraviolet radiation (UV radiation), a higher proportion of dark-skinned inhabitants, low incomes in association with limited healthcare resources, and high biodiversity including oncogenic microbial pathogens (Fig. 1).

UV radiation is more intense in the tropics because the rays from the sun being perpendicular have a shorter path through the atmosphere and are therefore less absorbed by the atmosphere's layers. In fair-skinned populations, the incidence of three major UV-induced cancers – basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma (MM) – increases with diminishing latitude.

Skin pigmentation varies substantially across human populations. In the skin, melanin acts as an optical and chemical photoprotective filter which reduces the penetration of UVR into epidermal and subepidermal tissues. Melanin is synthesized in melanosomes, which are distributed to keratinocytes by the dendritic

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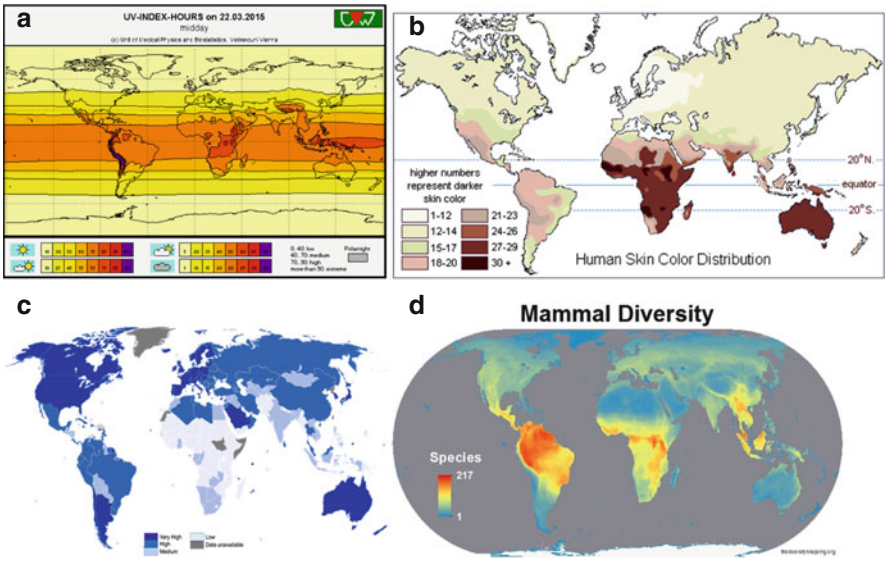

Fig. 1 Four global maps illustrating the four main factors associated with the epidemiological profile of skin cancer in the tropics: (**a**) more intense ultraviolet radiation (http://www-med-physik.vu-wien.ac.at/uv/uv_online.htm); (**b**) a higher proportion of dark-skinned inhabitants (Reproduced from http://anthro.palomar.edu/vary/ by permission of Dennis O'Neil); (**c**) low incomes in association with limited healthcare resources (Illustrated with a map of the Human Development Index: World map indicating the categories of Human Development Index by country based on 2013 data; http://hdr.undp.org/en/2014-report); and (**d**) high biodiversity including oncogenic microbial pathogens (Illustrated by map of mammal diversity: Jenkins et al. [1]; http://biodiversitymapping.org/)

processes of melanocytes. The superior photoprotection of highly melanized skin (dark skin) is due to the high density and distribution of melanosomes within keratinocytes in the epidermis. In 1988, Fitzpatrick describes a scale of 6 phototypes that takes into account both the color of the skin, the susceptibility to sunburn, and the ability to tan after exposure to UVR [2]. Individuals with phototype I (generally with red hair) and II (generally with blond hair and blue eyes) tan little or not at all. The risk of photo-induced skin cancer is very high. People with phototypes III (generally brown hair) and IV (generally dark hair, brown eyes) tan easily. Sunburns are rare. Individuals with skin types V and VI have, respectively, brown or black skin, tan deeply, and rarely or never burn. Relationship between skin pigmentation in indigenous human populations and latitude is traceable to the strong correlation between skin color and UV radiation intensity. The clinal gradation of skin coloration observed among indigenous peoples is correlated with UV radiation levels and represents a compromise solution to the conflicting physiological requirements of photoprotection and vitamin D synthesis [3].

Low- and middle- income countries predominate in the tropics. Limited healthcare resources and limited access to healthcare are very frequent. The main

consequences are diagnostic delays, imprecise diagnoses, and limited therapeutic means. As with other cancers, limited access to pathological examinations, radiotherapy, and chemotherapy complicates the management. However, more than other cancer types, skin cancers can be diagnosed early by clinical examination and can in most cases be treated with surgery under local anesthesia.

Viral infectious agents are responsible for primary cutaneous cancers or cancers with cutaneous focus more often in low latitudes than in high latitudes. The main viruses involved are HHV8, oncogenic HPVs, HIV, and HTLV-1.

2 Epidemiology of Skin Cancer in the Tropics

Despite their frequency, BCC and SCC are not usually recorded by cancer registries due to their high frequency and low to very low case fatality rate. However, it is estimated that the five most common skin cancers in the world are in decreasing order of frequency: BCC, SCC, MM, Kaposi sarcoma (KS), and cutaneous lymphomas. The geographical distribution of these skin cancers shows variations. The first three are most often UV induced, reaching extremely high standardized incidence rates in tropical and subtropical areas where people mostly have fair skin (phototypes I and II). In Australia, a partially tropical country where the population is mainly fair skinned, every year 80 % of new cancers are skin cancers, especially BCC and SCC, respectively, 20 and 10 times more common than MM [4]. Nevertheless, MM is the fourth most common cancer in men (when excluding BCC and SCC) in Australia [4]. Table 1 summarizes and compares the Australian data and shows the influence of environmental ultraviolet radiation (latitude) and constitutional defense ability from ultraviolet radiation in white skin (tan ability) and black skin (indigenous, i.e., Australian Aborigines) [4–7].

In people with dark skin, the incidence of all UV-induced skin cancer is considerably lower. Thus, in the tropics, the incidence of MM is very high among people with fair skin and low in patients with dark skin. The main location of MM is the sole of the foot in these populations from Africa, Asia, and among the Australian Aborigines. This is a variety of MM called acro-lentiginous melanoma (ALM), which is not photo-induced unlike the other forms of cutaneous MM [8].

Kaposi sarcoma (KS) is due to HHV-8, a virus of the herpes virus group, and its incidence increases dramatically when there is a coinfection with HIV. The incidence of KS is very high in countries where these two viral diseases exist simultaneously with high incidence rates. Thus, KS is the most common cancer in several East African countries [9, 10].

In the tropics, the most common lymphoma involving the skin are the adult T-cell leukemia/lymphoma (ATLL) associated with HTLV-1 and mycosis fungoides.

The dermatofibrosarcoma protuberans is rare but could be a bit more frequent in black skin.

Table 1 Age-standardized WHO incidence rates (per 100,000 in habitants/year) for the three principal skin cancers occurring in Australia and associated factors (latitude, skin type categories, ethnic group). Impact of environmental ultraviolet radiation (latitude) and constitutional defense ability from ultraviolet radiation in white skin (tan ability) and black skin (indigenous, i.e., Australian Aborigines)

		BCC	SCC	MM	All cancers[a] except skin cancers
Total by cancer[b] [4, 5]		884	387	40	313
Latitude[b] [4, 6]	High, nontropical[c]	547	232	36	
	Median, partially subtropical[d]	959	432	47	
	Low, partially tropical[e]	1,662	794	65	
Skin type categories[b] [4]	Tans deeply	585	215		
	Tans moderately	722	319		
	Does not tan	1,271	611		
Ethnic group[f] [7]	Indigenous[g]			8	
	Non-Indigenous			32	

BBC basal cell carcinoma, *SCC* squamous cell carcinoma, *MM* malignant melanoma
[a]Including Kaposi sarcoma, lymphoma, and leukemia
[b]2002
[c]High latitude (>37°S)
[d]Median latitude (29°S–37°S)
[e]Low latitude (<29°S)
[f]2004–2008
[g]Aborigines (non-métis-Aborigines have black skin, Phototype VI)

3 Risk Factors and Pathogenesis

UV radiation is strongly associated with the three most frequent skin cancers: BCC, SCC, and MM. Schematically, UVB radiation can directly alter the DNA of epidermal cells, while the oncogenesis due to UVA radiation is more indirect. Spatiotemporal and meteorological factors affect the intensity of radiation: latitude, altitude, environment (sand, snow, water), time of day, period of the year, clouds, air humidity, ozone layer's density, etc. Latitude is an important factor affecting the risk of photo-induced skin cancers; the greatest risk is in the tropics (see Table 1). The temporal profile of the UV radiation dose influences the type of cancer: acute intermittent exposures (with sunburn) are rather involved in BCC and superficial spreading melanoma (SSM), whereas chronic exposure is rather associated with SCC and lentigo maligna (LM). Individual and collective behavioral factors (work, leisure activities and sports, fashion, knowledge of the sunbeam's risks, sunbed room) modulate exposure to UV radiation [11].

The pigmentation of the skin is mainly due to melanin. In the tropics, particularly in Africa, people with dark skin (phototypes V and VI) predominate. This dark pigmentation provides excellent protection against UV-induced cancers. This protection is abolished in melanocytic pathologies: genetic diseases like albinism or acquired diseases like vitiligo [12].

Age is a factor strongly associated with skin cancer, whether it is UV induced (BCC, SCC, MM) or not (classical or endemic KS). For UV-induced cancers, it is difficult to distinguish between the real influence of age and the cumulative dose of UV radiation-related to a longer exposure time. Overall incidence rises sharply from the fourth decade onward. In tropical regions, populations are generally young; with the demographic transition expected in the coming years, we may see an aging of the population which will cause increased incidence of skin cancer.

Sex is an important risk factor in KS (especially for non-HIV-associated forms with a sex ratio of around 10:1) and a relative factor concerning the location of MM (back in men, lower limbs in women). Moreover BCC and SCC are slightly more common among men (probably due to gender differences in exposure to the sun).

Genetic predisposition to skin cancer may exist. Some genetic diseases are accompanied by a specific gene mutation that constitutes a high-risk factor for skin cancer. This applies, for instance, to xeroderma pigmentosum (BCC, SCC, MM), Gorlin syndrome (BCC), or the most common mutations demonstrated in approximately 30 % of familial melanoma (CDKN2A gene mutation) [13]. Other predispositions are not yet clearly identified but likely involve genetic polymorphism predisposing as having a large number of nevi (MM). Skin phototype is also genetically determined.

Some viruses can cause skin cancers: HHV8 and KS especially when there is HIV coinfection, oncogenic HPV types and anogenital cancers (increased risk in case of HIV coinfection), HTLV-1 and adult T-cell leukemia/lymphoma (ATLL), Epstein-Barr virus (EBV) and Epstein-Barr virus-associated B-cell lymphomas, and Merkel cell polyomavirus and Merkel cell carcinoma (MCC). The pathophysiology of viral oncogenesis is described in the relevant chapters of this book. All, except perhaps MCC, are frequently described in the tropics.

Immunosuppression induced by immunosuppressive therapy in organ transplant recipients or caused by prolonged CD4+ lymphopenia in patients HIV+ promotes oncogenesis and skin cancers. In organ transplant recipients, UV-induced skin cancers are increased, especially SCC. In the tropics the risk could be higher because the UV radiation is more intense.

Some medications induce SCC: B-RAF inhibitors (vemurafenib) and voriconazole. These expensive drugs are currently not readily available in the tropics.

Various situations can promote the occurrence of skin cancer: chronic inflammatory conditions (chronic infectious dermatoses, ulcers or old burn scars) and predisposing or precancerous dermatologic lesions (actinic keratosis, lichen sclerosus, discoid lupus). Because mutagenic natural substances exist, plants applied on ulcers in the context of traditional medicine could be at risk, but data are lacking. Carcinogenesis is then of the SCC type.

4 Major Types of Skin Cancer in the Tropics

Connectivity – Internet or mobile phones – being rapidly expanding into many of low- and middle-income countries, a quick access to information and to guidelines could become easier, with updated classifications and updated therapeutic

Table 2 First-line treatment for invasive skin carcinomas, invasive skin melanoma, and Kaposi sarcoma in the context of limited healthcare resources when standard treatment is not available

	Localized tumor	Regional disease treatable by local modalities	More advanced or generalized disease[a]
Melanoma	Surgical excision[b]	Primary tumor excision[b] and regional lymphadenectomy	Surgical resection of isolated metastases Palliative local therapy Other[c]?
Basal cell carcinoma	Surgical excision[d,e], electrodesiccation-curettage[f]	Surgical excision or radiation therapy	Other[g]?
Squamous cell carcinoma	Surgical excision[h]	Primary tumor excision[h] and regional lymphadenectomy or radiation therapy	Radiation therapy, other[i]?
Kaposi sarcoma:			
HIV+	Antiretroviral therapy	Antiretroviral therapy ± radiation therapy or chemotherapy[j]	Antiretroviral therapy ± chemotherapy[j]
Non-HIV	Surgical excision or electrodesiccation-curettage or radiation therapy	Surgical excision or electrodesiccation-curettage or radiation therapy or chemotherapy[j]	Chemotherapy[j]

[a]Metastases (except regional adenopathy treatable by local modalities)
[b]Margins with 1 cm to 3 cm, depending on tumor thickness and location
[c]Immunotherapy (+/−) or signal transduction inhibitors (if B-RAF mutation) (+/−) or chemotherapy (dacarbazine)
[d]Nodular form: margins ranging from 3 to 10 mm, depending on the diameter of the tumor; margin evaluation by pathologist
[e]Infiltrating forms or ulcerating tumors: margins ranging from 5 to 10 mm; margin evaluation by pathologist
[f]Superficial forms
[g]Chemotherapy (cisplatin) or signal transduction inhibitors (Hedgehog pathway inhibitor)
[h]Margins ranging: 4 mm if well-differentiated tumors up to 19 mm in diameter, 6–10 mm for larger or less-differentiated tumors or tumors in high-risk locations (e.g., scalp, ears, eyelids, nose, and lips); margin evaluation by pathologist; reexcision may be required if the surgical margin is found to be inadequate
[i]Chemotherapy (cisplatin)
[j]Bleomycin, liposomal doxorubicin, or liposomal daunorubicin, combination of doxorubicin, bleomycin, and vincristine or bleomycin and vincristine

indications for skin cancers. For example, this information is freely available in English or Spanish languages on the website "http://www.cancer.gov" or in French language on the website "http://www.sfdermato.com." The challenges are rather to establish correct diagnosis and to access to treatment options. Here we briefly describe main skin cancers. Table 2 provides guidance on the available treatment options in cases of limited healthcare resources.

4.1 Basal Cell Carcinoma

4.1.1 BCC: General Information

BCC is the most common of all cancers. It is also the least dangerous because it is both slow growing and characterized by an almost total absence of metastatic spread. The most common location is the head, especially the face and nose. Surgical resection is the standard treatment that can sometimes require plastic surgery to optimize the aesthetic and functional aspects. BCC appears on healthy skin, and there is no mucosal involvement. The recurrence risk is higher for lesions in periorificial areas of the face.

There are three main types of BCC, from least to most aggressive: superficial (erythematous plaque), nodular (pearly appearance with telangiectasia), and infiltrating (scar plate). BCC usually progresses slowly in the form of a superficial spreading and sometimes evolves into ulceration (Fig. 2a). A spreading toward profound tissue layers such as muscles and bones by contiguity may appear over time with inability to achieve a complete surgical resection.

The standard treatment consists of a surgical excision of the entire lesion with pathological control including section edges to ensure that the removal is complete [14, 15]. Recommended margins depend on several clinicopathological factors. The margins vary from 3–4 mm to over 10 mm and are based on the risk of local recurrence. Surgical resection complemented by pathological examination of frozen sections or Mohs surgery can reduce these margins especially for infiltrating type. Nonsurgical treatments are possible: radiotherapy, cryotherapy, electrodesiccation-curettage, electrocautery, topical imiquimod, and phototherapy; these three techniques are to be reserved for superficial forms of BCC. In case of advanced forms, therapeutic possibilities involve chemotherapy, targeted therapy (in development), or radiotherapy.

4.1.2 BCC in the Tropics

Among the long-established populations in the tropics, there is an important melanin pigmentation that protects the skin from UV radiation resulting in a relatively low incidence of BCC. BCC is usually pigmented or "tattooed" and rather affects skin phototype IV to V. The darkest phototypes (VI) are virtually unaffected by this type of cancer. Among people with very fair skin in the tropics, carcinoma incidence rates are extremely high as previously described (see Table 1). The risk of Caucasian Australians developing a BCC before age 70 is greater than 50 % [4].

4.2 Squamous Cell Carcinoma

4.2.1 SCC: General Information

SCC has metastatic potential, which depends on: 1) clinical criteria: type, size (very low if less than 1–2 cm in diameter), location, existence and nature of previous precancerous lesion, recurrence, and neurological symptoms of invasion; 2)

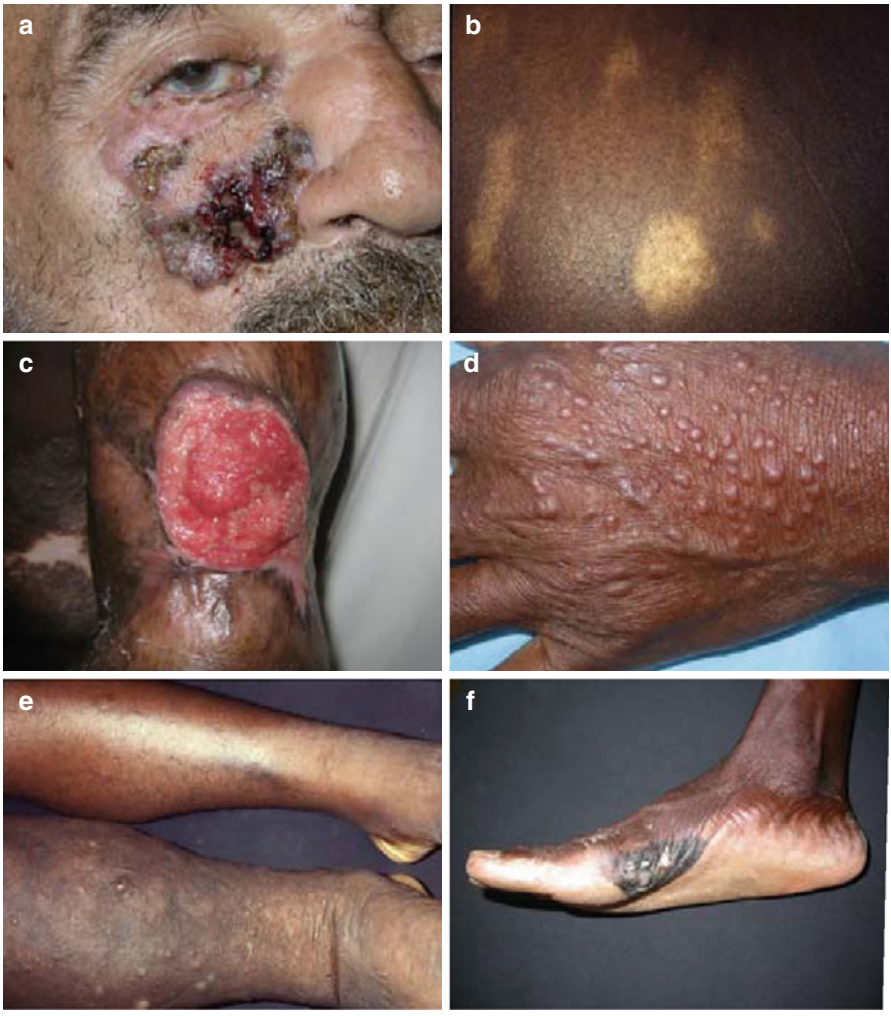

Fig. 2 Pictures of different types of skin cancer: (**a**) recurrent nodular-ulcerative BCC partially pigmented on the face with diagnostic delay; (**b**) hypochromic mycosis fungoides on black skin – early lesions; (**c**) SCC developing on burn scars (left arm); (**d**) multipapular type of ATLL in a HTLV-1+ woman (back of the left hand); (**e**) KS strictly localized to the right lower limb with lymphedema and nodules in a patient coinfected with HHV8 and HIV – absence of the characteristic purple color of KS on dark skin; and (**f**) MM-type ALM located on the sole of the foot in a patient of African origin

histopathologic signs: depth of dermal invasion, degree of differentiation, and histological type; 3) association with immunosuppression.

The cancer progression is initially local (ulceration, sometimes deep) or locoregional (lymph node metastasis in the first lymph node) and then metastatic. SCCs in situ may have specific clinical aspects: Bowen's disease or Bowenoid papulosis. SCC can grow on the mucous membranes (labial, buccal, anogenital) with possible

involvement of oncogenic HPV. SCC frequently appears on precancerous lesions like actinic keratosis and is then mostly UV induced. Sometimes SCC develops from chronic cutaneous inflammation, sites of prior burns (Fig. 2c), or long-standing skin ulcers.

The standard treatment for localized forms or forms with locoregional lymph node involvement is surgical excision with 5–10 mm margins for the primary tumor, depending on the criteria mentioned above [14, 16].

Other therapeutic methods can be used such as radiotherapy, cryotherapy, electrodesiccation-curettage, and electrocautery. Chemotherapy is rarely effective on metastasized forms; nevertheless, it can reduce the size of locally very advanced lesions which then allows surgery or radiotherapy. Targeted therapies are currently under development. For SCC in situ, nonsurgical treatment can be discussed as, for instance, cryotherapy, topical 5FU, or photodynamic therapy.

4.2.2 SCC in the Tropics

In patients with white skin living in low latitudes, the SCC incidence is very high and situated between BCC and MM [4] (Table 1). SCC usually occurs in a context of actinic skin with multiple actinic keratoses, solar lentigines, or epidermal atrophy. In people with darker skin, SCC is much less common but more common than BCC and MM [17]. On all skin types, some chronic tropical infectious, chronic ulcers, or chronic inflammatory dermatoses can become cancerous, usually after a long-standing evolution of 10 or more years [17, 18]. This applies to plantar ulcers in leprosy, phagedenic ulcers, chromomycosis, lobomycosis, Buruli ulcers, burn scars, chronic cutaneous lupus, etc. [19–21]. The application of plants on wounds, during traditional treatment, can question the carcinogenic potential of natural substances. A frequent problem is the difficulty for pathologists to differentiate between pseudoepitheliomatous hyperplasia (frequent in biopsies of ulceration edges) and SCC. In case of doubt, it is necessary to repeat biopsies in the middle of the ulcerated area.

4.3 Melanoma

4.3.1 MM: General Information

MM is less common than BCC and SCC in high latitudes; however, its incidence has increased significantly in people with very fair skin over the last 30 years. MM's metastatic potential depends on tumor thickness measured during pathological examination according to Breslow. Breslow thickness below 1 mm has a good prognosis; beyond 1–1.5 mm, prognosis is worse, especially if the lesion is ulcerated. A relatively small tumor mass can spread quickly, resulting in a melanoma case fatality rate of more than 10–20 % of all cases.

The extension is sometimes locoregional (lymph node metastasis). Lymph node dissection of the sentinel node does not improve survival. Visceral metastases occur either simultaneously or later. Primitive mucosal lesions (mouth, vagina) or other localizations like intraocular lesions are rare. MM most often appears on healthy skin (about 80 % of all cases), more rarely from a nevus. Patients with a giant congenital nevus have a high risk of developing MM.

The risk factors of MM are fair skin phototype (type I and II mainly) and ethnicity; UV radiation intensity and cumulative dose depending on latitude, altitude of residence, the type of sun exposure (intermittent/occasional, resulting in sunburn or not), and the sun-exposed body regions; age (incidence increases sharply after the age of 40; melanoma is very rare in children); personal and family history of melanoma; high number of nevi (>50 or >100) and/or atypical nevi; and certain genetic diseases (xeroderma pigmentosum) or predisposing mutations (10 % of all patients) [13].

The main types of melanoma are superficial (SSM), most common in white skin; nodular (NM), with a poorer prognosis because usually diagnosed at a later stage; acral (ALM), most common in dark or black skin; and lentiginous (LM), a form of melanoma in situ that occurs on the sun-exposed skin of elderly people, mainly on the face. Photoinduced melanomas are either induced by intermittent sun exposure (including sunburn) like in SSM and NM or by a high cumulative UVR dose in case of chronic exposure as in LM. The latter are very rare on black skin (phototype VI). On the contrary, plantar, palmar, and subungual (mainly in ALM) MMs do not seem to be induced by sun radiation [8]. In the USA, ALM incidence, although low, is similar in white and black populations [8].

The surgical margins of the primary lesion vary from 5 to 30 mm according to the Breslow depth [14, 22, 23]. In case of metastases, there is no curative treatment except for very rare cases with a single resectable metastasis. Chemotherapies are ineffective. The recent development of targeted therapies and immunotherapies in metastatic melanoma allows prolonged remissions, but these treatments are currently very expensive. Radiation therapy can sometimes be useful.

4.3.2 MM in the Tropics

ALM is the most common MM in Africa, among Aborigines in Australia, and among Chinese and Indians in Asia (Fig. 2f). Diagnostic delays are very frequent in Africa, so the prognosis is bad [24]. A differential diagnosis problem arises in clinical examination of the hands and feet in Africans because of the high frequency of palmoplantar pigmentations and pigmented nail strips [25]. Furthermore, on physical examination, achromic melanoma can be confused with KS or pyogenic granuloma.

A study in tropical area in Australia shows that sunscreen use in adults is beneficial in preventing MM [26]. These should be a general recommendation for fair-skinned populations living in the tropics.

4.4 Kaposi Sarcoma

4.4.1 KS: General Information

KS is usually considered as a cancer, but this is subject to controversy. Pathophysiology is probably based on oligoclonal proliferation of spindle-shaped cells of lymphatic endothelial origin, which form vascular channels followed by an extravasation of red blood cells.

The viral origin has been proven and involves HHV-8, a virus of the herpes group. Men are much more affected than women especially in forms without associated immunosuppression (sex ratio = 10:1). The global distribution of HHV-8 in human populations shows a north-south gradient, particularly in Africa. Some forms of immunosuppression, especially a coinfection with HIV, greatly increase the risk of KS and in particular of disseminated forms. KS mostly develops on skin especially of the lower limbs, but all organs may be affected except the nervous system.

The classification is epidemiological and clinical: classic or Mediterranean form mostly in the elderly; endemic (or African) form in Africa, which is more diffuse and occurs at an earlier age; associated form related to iatrogenic immunosuppression in organ transplant recipients; and AIDS-related epidemic forms with a high frequency of organ involvement.

The clinical appearance of skin lesions depends on the patient's pigmentation. On fair skin and mucous membrane (mouth, digestive tract, bronchi), lesions adopt their characteristic red maroon or purple color. On dark skin, lesions are pigmented and less typical. The lesions may be macular, papular, plaque like, nodular, or tumoral. The existence of lymphedema was first reported in African patients.

It is important to confirm the diagnosis by pathology. Whenever a KS is suspected, serology or a quick HIV capillary blood test must be carried out because the initial therapeutic management of KS in HIV+ patients is specific.

The main complication is related to the development of visceral lesions including pulmonary and digestive extensions. Pulmonary extensions are more severe (respiratory failure). Digestive forms can result in bleeding. Lymph node damage can cause dramatic lymphedema of the limbs or genitals.

There are various treatment options: surgery, radiotherapy, cryotherapy, chemotherapy, treatment of immunosuppression, and immunotherapy [14]. It should be noted that bleomycin is a relative inexpensive and effective drug in many cases of KS. Its advantage resides in the absence of induce cytopenias. Nevertheless, the total dose cannot exceed a certain maximum because of the risk of pulmonary fibrosis. The main indications for treatment are: (1) KS associated with HIV: treatment always starts with HIV antiretroviral treatment which alone can make the lesions disappear; however, immune reconstitution inflammatory syndromes are possible; (2) KS with visceral involvement: indication of chemotherapy (+/− antiretroviral treatment of HIV +); (3) cutaneous Kaposi with few lesions in the elderly: a local treatment may be sufficient.

4.4.2 KS in the Tropics

The epidemiology of KS in Africa has its particularities. It is the most common of all cancers diagnosed in Central and East Africa including Uganda due to extreme endemicity of HHV-8 in this region (prevalence > 50 %) combined with a not yet controlled HIV epidemic [9, 10]. Furthermore symptomatology of KS skin lesions is different, the purple-red appearance of the lesions being masked by the melanin pigmentation of dark skin (Fig. 2e). Finally in Africa, pediatric forms have been described which then concern lymph nodes first.

4.5 Other Types of Skin Cancer in the Tropics

Mycosis fungoides: a cutaneous epidermotropic T-cell lymphoma. It is rare, but incidence rate is highest among black in the USA. Mycosis fungoides has the particularity on black skin to begin with hypochromic lesions that can make the diagnosis difficult (Fig. 2b).

Adult T-cell leukemia/lymphoma (ATLL): the disease is due to a virus named HTLV-1. Skin lesions are frequent and polymorphic (Fig. 2d). The type of skin lesion is an independent prognostic factor in some studies [27].

Dermatofibrosarcoma protuberans: rare but slightly more common on black skin [28].

Dermatoses in paraneoplastic syndromes: among paraneoplastic dermatoses, one is frequently evoked in patients of African origin, acanthosis nigricans, not because it is more common in black skin but because it can be confused with pseudoacanthosis nigricans affecting mostly black women who are overweight.

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Epithelial Ovarian Cancer

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1 Incidence and Epidemiology

Ovarian cancer is the seventh most common cancer in women worldwide with age standardized rate of 6.1 per 100,000 women [1]. Ovarian cancer is a disease of older women with majority (>80 %) of cases diagnosed in women over 50 years. The median age of patients is somewhat lower in many developing countries because of their population structure.

2 Clinical Presentation

The symptoms of ovarian cancer are nonspecific and include bloating, dyspepsia, nausea, change in bowel habits (constipation or diarrhea), early satiety, abdominal or pelvic pain or discomfort, urinary frequency or urgency, dyspareunia, palpable pelvic or abdominal mass, and symptoms of intestinal obstruction [2]. Persistent symptoms should trigger further evaluation and investigations. Past history of breast or endometrial cancer in the patient or a family history of breast, ovarian, endometrial, or colonic cancers needs to be elucidated in all patients. Clinical examination should include a thorough abdominal and pelvic (per vaginal and per rectal) evaluation as well as examination of lymph nodes in cervical (especially supraclavicular), inguinal, and axillary areas and breast examination.

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3 Diagnostic Evaluation and Workup

After a full clinical assessment, the following investigations should be done to accurately differentiate between benign and malignant masses, determine the extent of disease, and assess operability.

3.1 Tumor Markers

Serum CA-125 is routinely used to aid diagnosis and follow-up patients. It is elevated in about 50 % of early stage and 85 % of advanced stage patients. It is not specific for ovarian cancer, and elevated levels may be found in non-gynecological malignancies (e.g., lung, breast, pancreatic, and colon cancer) and benign disease (e.g., pelvic inflammatory disease, endometriosis and ovarian cysts, abdominal tuberculosis). Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are also sometimes measured when it is unclear whether an ovarian mass is of gastrointestinal or ovarian origin.

3.2 Colonoscopy and/or Gastroscopy

These may be considered in an occasional patient with predominant gastrointestinal symptoms or family history of colorectal cancer, particularly when CA-125/CEA ratio is $\leq$25.

3.3 Imaging

Ultrasonography of abdomen and pelvis is usually recommended as the first imaging investigation in women presenting with adnexal mass. A number of morphological features such as size (>6 cm), multilocular cysts, solid papillary projections, irregular internal septations, and ascites are highly suggestive of ovarian cancer. A contrast-enhanced CT scan of the abdomen and pelvis can be performed to determine the extent of disease to aid surgical planning; however, it is not essential, particularly in resource-constrained settings. Chest radiograph should be performed to look for pleural effusions; however, an effusion cannot be regarded as malignant unless confirmed by cytology.

3.4 Pathology

In a considerable fraction of advanced stage patients, diagnosis can be established by demonstration of adenocarcinoma cells in ascitic fluid cytology in an appropriate clinical setting. It should be noted that apparently early stage disease should be taken up for

staging laparotomy on the basis of clinical and radiological evaluation without cytological or pathological confirmation in order to avoid tumor capsule breach and spillage [3]. However, in some clinically advanced stage cases being planned for neoadjuvant chemotherapy, image guided biopsy may be performed to establish diagnosis.

Ovarian cancer is not a single entity but represents tumors of epithelial (>90 %), germ cell, or sex cord stromal origin. The World Health Organization histological classification divides epithelial tumors into serous, mucinous, endometrioid, clear cell, and mixed varieties. Morphology remains the mainstay of diagnosis, and considerable expertise is required to correctly classify these tumors. Immunohistochemistry (IHC) is of value in supplementing the diagnosis, but is not essential. Its main utility is in differentiating primary from metastatic ovarian adenocarcinomas based on markers like CK7, CK20, CA125, CEA, and CDX2 [4]. Although important from prognostic and biological standpoints, current treatment paradigms do not yet differentiate between various subtypes of epithelial ovarian cancer. However, over the next few years, it is likely that treatment algorithms will be subtype specific.

It is important to correctly diagnose borderline tumors (low malignant potential), which exhibit cytological characteristics of malignancy but do not invade the stroma. They are frequently seen in young women, diagnosed in early stage, and have an excellent prognosis with 5-year survivals exceeding 80 %. They are managed primarily by surgery, and these patients don't routinely receive chemotherapy.

4 BRCA Mutations in Ovarian Cancer

Genomic analysis of germ line and tumor DNA shows that 20 % of women with high-grade serous ovarian cancer harbor germ line mutations in BRCA 1/2 genes. It is now clear that the confirmed diagnosis of high-grade serous disease should lead to genetic counseling and testing for BRCA mutations. This has important implications for women who are positive for BRCA mutations and their first degree relatives. There is also evidence of somatic mutations in BRCA genes in about 5 % of women with high-grade serous disease, which may have important implications on sensitivity to systemic chemotherapy as well as novel drugs such as PARP inhibitors. However, it is not absolutely essential to obtain germ line testing in all such patients at the time of diagnosis, especially in resource-constrained settings, because of the lack of impact on first-line treatment decisions.

5 Management of Early Stage Ovarian Cancer

5.1 Surgery

Ovarian cancer is staged surgically with pathologic confirmation. Appropriate surgery is of paramount importance for correct staging, planning adjuvant treatment, and prognostication. Surgical staging for ovarian cancer requires a

laparotomy by vertical midline incision with adequate exposure for thorough examination of the entire abdomen and pelvis. Adequate surgery should consist of the following:

- Peritoneal washings taken before manipulation of the primary tumor
- Bilateral salpingo-oophorectomy and hysterectomy
- Multiple peritoneal biopsies from all abdominal peritoneal fields
- Infracolic omentectomy
- Appendectomy in case of mucinous histology

The value of systematic pelvic and retroperitoneal lymph node dissection up to the renal veins in every case is not conclusively proven. Patients with apparently early stage disease, referred after an inadequate surgery, should have comprehensive surgical staging if feasible [5].

5.2 Adjuvant Chemotherapy

Based on several prognostic factors, early stage ovarian cancer can be classified into low or high risk for recurrence with following recommendations for adjuvant treatment:

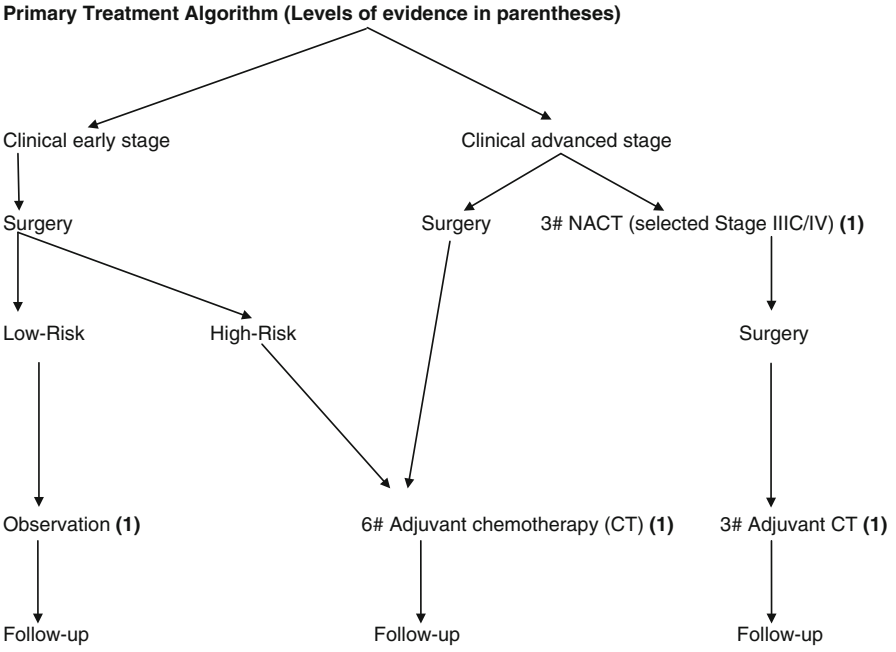
- *Low risk* – includes stage 1A and 1B (intact capsule, no excrescences, no malignant ascites, negative washings) with grade 1 and non-clear cell histology. No adjuvant therapy is indicated for these patients. However, it must be noted that patients can be considered low risk only after a meticulously performed staging laparotomy.
- *High risk* – includes all patients with stages 1C and II disease and patients with stages 1A/1B with grade 2 or 3 or clear cell histology. Adjuvant chemotherapy with six cycles of platinum-taxane (usually paclitaxel-carboplatin) is considered the standard of care in these patients.

These recommendations are based on a number of trials and their meta-analysis (5 prospective trials enrolling 1,277 women, 46–110 months follow-up) which showed [6] that patients who received adjuvant chemotherapy had better overall survival (OS) (HR = 0.71, 95 % CI 0.53–0.93) and progression-free survival (PFS) (HR = 0.67, 95 % CI 0.53–0.84) compared to those who did not. The optimal duration of treatment remains controversial. In one randomized trial there was no proven superiority of 6 versus 3 cycles with respect to both DFS and OS [7]. However, subgroup analysis suggested a benefit in serous tumors [7]. Six cycles are considered standard in early stage disease with three cycles being an acceptable alternative in some patients.

6 Management of Primary Advanced Ovarian Cancer (Fig. 1)

6.1 Surgical Management

In advanced ovarian cancer, the aim is to achieve optimal cytoreduction, currently defined as complete resection of all disease with zero residuum (R0), ideally by a specialized gynecologic oncologist. This has been shown to be associated with a significantly increased PFS and OS [8]. However, in areas of the world which lack or are deficient in specialized gynecology oncology surgeons, ovarian cancer surgery can also be undertaken by gynecologists with training in gynecologic oncology surgery. A maximal surgical effort, including (if required) intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph



- Low Risk-Stage IA/IB , Grade 1, Non-Clear cell Histology

- High Risk – Stage IA/IB, Grade 2/3, Clear cell histology, Stage IC, Stage II

Fig. 1 Algorithm for Ovarian cancer management

nodes, and splenectomy, should ideally be undertaken to achieve optimal cytoreduction. In advanced stage disease, systematic retroperitoneal lymph node dissection may be undertaken if adequate intraperitoneal cytoreduction has been achieved.

Although primary cytoreductive surgery is the standard approach in patients with advanced ovarian cancer, neoadjuvant chemotherapy followed by interval surgery is a valid option when optimal debulking is not feasible due to poor performance status or extensive tumor dissemination. Three randomized trials have shown that neoadjuvant chemotherapy followed by interval surgery is not inferior to primary debulking surgery with respect to overall survival, while treatment-related morbidity is lesser with neoadjuvant approach [9–11]. However, there remains some controversy about the role of neoadjuvant therapy before surgical debulking if the disease is surgically resectable and whether this should be the chosen option if initial disease is debulkable. Thus, when access to expert surgical resources is scarce, neoadjuvant chemotherapy followed by interval surgery is an acceptable, evidence-based, alternative in patients with advanced stage disease. The same regimen (paclitaxel-carboplatin) which is used after primary surgery is also used in the neoadjuvant approach, and surgery is usually sandwiched between the third and fourth cycles of chemotherapy.

6.2 Chemotherapy

6.2.1 Standard Intravenous Chemotherapy

The combination of paclitaxel (175 mg/m^2 as a 3-h infusion) and carboplatin (dosed to area under curve of 5–7), administered every 3 weeks for a total of 6 cycles, is the standard first-line adjuvant chemotherapy regimen in advanced stage ovarian cancer. This recommendation is based on a number of studies which proved the superiority of taxane-platinum compared to the previous standard of cyclophosphamide-platinum in patients with previously untreated stage III–IV disease [12, 13]. However, there was no superiority of paclitaxel-platinum over single-agent platinum in two other randomized trials [14, 15]. The latter results have been interpreted variably, including the possibility of pharmacological antagonism between cyclophosphamide and cisplatin and considerable crossover to paclitaxel in single-agent platinum arms. The latter argument suggests that these were really sequential, platinum followed by paclitaxel, strategies rather than true single-agent ones. The current broad consensus is that paclitaxel-platinum is the standard first-line regimen in advanced ovarian cancer. However, single-agent platinum is an appropriate alternative in frail patients and when use of taxanes is not feasible. Carboplatin and cisplatin can both be used in this setting although the former is preferable.

When patients have preexisting neuropathy or are at significant risk of developing it, docetaxel-carboplatin is an acceptable alternative to paclitaxel-carboplatin [16]. For those patients who develop hypersensitivity reaction to paclitaxel, the combinations of pegylated liposomal doxorubicin with carboplatin or gemcitabine with carboplatin are considered acceptable alternatives [17, 18].

6.2.2 Dose-Dense Chemotherapy

A Japanese study compared 3-weekly paclitaxel and carboplatin with the same dose of carboplatin every 3 weeks (AUC 6) and paclitaxel administered in a weekly dose of 80 mg/m^2 for 18 cycles and proved the superiority of weekly regimen in terms of both PFS (28.2 vs. 17.5 months, HR = 0.76, 95 % CI 0.62–0.91; $p = 0.0037$) and OS (100.5 vs. 62.2 months, HR = 0.79, 95%CI 0.63–0.99; $p = 0.039$) [19]. However, dose-dense chemotherapy was more toxic, and more patients in the dose-dense therapy arm discontinued chemotherapy compared to the standard chemotherapy arm. A second randomized trial (MITO-7) failed to prove the superiority of dose-dense regimen compared to the conventionally scheduled one, albeit with reduced dose intensity of paclitaxel in the dose-dense arm as also less toxicity [20]. Of note, unlike the Japanese trial, both paclitaxel and carboplatin were scheduled in a weekly manner in MITO-7. A third trial of weekly paclitaxel also failed to prove its superiority over every 3 week paclitaxel, when patients in both arms were allowed to take bevacizumab [21]. At present conventionally scheduled (every 3 weeks) chemotherapy is still considered the standard of care.

6.2.3 Intraperitoneal Chemotherapy

Intraperitoneal chemotherapy involves administration of a part of the regimen, usually the platinum agent, directly into peritoneal cavity through a catheter. A meta-analysis of five clinical trials confirmed benefit of intraperitoneal chemotherapy in OS [22] which led to a National Cancer Institute alert recommending that intraperitoneal therapy should be considered in patients with small volume (<1 cm) or no residual disease after surgery. Subsequently one more randomized trial [23] showed an improvement in OS with intraperitoneal cisplatin plus intraperitoneal paclitaxel plus intravenous paclitaxel, delivered in a day 1 and day 8 schedule compared to standard intravenous paclitaxel and carboplatin. However, because of difference in paclitaxel schedule and cumulative dose of platinum between the 2 arms, there is some debate whether the improved results are due to intraperitoneal administration or a partial weekly schedule of administration. Intraperitoneal chemotherapy has not been adopted as a standard treatment in the majority of centers worldwide because of its difficult and specialized delivery, greater toxicity, and lingering doubts about incremental efficacy compared to intravenous chemotherapy.

The addition of a third drug to taxane-platinum and maintenance/consolidation strategies has failed to improve outcome, and should not be routinely practiced.

6.2.4 Targeted Therapy

Angiogenesis is an important component driving the growth of ovarian cancer, and targeting this pathway may improve outcome. Two randomized trials have assessed the addition of bevacizumab, a monoclonal antibody against vascular endothelial

growth factor (VEGF), to the combination of paclitaxel and carboplatin in first-line adjuvant setting [24, 25]. Both studies reported a modest improvement in radiologically defined PFS (14.1 vs. 10.3 months in GOG 218, $p=0.001$ and 24.1 vs. 22.4 months in ICON 7, $p=0.04$), but no improvement in OS or quality of life. Moreover, PFS curves tended to converge after bevacizumab was stopped at protocol-defined time points (12 and 15 months, respectively, in ICON-7 and GOG-218). Planned subgroup analysis suggested a significant overall survival benefit in suboptimally cytoreduced stage III/IV patients in ICON-7 trial, but this finding can only be considered exploratory rather than practice changing. The benefit of adding bevacizumab is seen only in women at high risk of recurrence, with no benefit in women with advanced disease who are optimally debulked. No predictive biomarker for bevacizumab activity has been identified to date. The clinical benefit of adding bevacizumab to standard adjuvant chemotherapy in advanced ovarian cancer has led to adoption of this strategy in some countries, but its routine use in a first-line setting would not be considered as the current standard of care in resource-constrained settings.

7 Management of Relapsed Ovarian Cancer

Most women with primary advanced ovarian cancer (approximately 75 %) develop recurrence at a median of 1–2 years after initial diagnosis. The role of secondary cytoreductive surgery is not definitely established but may be considered in a selected group of patients with platinum-sensitive localized relapse amenable to complete resection. In patients with platinum-sensitive relapse (disease-free interval of >6 months after completion of adjuvant chemotherapy), combination platinum chemotherapy (for, e.g., paclitaxel-carboplatin, liposomal doxorubicin-carboplatin, gemcitabine-carboplatin) is standard based on an individual patient data meta-analysis, which has demonstrated improvement in OS and PFS compared to single-agent platinum [26]. In patients with platinum-resistant or refractory disease (disease-free interval <6 months after completion of adjuvant chemotherapy or progressive disease on primary treatment), single-non-platinum agent is the preferred chemotherapy option. Numerous agents like docetaxel, weekly paclitaxel, topotecan, oral etoposide, liposomal doxorubicin, capecitabine, etc., have been used with consistently low response rates of less than 20 %.

Again, addition of bevacizumab to standard chemotherapy in patients with platinum-sensitive and platinum-resistant relapsed ovarian cancer has led to modest benefits in PFS with no impact on OS [27, 28]. However, when feasible, its use may be considered in relapsed patients who have significant ascites and do not have features of intestinal obstruction. Recently poly(ADP-ribose) polymerase inhibitor, olaparib, has been found to be of utility in platinum-sensitive recurrence, especially in BRCA-mutated patients [29]. However, this treatment is currently not feasible for the large majority of relapsed patients in resource-limited settings.

Table 1 shows the various management options for epithelial ovarian cancer based on resource considerations.

Table 1 Management options for Epithelial ovarian cancer (based on resource considerations)

	No resource restrictions	Moderate restrictions	Severe restrictions
First-line stage IIIA–IV			
Surgery	Surgery	Surgery	Surgery
Systemic therapy	Carboplatin and paclitaxel	Carboplatin and paclitaxel	Cisplatin
Targeted therapy	Bevacizumab in high-risk disease		
Platinum-sensitive recurrence			
Surgery	Surgery if limited disease		
Systemic therapy	Platinum doublets	Platinum doublets	cisplatin
Targeted therapy	? Bevacizumab		
	Olaparib maintenance in BRCA mutation carriers		
Platinum-resistant disease			
Systemic therapy	Sequential single-agent therapy: weekly paclitaxel or liposomal doxorubicin or topotecan or cyclophosphamide or etoposide	Sequential single-agent therapy: weekly paclitaxel or liposomal doxorubicin or topotecan or cyclophosphamide or etoposide	Sequential single-agent therapy based on cost: cyclophosphamide or etoposide or weekly paclitaxel or doxorubicin or topotecan
Targeted therapy	Bevacizumab		
Palliative care and symptom control	Integrate	Integrate	Integrate
Platinum refractory disease			
Systemic therapy	Sequential single-agent therapy: weekly paclitaxel or liposomal doxorubicin or topotecan or cyclophosphamide or etoposide	Sequential single-agent therapy: weekly paclitaxel or liposomal doxorubicin or topotecan or cyclophosphamide or etoposide	
Targeted therapy	Bevacizumab		
Palliative care and symptom control	Integrate	Integrate	Integrate

8 Follow-Up After Primary Treatment

The value of various follow-up strategies after primary therapy has not been conclusively established, and hence practice varies across different centers. Clinical evaluation (history and physical examination, including pelvic examination) is suggested

once every 3 months for first 2 years and once every 6 months thereafter. Serum CA-125 estimation is commonly performed during follow-up visits. However, randomized evidence suggests that early intervention with second-line therapy in asymptomatic patients based on elevated CA-125 levels did not improve survival while resulting in greater use of chemotherapy, compared to treatment based on clinical relapse [30]. CA-125 may still be useful during follow-up in order to alert the patient and physician to impending relapse and directing appropriate radiological evaluation. Similarly there is no or weak evidence for using routine radiology during follow-up in asymptomatic patients. It is of paramount importance to counsel and educate patients about symptoms and signs of recurrence so that they seek medical attention before severe presentations such as intestinal obstruction and massive ascites with significantly compromised performance status.

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Endometrial Cancer

Frédéric Beurrier, Nicolas Carrabin, Séverine Racadot, and Nicolas Chopin

1 Introduction

Endometrial cancers are sixth in incidence of female cancers [1]. The quality of care is uneven in different geographical areas. This is mainly due to the inequality of resources [2].

Endometrial cancers in low-income countries represent 4 % of new cases of cancers and 1.5 % of cancer deaths. The incidence is 5.5/100,000 and mortality 1.5/100,000 respectively. This cancer has generally a favorable outcome [42].

2 Epidemiology, Characteristics, and Specificities

The greatest challenge for developing countries is to obtain data. Indeed few countries keep updated a register of collecting reliable data and therefore exploitable [3, 4].

Mortality decreases globally. This decrease is correlated with a decrease in mortality due to cancer in developed countries and decrease of mortality due to infectious diseases in developing countries [5]. Prioritization of resources spontaneously oriented infectious diseases. But it is important to take into account that in these areas, 12.5 % of deaths are due to malignant diseases. This is more than mortality due to the acquired immunodeficiency syndrome, tuberculosis, and malaria associated [4]. There has been in the recent decades a major increase in the incidence of cancer in developing countries [6].

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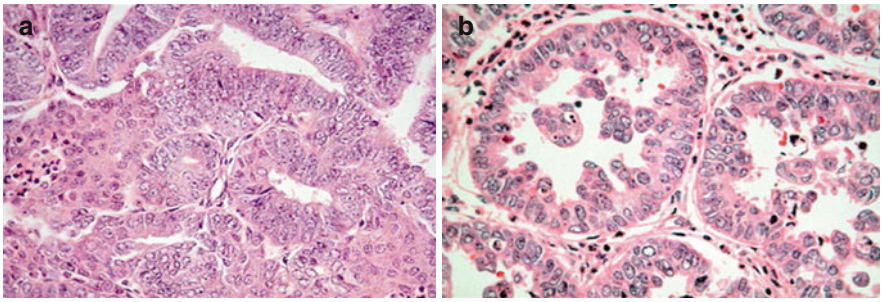

Fig. 1 Histological stages. (**a**) Type I: endometrioid adenocarcinoma. (**b**) Type II: serous papillary adenocarcinoma

Some countries provide less than 1 % of their budget to research [4]. Cancer research is critical to the care of patients. International studies were all conducted in developed countries. It is likely that the results are not transferable to developing countries where tumor characteristics [4], as well as patients and available treatments are certainly different [2].

Endometrial cancers correspond to different histological features. This has been well demonstrated by epidemiological studies and by molecular biology.

There are two histological types of endometrial cancers [7] (Fig. 1):

- Type I is endometrioid adenocarcinoma.
- Type II is high-grade tumors which include clear cell, serous papillary, and carcinosarcoma.

Type I cancer affects older menopausal women who have diabetes, hypertension, and overweight [8–10]. The mechanism behind this type of cancer is hyperestrogenism [8].

Type II cancer affects younger women without overweight. This cancer type has worse prognosis [11].

Type I cancer represents 80–90 % of endometrial cancers in developed countries [12] and only 75–80 % in developing countries [13, 14]. Patients in developing countries are younger than in developed countries [3, 13, 15]; overall incidence of this cancer is increasing. It is due to the aging population and lifestyle changes (obesity, diabetes, hypertension) leading to an increased incidence of type I [6, 16]. Five-year survival is 85 and 30 % in type I and type II endometrial cancers, respectively [11, 12].

3 Presentation and Initial Diagnostic Procedure

The diagnosis is suspected on genital bleeding in 78–90 % of cases [3, 12]. Diagnosis is made at a later stage [17]; in developing countries [3], prognosis is thus worse [2].

Ideally the initial diagnostic procedure combines a biopsy though the Cormier picker or hysteroscopy curettage to allow diagnosis of histological type and grade. Pelvic MRI, thoracoabdominal and pelvic CT scan, or a PET scanner is mandatory

to determine the stage. Once the type, grade, and stage have been determined, the treatment can be proposed and adapted according to the FIGO classification [18].

Despite a full pretherapeutic assessment, it is observed that an undervaluation of grade and/or histological type is 20–38 % of cases [19]. Myometrial infiltration on MRI is undervalued in 35 % and over evaluated in 10 % of cases, respectively [20].

PET scan is more accurate for the preoperative diagnosis of lymph node involvement. The sensitivity is 53.3 %, specificity 99.6 %, and accuracy 97, 8 % [21]. Standard imaging techniques (CT or MRI) are based only on morphological information. To be relevant, abnormalities must be greater than 10 mm; with PET scan, there is a gain of sensitivity since the detection of lymph node metastases is 93.3 % for lymph nodes of more than 10 mm, 66.7 % for those of 5–9 mm, and 16.7 % for those of less than 5 mm [22].

Despite that, PET scan is not essential to patients care of and can be replaced by the association thoracoabdominal-pelvis CT scan and pelvic MRI. This reveals the difficulties in obtaining a reliable pretherapeutic diagnosis. But it is important to have this evaluation to be able to differentiate advanced from local stages.

4 Staging

The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) has actualized endometrial cancer staging in May 2009 [18] (Table 1).

Table 1 2009 FIGO staging system for carcinoma of endometrium

Stage I[a]	Tumor contained to the corpus uteri		
	IA	No or less than half myometrial invasion	
	IB	Invasion equal to or more than half of the myometrium	
Stage II		Tumor invades the cervical stroma, but does not extend beyond the uterus[b]	
Stage III[a]		Local and/or regional spread of tumor[c]	
	IIIA	Tumor invades the serosa of the corpus uteri and/or adnexas	
	IIIB	Vaginal and/or parametrial involvement	
	IIIC	Metastases to pelvis and/or para-aortic lymph nodes	
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]			Tumor invades bladder and/or bowel mucosa and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Distant metastases, including intra-abdominal metastases and or inguinal lymph nodes

FIGO = International Federation of Gynecology and Obstetrics
[a]Includes grades 1, 2, or 3
[b]Endocervical glandular involvement only should be considered as stage I and no longer as stage II
[c]Positive cytology has to be reported separately without changing the stage

Table 2 Classification of early stages endometrioid adenocarcinoma

	Grade 1	Grade 2	Grade 3
IA	Low	Low	Intermediate
IB	Intermediate	Intermediate	High

When comparing the 2009 to the 1988 classification, the following changes have been made: former stages IA and IB have been merged. The stage IIA was eliminated. The positive peritoneal cytology no longer upstages the disease because it is not an independent prognostic factor. Finally, stage IIIC was differentiated in stage IIIC1 and IIIC2 depending of pelvic or lomboaortic nodes involvement.

The European Society of Medical Oncology (ESMO) also proposed a histoprognostic classification which was revised in 2008 [23] (Table 2).

These changes require an adaptation of the surgical management. Type I stage IA grade 1 and 2 (low-risk) patients do not require lymph node dissection. The benefit of the node staging is lower than the risk of complications. The risk of harm is less than 5 % [19] even 0 % if tumor size is less than 2 cm [24].

In other cases the complete lymph node dissection (pelvic and para-aortic) is the standard for high-risk patients, and this can be discussed in intermediate risks. The justification of extended lymphadenectomy is explained by the distribution of lymph node metastases: 33 % isolated pelvic, 16 % isolated lomboaortic, and 51 % combined lymph node involvement [25]. The lomboaortic dissection should be conducted to the renal vein because 60 % of supramesenteric-affected lymph node patients have no inframesenteric lomboaortic lymph node involvement [25].

In case of high-risk lesion with poor prognostic factors (type II), it is mandatory to perform peritoneal staging: omentectomy, peritoneal biopsies, and appendectomy.

5 Treatment

5.1 Surgical Management

International recommendations are weighted to the population profile of their specific features, medico-economic conditions, and opportunities of developing countries [26]. Surgery is the cornerstone of endometrial cancer treatment. The procedure should be immediately extended and adapted to clinical assessment if the disease is of high grade or of type II. This will avoid further surgery and therefore significant morbidity. The heterogeneity of surgical skill does not provide adequate treatment in all structures. Depending on the country, the surgical treatment is not suitable in 41–79 % of cases [3, 13, 27]. Inadequate surgical procedure does not set a reliable stage and leads to inappropriate adjuvant treatment in 20–40 % of cases [28].

The recurrence risk may therefore be as high as 68 % in these under staged patients [13, 27]. Five-year disease-free survival in types I and II stage I patients falls from 95 to 70 % in case of incomplete surgery [13].

It is important to remember that the nodal staging is mandatory because it is a prognostic factor; however, it is not therapeutic [6]. This is in favor of the management in two stages as proposed by some authors. A first single management for reliable diagnosis and then addressing the patient to a referral center are needed for further management [6]. This procedure allows patients to have access to a technical platform and surgical skills appropriate to their characteristics [6].

The lack of lymph node dissection in low-risk patients is still debated. Current recommendations in developed countries are consistent with therapeutic down-escalation. Some authors question this strategy because they suspect a decrease in disease-free survival in low-grade patients if the lymph node dissection was not performed [13]. Lymph node staging may have even a survival benefit for the three groups' stages in type I cancer [27]. This remains to be confirmed in powered prospective studies. The lack of lymph node dissection in low-risk patients in developing countries appears to be a futile concern at the sight of the difficulties encountered in the application of surgical standards due to the lack of adequately trained surgical resources [6].

The surgical management can be done through different approaches. Laparotomy is the most used because it is easier and a less expensive way. The recommendation in the developed countries is to extend the use of the laparoscopic approach. The reason is that it is equivalent in terms of oncological efficacy, but there is a gain on pain control, decreased transfusions needs and decreased lengths of stay, faster postoperative recovery, and a better quality of life [29, 30]. Again these considerations are not a priority. Moreover the learning curve to acquire a sufficient level of skill in laparoscopic surgery is much longer than this for laparotomy.

5.2 Adjuvant Treatments

5.2.1 Radiotherapy

Indication of adjuvant therapy is done on the knowledge of prognostic factors: FIGO stage, histological type, grade, vascular emboli, and age [31]. This explains partly the importance of a good initial surgical management.

International studies (PORTEC, GOG, ASTEC) have confirmed the place of radiotherapy and/or brachytherapy. The expected benefit is a better local control and an increased disease-free survival [32–34].

In low-risk disease, brachytherapy is discussed. Intermediate-risk patients require brachytherapy, and high-risk patients will benefit from external radiotherapy and brachytherapy. These recommendations apply to developed countries, but they remain to be demonstrated in developing countries [13]. However, it is established that radiation does not compensates inadequate surgery [13].

5.2.2 Chemotherapy

In advanced stages, the standard treatment is chemotherapy. It is essential to take into account local technical possibilities and specific comorbidities of patients to whom chemotherapy is indicated. Associated disorders may increase the side effects of chemotherapy (tuberculosis, HIV, chronic liver disease, malnutrition) [35]. Access to supportive cares may decrease quality of life [36]. This may explain poor observance [2]. In metastatic disease the objective is clearly palliative [2]. Currently, carboplatin-paclitaxel regimen is the standard treatment [37]. This combination induces the better response rate (about 60 %) but is expansive [2]. This explains that chemotherapy agents are mostly used as monotherapy, mainly anthracyclines or platinum salts with response rates between 20 and 40 % depending on the studies [2, 38]. Paclitaxel only induces similar response rate but at a higher cost [2]. Chemotherapy is associated in a Cochrane study with longer overall survival (OS) (hazard ratio (HR) 0.86; 95 % confidence intervals (CI) 0.77–0.96; $P=0.005$) and with longer progression-free survival (PFS) ($n=1{,}526$; HR 0.82; 95 % CI 0.74–0.90; $P<0.0001$) [39].

Finally, the therapeutic alternative that looks nice in this context is hormone therapy. This therapeutic option is only recommended in endometrioid histology. Progesterone treatment induces an 18 % response rate with a very good tolerance. Tamoxifen or anastrozole is also active [40, 41]. Prognostic factors of response in metastatic endometrial cancers are: well-differentiated tumors, a long interval to relapse, and extrapelvic metastatic relapse.

6 Conclusion

It is essential to balance the treatment options according to the local medical situation. The main effort must focus on standardization and quality of initial surgical care. The debate on the therapeutic escalation is not the issue, as it is, for example, on the discussion of the incision or laparoscopic approach despite the recommendations in developed countries. The treatment of patients in appropriate structures is necessary even if it means that it is done in a second time. This means that tertiary centers are needed to deliver optimal surgical procedures and adapted radiotherapy. These conditions will provide the patients the best chance of cure.

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Cancer of the Penis, Anus, and Vulva

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1 Introduction

Cancers and precancerous lesions of the anus, vulva, cervix, and penis cancers are associated with human papillomavirus (HPV). A high incidence of HPV-related cancer among patients with HIV/AIDS has been reported probably due to a persistence of HPV infection among those patients. Indeed, patients with HIV/AIDS have 4.5 times higher risk of penile cancer, 29 times higher risk of anal cancer, and 6.5 times higher risk of vulvar/vaginal cancer in comparison with the general population [1]. Unlike cervical cancer which is a major public health issue in developing country, anal, penile, and vulvar cancers are rare diseases.

2 Anal Cancer

2.1 Epidemiology

While uncommon (0.43 % of all malignancies), the anal cancer is increasingly frequent, with an incidence increasing from 0.8 to 1.7 cases per 100,000 persons per year from 1975 to 2011, respectively, in the United States [2]. Squamous cell cancer

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(SCCA) is the most common histologic diagnosis (85 %), followed by adenocarcinoma (10 %). Cancers and precancerous lesions of the anus are associated with human papillomavirus (HPV), and since 2012, anal lesions are subclassified into anal intraepithelial neoplasia (AIN): AIN I would correspond to anal LSIL, and AIN II/AIN III would correspond to anal HSIL. The median age at diagnosis is 60 years. HPV is the most known risk factor associated with anal cancer, especially HPV16. Other well-identified risk factors were receptive anal sexual intercourses, high number of sexual partners, immunosuppression, and smoking. Among HIV-infected patients, it has been reported that lower CD4 counts were associated with anal intraepithelial neoplasia and antiretroviral therapy was associated with a decreased prevalence of AIN but not with a decreased prevalence of high-risk HPV [3].

2.2 Screening and Prevention

Although it is not a routine for the general population, screening by a digital anorectal examination has been recently recommended every 2 or 3 years for HIV population as well as a high-resolution anoscopy with cytological evaluation. However, high-resolution anoscopy with cytological evaluation is most often not available in developing countries.

It has been shown that quadrivalent HPV vaccine decreased by 50 % AIN incidence. HPV vaccination is now recommended in current practice for boys and girls in the United States. HPV vaccination is prohibitively expensive and inaccessible in most people living in developing countries.

2.3 Clinical Presentation, Staging

The clinical manifestations of anal cancer are frequently late and nonspecific, because often they are confounded with hemorrhoids. Symptoms are mainly represented by anorectal bleeding (45 %), followed by pain (30 %), but can be thin-caliber stools and changes in bowel movements. 20 % of patients are asymptomatic [4]. Anal cancers are currently staged according the tumor, lymph node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC), seventh edition [5].

2.4 Patterns of Extension and Prognosis

Anal cancer extension can be direct through adjacent structures, lymphatic (perirectal, pelvic, and inguinal lymph nodes) and hematogenously (liver, lung, etc.). Perirectal (N1) lymph node invasion is more frequent for tumors arising above the

dentate line, whereas tumors below the dentate line spread to inguinofemoral (N2) lymph nodes. Lymph node positivity is directly related to the extent of invasion of the primary tumor. Male gender, tumor diameter, and positive lymph nodes were the three independent prognosis factors predicting worse overall survival and disease-free survival in the two major randomized trials [6, 7].

2.5 Treatment

2.5.1 Anal Margin Cancer

For patients with T1N0, well-differentiated anal margin cancer, wide local excision is the gold standard treatment.

Patients with T2 or greater lesions should be treated with chemoradiation as anal canal cancers.

2.5.2 Anal Cancer

Localized Disease

Surgery

Since the development of chemoradiation regimens, APR which was the standard of care in the past decades should be reserved for salvage therapy after local relapse (10–30 % of cases) and/or for T4 lesions that did not achieve complete response after primary radiochemotherapy.

Radiotherapy

Exclusive radiotherapy is indicated for patients with T1N0 anal cancer.

Chemoradiation

Two large randomized trials have demonstrated the superiority of chemoradiation over radiotherapy alone, in terms of progression-free survival and locoregional control [8, 9]. Another randomized trial demonstrated the interest of the use of mitomycine C for patients with T3 or greater lesions, and this treatment represents actually the standard of care for such advanced lesions [10]. Actually, the standard of treatment is full dose of 5-fluorouracil and mitomycine C for patients with a normal blood sample and/or in HIV patients with more than 200 CD4/m^3 and a reduction of the dose of mitomycine C (5 mg/m^2) for patients with abnormal blood count and or less than 200 CD4/mm^3 [10]. The use of cisplatin instead of mitomycine C, as well as induction and maintenance chemotherapy, has been disappointing [11, 12].

Metastatic Disease

There is no consensus on chemotherapy regimens regarding metastatic anal cancer, but the most commonly regimen used is 5-fluorouracil plus cisplatin [13].

3 Penile Cancer

3.1 Introduction

Penile cancer is a rare disease and mainly affects elderly patients. It is associated with human papillomavirus (HPV) infection which is present in 15–80 % of patients. HPV 16 and HPV 18 are the most common serotypes (60 % and 13 %, respectively).

Incidence of penile cancer is much higher in low and middle income countries than in Western countries. The disease frequently develops in men of low socioeconomic status and poor standards of penile hygiene [14]. Incidence is less than 1/100,000 males in Western countries, 3/100,000 in rural India, and 8.3/100,000 in Brazil. Uganda is the country with the highest cumulate rate of penile cancer (1 % by age 75 years). 95 % of penile cancers are squamous cell cancers.

3.2 Prevention

It has been shown that circumcision protects against penile cancer. Neonatal circumcision reduces the risk of penile cancer by at least ten times [15], and circumcision in the childhood reduces the risk by 3–5 times. Adult circumcision does not protect against penile cancer.

3.3 Treatment

3.3.1 Localized Disease

Cancer In Situ and Noninvasive Verrucous Cancer

Circumcision followed with 5-fluorouracil topical treatment if the lesion was not completely excised by the biopsy is indicated.

Persistent lesion could be treated with topical 5 % imiquimod as second-line treatment.

Surgical excision is reserved for refractory or extensive lesions.

Invasive Cancer

For distal penile T1 tumor, conservative surgery with partial penectomy is indicated. Conservative external beam radiotherapy or interstitial brachytherapy after circumcision is also an effective treatment in penile cancer, for tumor less than 4 cm without corpus cavernosum infiltration.

For proximal penile T1 or tumor with less than 2 cm margins, total penectomy with perineal urethrostomy is recommended.

For T4 tumor, emasculation consisted with penectomy, scrotectomy, and bilateral orchidectomy is recommended.

For nonresectable T4 tumor or fixed lymph node, neoadjuvant chemotherapy or concomitant chemoradiotherapy could be proposed before surgery.

Lymph Node Management

Penile cancer is a lymphophilic tumor. Prophylactic elective lymph node dissection is recommended in T2, T3, or T4 and/or high-grade tumors.

Inguinal lymphadenectomy is indicated in case of palpable inguinal lymph nodes. It is important to note that lymphadenectomy is curative in only 50 % of cases.

Postoperative radiation is indicated in patients with positive surgical margin, extensive lymph node metastasis, extracapsular lymph node spread, or pelvic lymph node involvement.

For pN2 or pN3 disease, adjuvant chemotherapy could be proposed after tumor resection and lymphadenectomy.

3.3.2 Metastatic Disease

Several chemotherapy drugs such as 5-fluorouracil, cisplatin, methotrexate, or bleomycin have been shown to be active in penile cancer.

Chemotherapy in penile cancer is delivered as palliative treatment.

4 Vulvar Cancer

4.1 Epidemiology

Vulvar cancer is a relatively rare disease. With 27,000 new cases worldwide for a year, age-adjusted incidence is 0–4.6 /100,000. Lower rates are observed in Asia and Africa than in other parts of the world. It represents less than 5 % of gynecologic malignancies [16, 17]. Vulvar squamous cell cancer (VSCC) represents more

than 90 % of the tumor. Morphological variants have been described including keratinizing, basaloid, warty, and verrucous cancer.

Human papillomavirus (HPV) DNA prevalence varies from 20 to 40 % [18, 19], and two pathways are distinguished: HPV-dependant and HPV-independent tumor [20]. In the first group, HPV 16 represents 75 % of the cases and usually is related to usual vulvar intraepithelial neoplasia (uVIN) as precursor. During last decades, VIN incidence increases. The risk of transformation toward VSCC represents approximatively 10 % of the case and only 3 if VIN had been treated. This pathway is associated with younger age, smoking, high sexual partner number, and compromised immune status [20–22]. The HPV-independent type is more often associated with p53 mutation. It occurs mainly in older women and is associated with lichen sclerous or chronic dermatosis with autoimmune diseases. Differentiated VIN (dVIN) is considered as the precursor and has a higher progression risk toward VSCC. Prognosis seems to be worse than HPV-dependent cancer [20–22].

It has been reported that HIV infection increased women's risk for genital warts and vulvar intraepithelial neoplasia (VIN). However, most warts among HIV-infected women with high CD4 counts have regressed spontaneously or responded to therapy. Low CD4 cell counts (<500/mm^3) were associated with an increase incidence of VIN2+ [23].

4.2 Diagnostic and Staging

Vulvar cancer does not express specific symptoms, and diagnosis is often delayed in particular in elderly. Diseases can be revealed by itching, dyspareunia, soreness, and burning sensations. Staging is based on clinical examination to define topography and extension. Tumor is mainly located on the labia (80 %), clitoris (10 %), or lower commissure (10 %). Since up to 50 % of the lesions appear multifocal or multicentric, inguinal and femoral lymph nodes are the main involved nodes. Because of possible HPV infection, the entire anogenital track (vagina, cervix, anal canal) has to be clinically examined; if necessary, the clinical exam may be completed by vulvoscopy, colposcopy, and anoscopy. Locally advanced diseases may involve the vagina, urethra, and perineum; cystostoscopy and rectoscopy can also be required. Imaging is not routinely required, but for locally advanced diseases, it may help to clarify extension to the vagina, the urethra, the surrounding tissues, and the lymph nodes. Tumor staging is based on TNM (Union for International Cancer Control, UICC) [24] and FIGO (International Federation of Gynecology and Obstetrics) classifications [25].

4.3 Prevention

By introducing the HPV 16 and HPV 18 immunizations, a reduction by half the incidences in young women can be anticipated [26]. A long-term reduction of the incidence of vulvar cancer in elderly women is improbable due to the HPV independence of the tumor in this subgroup of patients.

4.4 Treatment

4.4.1 Surgery

Surgery is the first-line treatment. Surgical procedure is adapted to the location and extension of the tumor and conservative approach such that radical local excision is favored over radical surgery [27]. 1–2 cm macroscopically margin is often recommended, and a <0.8 cm histopathologic tumor-free margin is considered as a prognostic factor [28].

Inguinofemoral lymph node involvement is one of the most important prognostic factors [29] and is correlated to the tumor infiltration depth [30]. Except for microinvasive tumor (<1 mm), inguinofemoral lymphadenectomy staging is recommended in patients with clinically nonsuspicious groins: ipsilateral lymph node dissection for lesions more than 1–2 cm lateral to the midline structures and bilateral lymph node dissection for lesions less than 1 cm from the midline structures. Lymphadenectomy has a substantial morbidity (leg edema, lymphocele, wound complications, erysipelas) [31].

4.4.2 Adjuvant Radiotherapy

Lymph node metastases are the most important prognostic factor, and adjuvant radiotherapy was shown a benefit on locoregional control and survival when 2 or more nodes are involved or associated with extracapsular spread [32, 33], whereas its impact is still unclear for isolated node metastases [34–36]. Criteria for adjuvant radiotherapy to the vulva are debated. Lymphangio-invasion, tumor size, closed margin, and depth infiltration may have a negative impact on local recurrence and radiotherapy is probably required [28, 29, 37, 38]. Postoperative chemoradiation is not a goal standard. Some authors suggest a benefit for selected patients [39].

4.4.3 Neoadjuvant Chemoradiotherapy

Combined chemoradiation is mainly used in advanced vulvar cancer involving neighboring structures (muscles, bone) where exenteration and/or (partial) resection would be necessary to remove the cancer tissue with clear resection margins [40, 41]. Primary neoadjuvant setting is an option to reduce tumor volume, achieve resectability of the tumor, and reduce the extent of surgery in 30–70 % of cases [42, 43].

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Gestational Trophoblastic Diseases

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1 Introduction

Gestational trophoblastic diseases (GTDs) constitute a continuum from benign hydatidiform mole to the potentially metastatic invasive mole and placental site trophoblastic tumour to the highly metastatic choriocarcinoma. They represent abnormal proliferation of the fetal trophoblastic tissue [1]. The versatility of the tumour marker, beta-human chorionic gonadotrophin (β-hCG), and the sensitivity of the malignant solid diseases to combination chemotherapy [2], coupled with efficient regionalisation of treatment centres [3], have resulted in survival figures of more than 90 % in the few cases reported from developed countries in the last half century [2]. Numerous socio-economic and cultural factors including poor healthcare system account for the persistently high proportion of GTDs [4] among gynaecological cancers (Fig. 1) and their poor survival rates in developing nations [5].

2 Epidemiology

Published rates of the diseases differ worldwide, being high in Asia, intermediate in Africa and lowest in the United States (USA) and Europe (Table 1). The reasons for these differences are not yet fully known but may be related to collection and

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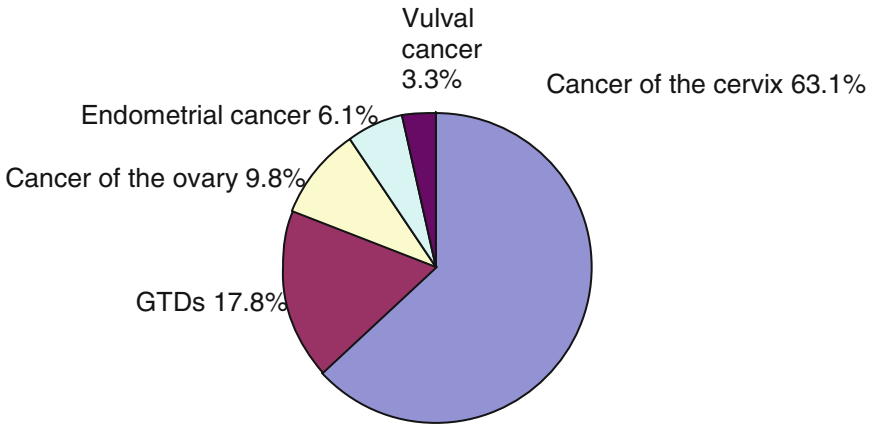

Fig. 1 Distribution of gynaecological malignancies at Ibadan, Nigeria (Adapted with permission from Odukogbe et al. [4])

Table 1 Distribution of GTDs in regions of the world

Location	Molar pregnancies/1,000 pregnancies			GTNs[b]	Author/s, date
	All molar	Complete	Partial		
Worldwide	–	0.5–2.5	–	–	Bracken, 1987 [6]
Japan	1.92	–	–	–	Ishizuka, 1976 [7]
Venezuela	–	–	–	0.70[a]	Corté-Charry et al, 2006 [8]
Malaysia	2.8[a]	–	–	1.59[a]	Sivanesaratnam, 2003 [9]
Nigeria	0.82–4.88[a]	–	–	–	Hendrickse et al, 1964 [10] Ayangade, 1979 [11] Ogunbode, 1978 [12] Egwuatu and Ozumba, 1989 [13]
Europe/USA	0.6–1.1	0.33	–	–	Palmer, 1994 [14] Smith and Smith, 2003 [15]
Ireland	–	0.51	1.44	–	Jeffers et al, 1993 [16]
Turkey	10.6[a]	–	–	12.9[a]	Gül et al, 1997 [5]

[a]Indicates the use of total deliveries as the denominator

[b]GTNs – gestational trophoblastic tumours

interpretation of data [17]. The risk of molar pregnancy has been related to the woman's obstetric history through prior incidence of abortions – both spontaneous and induced – and to previous hydatidiform mole [18]. Women at the extremes of their reproductive lives have been shown to be at increased risk of having GTDs. A study documented the relative risks as follows: women aged 21–35 years (RR = 1.0), teenage women (RR = 1.9), those aged 36–40 years (RR = 1.9) and those above 40 years (RR = 7.5) [19]. Linkages to advanced paternal age lend credence to the possibility of defects in gametogenesis as an aetiological factor [19]. Other factors implicated

are nutritional deficiencies [20] and prolonged use of oral contraceptive pills (OCPs) [21]. This risk from OCP use however forms a very low proportion of the diseases and does not merit advising against use of the pills, especially in poor, overpopulated countries and because of the protection from ovarian and endometrial cancers.

3 Disease Types

3.1 Hydatidiform Mole

Recent genetic researches have confirmed this to arise from defects of fertilisation leading to the formation of diploid, triploid or very rarely tetraploid chromosomes. The two varieties share histological and clinical characteristics and may be indistinguishable by these means in early cases, but differentiation is made possible through genotyping and chromosome in situ hybridisation [1, 22]. Although both are benign, about 10–20 % of cases will develop malignant change requiring chemotherapy [15, 23], the complete type with higher propensity than the partial variety [1]. The distinguishing features are shown in Table 2.

Most patients present with vaginal bleeding after a period of amenorrhea. This occurs in about 84 % of cases [24] usually before the 12th week of gestation and may be accompanied by passage of vesicles, particularly in complete moles. Other features are hyperemesis gravidarum, clinical hyperthyroidism and pre-eclampsia before the 24th week of gestation. Anaemia, pelvic sepsis and uterine enlargement and fetal heart tones may be present (the last only in partial moles). Investigations include urinary or serum β-hCG measurements, ultrasound scanning, full blood count and liver, renal and thyroid function tests which will help to differentiate from other diseases.

Table 2 The distinguishing features of the disease

Feature	Complete mole	Partial mole
Cytotrophoblast Syncytiotrophoblast	Generalised, diffuse hyperplasia of both	Focal and minimal hyperplasia
Chorionic villi and central cistern formation	Generalised oedema	Focal oedema
Fetal parts	Absent	Present. Occasionally to term
Chromosomal constitution	Diandric diploidy (duplication of paternal DNA). 95 % are 46XX, 5 % 46XY	Maternal and paternal chromosomes. 90 % are 69XXY (23,X and 23,X;23,Y)
Ratio	2.8	1.0
Characteristic ultrasound scan picture	Common, ‘snow storm’ appearance	Rare
Malignant change	6–32 %, 33 % of these are metastatic	0.5–3 %. Non-metastatic

Treatment options include mechanical and/or medical evacuation, hysterotomy, hysterectomy and decompression of ovarian cysts. However, suction evacuation under oxytocic cover is most commonly employed.

Follow-up entails structured clinic visits with assessment of clinical/laboratory evidence of persistent disease and development of gestational trophoblastic tumours. Effective contraception is used to delay or avoid pregnancy for 1–2 years so as not to confuse interpretation of serum or urine β-hCG results.

3.2 Invasive Mole

This entity, more likely to follow complete rather than partial mole, has the pathologic features of the former. But unlike these two precursor diseases, it invades the implantation site into the myometrium and may perforate the uterine wall. Penetration into the uterine venous plexus can lead to metastasis to the lungs and lower genital tract where in the latter case it is seen as a suburethral or upper vaginal nodule [18]. It presents as lower genital tract bleeding or with chest symptoms. Intraperitoneal haemorrhage may give rise to acute abdomen and, when severe, signs of shock. Diagnosis is usually difficult, but when suspected, computerised axial tomography (CAT) scan or magnetic resonance imaging (MRI) may be helpful. Uterine curettings yield poor results since they are very unlikely to show myometrial invasion. The best method is histological examination of hysterectomy specimen. Development into choriocarcinoma is not common.

3.3 Placental Site Trophoblastic Tumours

These are rare, but can occur after any form of pregnancy [23] (hydatidiform mole, abortion, ectopic and term gestations). They are composed mainly of intermediate (non-villous) trophoblastic cells from sites of placental implantation. They invade deep into the myometrium. Their production of β-hCG is low [18] and variable on account of the sparse population of syncytiotrophoblastic cells, thus making monitoring with this marker much less reliable compared to the other three diseases. These intermediate cells however elaborate the human placental lactogen (hPL). Diagnosing the disease is difficult as it may be confused with early stages of choriocarcinoma or present as a benign disease. Many workers are researching the use of alternative markers such as the proportion of hCG to free beta subunit [25] and carcinoembryonic antigen elaborated by both syncytio- and cytotrophoblasts [26]. However, much larger studies are still required in order to validate their usefulness. Accurate pathologic diagnosis in 60 % of cases following uterine curettage was achieved in the study by Li et al. [27].

3.4 Gestational Choriocarcinoma

Choriocarcinoma is a very highly malignant disease and the most invasive of all, arising from rapidly proliferating villous trophoblasts [28], also following any pregnancy, although it retains the characteristics of the blastocyst. It is usually referred to as the 'great imitator', since it can affect almost all tissues in the body giving rise to a medley of symptoms and signs. In the reproductive age women, it must be considered whenever clinical features of diseases appear unusual.

In the series from the National Institute of Health (NIH), USA, 46 % followed hydatidiform mole, 24 % after term delivery and 30 % after abortion. The tumour is highly vascular with wide areas of necrosis and haemorrhage. Morbidity and mortality from choriocarcinoma are thus related mainly to vascular erosion of vital structures or haemorrhage.

Since the two cell types predominate and proliferate extensively, secretion of β-hCG in high quantities occurs. The concentrations of this marker reflect tumour burden and response to treatment.

The diagnosis is also suspected when the β-hCG level is plateauing or rising post-evacuation of molar or normal pregnancy and metastasis or abnormal bleeding occurs and is confirmed by histology of specimen obtained.

Staging of the gestational trophoblastic tumours utilises the International Federation of Gynaecology and Obstetrics (FIGO) criteria, while disease categorisation to high- or low-risk group uses the World Health Organization (WHO)'s prognostic index scoring system.

Over 25 different chemotherapeutic regimens are in existence all over the world with single agents for low-risk nonmetastatic or metastatic diseases and combination regimes for high-risk metastatic diseases.

Surgery in the form of hysterectomy, craniotomy or thoracotomy may be indicated when there is inadequate response to chemotherapy. Radiotherapy may also be used. Clinical trials are ongoing for immunotherapy.

4 Issues Related to the Presentation, Management, Prognosis and Control of Gestational Trophoblastic Diseases in the Developing Countries

- Serum and urine pregnancy tests and ultrasonography are being increasingly used to diagnose pregnancy early, especially in the urban areas. However, the average gestational age at first antenatal consultation is late, for example, in late second trimester in Ibadan, Nigeria [29], implying that most cases of molar pregnancy are not seen early. These diagnostic services need to be extended to the over 60 % of reproductive age women living in the rural areas to enable early referral of cases of GTDs to specialised centres.

- Pathological diagnosis faces many challenges in sub-Saharan Africa [30]. Repeated evacuations following spontaneous or induced abortion are undertaken by some health practitioners with non-submission of specimens for histology. This causes delays in diagnosing GTDs and commencing effective treatment. Karyotyping facilities are very scarce, resulting in inability to distinguish between complete and partial moles.
- Authentic laboratory quantitative measurement of serum and urinary β-hCG is still very expensive and concentrated in few centres, even in urban areas, with results sometimes taking up to a week to become available. This delays decision making for diagnostic and chemotherapy administration purposes. However, the surrogate, semi-quantitative pregnancy test in serial dilution if correctly and consistently applied in rural areas is sensitive enough for triaging prior to referral.
- Chemotherapeutic drugs are expensive when available; require stringent, difficult-to-attain storage conditions; and are associated with complications which may require barrier nursing, intravenous hyperalimentation and haematological rescue. When these challenges lead to too much delay before commencement of, and in-between courses, the risk of developing drug resistance increases, with fatal outcome.
- Haemorrhage, hypovolemic shock and anaemia often complicate these diseases and their treatment. Blood transfusion services are still very poorly organised with huge unmet needs. Death from haemorrhage accounts for much of the mortality figures.
- Acceptance of surgery by patients is still low unless complications set in. This creates challenges when surgical management to reduce tumour bulk such as hysterectomy becomes essential most especially in young nulliparous/low parity patients.
- Follow-up of the patients after treatment for hydatidiform mole or gestational trophoblastic tumours is hampered by poor understanding of the diseases by patients and relations; financial constraints, transportation and accommodation problems. This has led to the practice of administering short courses of single agent chemotherapy routinely after evacuation of all molar pregnancies prior to discharge, while others limit this to high-risk complete moles only [18, 31]. There are obvious risks such as development of drug resistance and death from chemotherapy, although more studies are needed to assess these risks.
- There is absence of well-coordinated national/regional programmes of management and control of GTDs, with general absence of sophisticated diagnostic facilities. Researches rely on hospital-based figures [5, 8] due to lack of funds and/or infrastructures to conduct population-based studies. Therefore, the true incidence and prevalence figures are difficult to determine translating to inadequate and inefficient prevention/control measures [28]. Training of specialist personnel is also grossly inadequate.
- User rates of modern contraceptives are still very low in many African countries resulting in high rates of normal and abnormal pregnancies including gestational trophoblastic diseases. Innovative strategies are needed to increase take-up and continued user rates of effective contraception.

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Central Nervous System Tumors

Luiz Victor Maia Loureiro, Suzana Maria Fleury Malheiros, and Luis Souhami

1 Introduction

In the last decade, newer developments in histopathological classification, biology, and imaging have changed the management of CNS tumors and have contributed to the implementation of new treatment approaches in many CNS pathologies.

High-grade gliomas account for the majority of primary CNS tumors and are the most challenging due to its broad spectrum of aggressiveness, dismal prognosis, and the paucity of treatment alternatives. The adoption of multimodality therapy – comprising neurosurgical resection, radiotherapy, and chemotherapy – as the standard approach still finds many obstacles in developing countries, especially in publicly funded health systems due to economic constraints. Thus, high-grade gliomas, and in particular glioblastoma (GBM), will be the focus of our discussion. Low-grade gliomas will be only briefly reviewed.

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Taking into account the deadliest glioma, i.e., GBM, the median overall survival (OS) has only increased about 5 months over the past 30 years [1, 2] reaching a median of 14 months with a 2-year survival rate of about 30 % [1]. In the developing world, the median estimated OS is typically less than 12 months although a high variability exists among different regions [3], highlighting the heterogeneity of healthcare.

Much of the hindered OS in developing countries might be explained by the shortage of trained neuro-oncologists, neurosurgeons, and technical resources [4, 5]. Another relevant aspect is the delay in admission to the healthcare system, which may be unveiled by the interval needed to start diagnosis and treatment. In adverse prevailing conditions, patients had a longer interval from first symptoms to neurosurgical intervention, and patients who are referred later may present more advanced disease [3, 5, 6].

Prognostic factors in glioma patients include histological grade, age, performance status, extent of resection, and mental status and taken together may guide treatment decisions, particularly in developing countries, according to the recursive partitioning analysis classification (RPA class) [7]. Some molecular markers may also be helpful as prognostic factor or potential predictors of treatment response such as mutation of the isocitrate dehydrogenase gene (IDH1) [8] and O6-methylguanine-methyltransferase (MGMT) methylation status, particularly in elderly patients [9].

2 Surgical Approaches

The initial treatment approach to CNS tumors is cytoreductive surgery. The goal pursued by the neurosurgical intervention is maximal safe and feasible resection with preservation of neurologic function. The extent of surgical resection is predictor of longer survival irrespective of the use of chemotherapy or radiotherapy [10]. Biopsy only is not a reasonable option whenever resection is feasible.

Several intraoperative techniques have been analyzed to improve the extent of resection such as intraoperative cortical stimulation, intraoperative MRI, and fluorescence-guided resection with 5-aminolevulinic acid. However, these are expensive technics, not widely available, and none of these approaches have significantly improved the OS rate, although accounted to increased resectability [11].

In a scenario with insufficient resources, a practical approach is to perform a maximal and safe resection in patients presenting good preoperative performance status – a *Karnofsky* performance status of $\geq$70 % – and with tumors located in non-eloquent or low functional areas. A stereotactic biopsy must be reserved for patients with poor performance status, multicentric disease, or for disease located in highly functional areas.

A proper surgical intervention is even more critical in patients harboring a low-grade glioma. Several reports have shown the survival impact a complete or near complete resection has in this group of patients [12].

3 Radiotherapy

Since the late 1970s, radiotherapy has played a key role in the multimodality treatment strategy, significantly boosting the survival of high-grade gliomas patients [13]. Over the years, attempts to improve outcomes by changes in radiotherapy schedules, doses, and techniques have met with little success [13]. Currently, the typical treatment regimen is 60 Gy divided in 30 fractions over 6 weeks. Similar results have been achieved with 40 Gy divided in 15 fractions in elderly patients or in those with poor performance status [14].

Growing concerns are associated with numerous factors that may impact on the immediate access to radiotherapy, such as imbalance between supply and demand, social-economic status, and access to a radiotherapy facility [15]. However, at this time there are not enough data to assure that longer waiting times to postoperative radiotherapy might be detrimental. Conversely, some authors showed unexpected results with a positive association with OS for patients who waited longer for radiotherapy [16].

Actually, no reasonable explanation justifies delaying the prompt initiation of radiotherapy, except for post-surgical wound healing and clinical performance status [15]. However, the absence of an obvious detrimental effect on OS, concerning the interval to start the radiotherapy, might minimize the anxiety of health professionals and their patients when faced with the waiting lists of radiotherapy, particularly in the under developing countries. On the other hand, patients submitted to a limited neurosurgical approach, as biopsy only, should have their radiotherapy program prompted delivered, whenever possible, in order to obtain the most benefit after recovery from surgery.

Although there is no immediate role for radiotherapy in low-risk, low-grade glioma patients, radiotherapy has been accepted as a reasonable adjuvant treatment approach in high-risk, low-grade gliomas (i.e., symptomatic patients, ≥40 years old, or progressive disease, particularly in large (>5 cm) astrocytic tumors) [17]. In this setting, lower doses (50–54 Gy) can be effective and less toxic [18, 19].

4 Chemotherapy

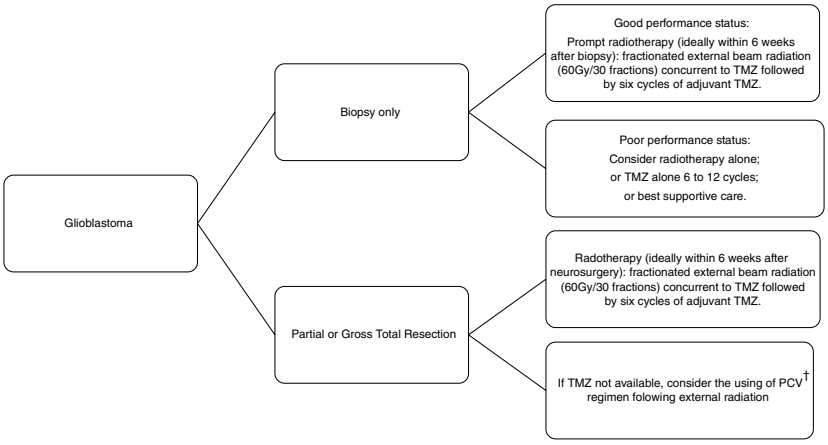
The use of TMZ, since the beginning of the 2000s, has brought an additional survival advantage for patients with GBM [1]. Since then, the standard scheme is the use of TMZ concurrent to radiotherapy (75 mg/m^2 daily) followed by up to six cycles of adjuvant TMZ (150–200 mg/m^2 daily for 5 days, every 28 days). Other treatment schedules have not been proven more effective.

Although cost-effective, this is still an expensive treatment strategy with incremental cost-effectiveness ratios more than US$100,000 per quality-adjusted-life-year [20], what might turn TMZ a chemotherapeutic agent beyond the scope of

low-income nations. Where the gap between costs and payment capacity is too great, it is reasonable to consider the implementation of nitrosourea-based adjuvant treatment, such as PCV regimen (procarbazine, lomustine, and vincristine) whenever available, taking into consideration the higher toxicity profile of the combination.

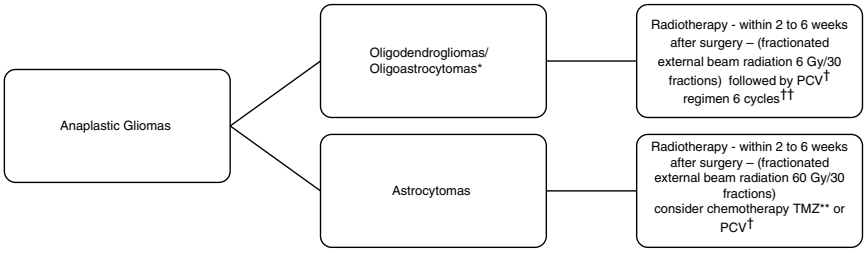
No randomized comparison between TMZ and PCV regimen has been performed in the adjuvant setting for high-grade gliomas. However, there are randomized data showing that the use of adjuvant PCV, either before or after radiotherapy, for anaplastic oligodendroglioma tumors, particularly for the population with 1p/19q co-deletion [21, 22], leads to an improved survival. There is still debate regarding the role of TMZ in that setting [23, 24]. Additionally, PCV has also been shown to benefit the high-risk, low-grade glioma group when added after the adjuvant radiotherapy [25].

Figures 1, 2 and 3 show the proposed algorithm for the management of glioblastoma, anaplastic glioma, and low-grade glioma.



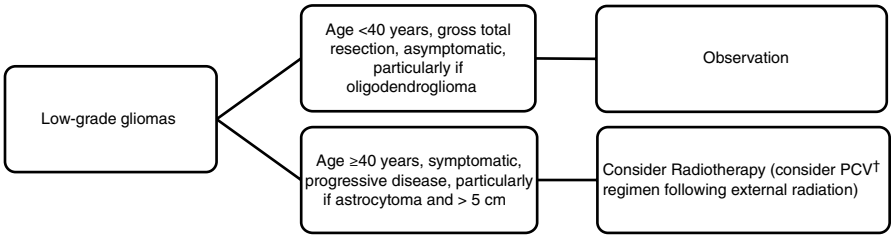
** standard regimen: TMZ (temozolomide) concurrent to RT (75mg/m² daily up to 49 days) followed by up to six cycles of maintenance TMZ (150 to 200mg/m² daily for five days, every 28 days).
† PCV regimen: lomustine 110 mg/m² D1; procarbazine 60mg/m² D8 to 21; vincristine 1,4 mg/m² up to 2 mg D8 and D29

Fig. 1 Proposed management for patients with glioblastoma



* Specially for 1p/19q co-deletion population
** Standard regimen: TMZ (temozolomide) concurrent to RT (75mg/m² daily up to 49 days) followed by up to six cycles of maintenance TMZ (150 to 200mg/m² daily for five days, every 28 days).
† PCV regimen: lomustine 110 mg/m² D1; procarbazine 60mg/m² D8 to 21; vincristine 1,4 mg/m² up to 2 mg D8 and D29
†† Consider using of Temozolomide instead of PCV (procarbazine, lomustine and vincristine) regimen

Fig. 2 Proposed management for anaplastic gliomas in patients with good performance status after maximal, safe resection of the tumor with preservation of neurologic function



† PCV regimen: lomustine 110 mg/m^2 D1; procarbazine 60mg/m^2 D8 to 21; vincristine 1,4 mg/m^2 up to 2 mg D8 and D29

Fig. 3 Proposed management for patients with low-grade glioma

In the recurrent setting, re-operation and re-irradiation may be the primary option since chemotherapeutic agents have proven modest activity. Thus, the therapeutic strategy must be tailored individually. Antiangiogenic therapy, such as the anti-VEGF monoclonal antibody bevacizumab, has been used due to its dramatic radiological response and improved progression-free survival [26]. However, the short-lasting response, the absence of a clear benefit in OS, the potential for inducing changes in the biological behavior of the tumor resulting in a more invasive and aggressive tumor, and its excessive cost make this approach still debatable, particularly in under developing countries.

Age, performance status, and extent of resection are important prognostic factors for glioma patients. For instance, elderly patients are expected to present shorter OS and higher treatment-related toxicity. In this age group, treatment options include best supportive care, short course radiotherapy, TMZ alone (especially in patients with MGMT methylated) [27], and chemoradiation. However, it is usually recommended that treatment decisions should not be based exclusively on chronological age but mostly on the patient's performance status [28].

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Thyroid Cancer

Michele Klain and Martin Schlumberger

1 Thyroid Nodules

Clinical thyroid nodules are frequent, being present in 4–7 % of an adult population, and are even more frequent in countries where iodide deficiency has not been corrected. Infra-clinical nodules are much more frequently found with the expanded use of neck ultrasonography [1, 4].

The risk of thyroid cancer among these nodules ranges between 5 and 15 %. However, in view of the high frequency of thyroid nodules and the slow progression rate of small thyroid nodules, even if malignant, there is a general agreement that only thyroid nodules above 1 cm in size with suspicious criteria at clinical examination or at neck ultrasonography deserve further investigations, including serum TSH determination and fine needle aspiration biopsy (FNAB).

Clinical suspicions increase in young patients (<20 years), in those with a hard, irregular, and fixed nodule that grows over time, with ipsilateral persistent lymph nodes in the lower part of the neck and with symptoms of compression, including hoarseness.

When serum TSH is elevated, a treatment with levothyroxine is given, and patients are seen again after 3 months; in contrast, when serum TSH is low or undetectable, the thyroid nodule is likely to be a toxic adenoma and in that case there is no indication for FNAB, but these nodules should be either surgically removed or treated with 131-I.

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Solid nodules above 1 cm in diameter should be submitted to FNAB when they are hypoechoic at neck ultrasonography and especially when other suspicious characteristics are present, including suspicious lymph nodes, microcalcifications, irregular infiltrative margins with the absence of halo, evidence for extrathyroid extension, and a taller than wide shape measured in the transverse dimension. Cytological slides may be sent for interpretation to a specialized center for interpretation with clinical and ultrasonography characteristics and details on nodule sampling.

The strategy will then depend on the cytological results: benign nodules only need follow-up every 12–24 months, without any treatment. Suspicious and malignant nodules are operated. Nodules with indeterminate cytological findings can be submitted to a second FNAB some months later, and then the decision to operate or not will be taken on the basis of clinical, ultrasonography, and cytological data. If not operated, the nodule is followed up every 12–24 months, and an increase in size should then lead to surgery.

2 Differentiated Thyroid Cancer: initial treatment

Most differentiated thyroid cancers can be efficiently treated with surgery that may be complemented by postoperative radioactive iodine (RAI) administration in case of high risk of recurrence or of tumor-related death [1, 4].

2.1 Surgery

Surgery is indicated in case of malignant or suspicious cytologic findings, and its extent depends on the tumor histology and tumor extent and also on the skills of the surgeon.

2.1.1 Thyroid Surgery

There is a general consensus to consider that a lobectomy only is sufficient in patients with unifocal papillary thyroid carcinoma <1 cm in diameter and may also be performed in patients with small minimally invasive follicular carcinoma ajouter (<4 cm). This applies only to patients with a normal contralateral lobe at neck ultrasonography and without evidence of extracapsular extension and lymph node involvement.

In the other patients, a near-total thyroidectomy is indicated that should be preferably performed by high-volume surgeons that are able both to leave only low-volume thyroid remnants and to avoid laryngeal nerve injury and hypopara-

thyroidism. Indeed, when the laryngeal nerve has been injured during the lobectomy performed to remove the tumor, it may be safer not to perform a contralateral lobectomy.

2.1.2 Lymph Node Surgery

Therapeutic lymph node dissection is performed in patients with evidence of lymph node involvement at clinical examination or at neck ultrasonography, and that should be confirmed preoperatively by FNAB.

Prophylactic lymph node dissection should be performed only by high-volume surgeons in specialized centers. In fact, this procedure may increase morbidity rate, and benefits in terms of a decreased risk of recurrence and of thyroid cancer death have not been demonstrated, in particular in low- or intermediate-risk patients.

2.1.3 Post-surgery RAI Administration

Benefits of postoperative RAI administration on the risk of recurrence and of cancer-related death have been demonstrated only in high-risk patients. Therefore, RAI may be avoided in low- and intermediate-risk patients who represent the large majority of patients and in all those with postoperative low-serum thyroglobulin (Tg) and with a normal neck ultrasonography in whom the risk of persistent disease is probably lower than 3 %. Of interest, in case of clinical recurrence in these patients, delayed RAI treatment may still be very effective.

In high-risk patients, postoperative RAI administration consists of the administration of 3.7 GBq (100 mCi) 131-I after prolonged withdrawal of thyroid hormone treatment or rhTSH injections (if rhTSH is available). These patients may easily be selected on the basis of surgical and pathological reports and on postoperative serum Tg level and neck ultrasonography, and benefits in terms of clinical recurrence and survival are likely to be obtained in no more than 30 % of these patients.

2.2 Follow-Up

2.2.1 Treatment with Levothyroxine

Levothyroxine is given postoperatively at doses that restore euthyroidism with a serum TSH level within the low normal range (0.5–2 mUI/L) in patients with no evidence of disease; in patients with persistent disease, because TSH is a growth factor for thyroid cells, the aim of levothyroxine treatment is to decrease serum TSH to an undetectable serum level.

2.2.2 Search for Persistent and Recurrent Disease

The absence of persistent disease is demonstrated at 9–12 months after initial treatment by an undetectable serum Tg with a sensitive assay in the absence of detectable anti-Tg antibodies and an absence of suspicious finding on neck ultrasonography. These patients have a low risk of recurrent disease, and serum TSH is maintained in the normal range, and subsequent follow-up consists only of an annual work-up on levothyroxine treatment with clinical examination and serum TSH and Tg determinations. No other test is warranted in the absence of abnormalities.

Several other situations may be encountered: in patients who had undergone near-total thyroidectomy and 131-I ablation, when an ultra-sensitive assay is used, a serum Tg level <0.2–0.3 ng/mL combined with a normal neck ultrasonography permits to exclude persistent disease; however, when Tg assays with a sensitivity of 1 ng/mL are used, a TSH-stimulated Tg measurement will be more sensitive for the detection of persistent/recurrent disease, and this may be achieved either following prolonged thyroid hormone withdrawal or preferably with injections of rhTSH that avoids hypothyroidism and maintains the quality of life, but may be non-affordable in some countries.

Patients with large normal thyroid remnants may have detectable serum Tg on levothyroxine therapy even when serum TSH is low or undetectable; this is frequently the case after thyroid lobectomy and also after less than a near-total thyroidectomy. In these patients, a neck ultrasonography that does not show any suspicious finding is reassuring, and the trend of serum Tg level over time will separate patients with persistent disease as indicated by an increasing trend from patients without disease with a stable serum Tg level or a decreasing trend.

Patients with evidence of persistent or recurrent disease may need further treatments. In case of small lymph nodes <8–10 mm in their smaller diameter, a follow-up may be sufficient with neck ultrasonography every 6–12 months. FNAB will be performed in case of increase in lymph node size, and malignant findings will then lead to surgery.

2.3 Treatment of Recurrent and Advanced Disease

2.3.1 Treatment of Neck Recurrence

It is based on surgery. In case of recurrence in neck lymph nodes >8–10 mm in their smaller diameter, a compartment neck dissection is performed, and in case of recurrence in a thyroid lobe after a lobectomy, the thyroidectomy is completed. It is important to operate at a stage when surgery is easily feasible and when all tumor foci may be resected, because at this stage other treatment modalities may be unnecessary and results are indeed better than at a later stage. A recurrence in the thyroid bed after a total thyroidectomy and a recurrence in soft tissues signals an

aggressive disease and may warrant a complete work-up to delineate the extent of disease and the potential involvement of the aerodigestive tract that may lead to complex treatment modalities. External radiation beam therapy or RAI administration may complement surgery whenever surgery is feasible, but benefits are still not demonstrated.

2.3.2 Treatment of Distant Metastases

Distant metastases from thyroid cancer of follicular origin are uncommon and occur in less than 10 % of patients with clinical thyroid cancer. Treatment includes levothyroxine administration at suppressive doses (TSH < 0.1 mUI/L), focal treatment modalities with surgery, external radiation therapy and thermal ablation (radiofrequency or cryoablation), and radioiodine in patients with uptake of 131-I in their metastases. RAI treatment consists of the administration every 6–12 months of 3.7 GBq (100 mCi) 131-I or more following prolonged thyroid hormone withdrawal.

One third of patients with distant metastases achieved a complete remission after repeated RAI treatments, and recurrent disease after complete remission occurred in less than 10 % of these patients. Predictive factors of tumor response among patients with RAI uptake include a younger age at discovery of metastases, a well-differentiated thyroid tumor histology, and small metastases with no or a low FDG uptake on PET scan. A favorable outcome is observed in patients with favorable predictive and prognostic characteristics, and in the absence of randomized trials, the benefits of RAI treatment cannot be ascertained and are not universally accepted.

Two thirds of distant metastases will become refractory to radioiodine at some point. In these patients, RAI treatment should be abandoned, and when there is a significant tumor burden and documented progression on imaging, a treatment with a kinase inhibitor may provide significant benefits. However, these treatments are expensive and should be given only in specialized centers.

3 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer is rare, representing less than 2 % of all thyroid cancers. These elderly patients with a rapidly growing tumor may transiently benefit from surgery whenever feasible [2]. Ideally, surgery should be followed by a combination of chemotherapy with doxorubicin and cisplatin and external beam radiation therapy, but this aggressive treatment provides benefits in only a small percentage of patients, and the patient should be informed as soon as possible after diagnosis on the prognosis and management options, including palliative care, on the limited benefits in case of extended tumor, and the potential high toxicity of these regimens to clarify his or her preference and expectations.

4 Medullary Thyroid Cancer

This complex tumor is rare (<5 % of all thyroid cancers) and should be managed in specialized centers. Treatment is based on total thyroidectomy and lymph node dissection but should also include the search for other endocrinopathies and for the familial origin of the disease, by searching for a germinal RET mutation [3].

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Uncommon Cancers

Gemma Gatta, Riccardo Capocaccia, and Annalisa Trama

1 Introduction

There is no globally agreed definition of rare cancers. In Europe, rare diseases, which comprise rare cancers, are considered those with a prevalence of <50/100,000 [1]. In the USA, the Orphan Drug Act defines rare diseases as those affecting <200,000 persons [2]. More specifically for neoplastic diseases, a published analysis of rare cancers in the USA employed the definition of <15 incident cases per 100,000 per year [3]. In Europe, the project Surveillance of Rare Cancers in Europe (RARECARE) [4] proposed a threshold of <6 incident cases per 100,000 per year. The overall burden of rare cancers on society has not been adequately estimated, although they are thought to constitute a major public health problem. Rare cancers should to be considered 'sentinel' cancers because very high levels or rapidly increasing incidence or mortality rates can indicate a strong exposure to a carcinogen. Exposure to specific carcinogens had increased the frequency of some rare cancers, such as mesothelioma due to asbestos [5], cancer of vagina in girls whose mothers took diethylstilbestrol [6], angiosarcoma of liver in vinyl chloride workers [7], etc., and in principle even make common a previously rare cancer. Furthermore, according to the distribution of the risk factors in populations, a rare cancer in one region can be a common cancer in another region. The most relevant is the nasopharyngeal cancer which is uncommon in the majority of the planet and common in the Middle East of Asia [8]. Rare cancers are often inadequately diagnosed and treated because their low frequency hampers the development of scientific knowledge and making adequate clinical expertise in many health-care structures.

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This chapter will compare the major epidemiological issues and results on rare cancers available for Europe with what is available for the tropical countries. It will discuss the validity, in the tropical countries' setting, of the European definitions and classifications of rare cancers. The principal source of data will be population-based cancer registries. For an estimation of the burden of rare cancers in the tropical countries, we will benefit of the two major IARC accessible tools GLOBOCAN [8] and Cancer Incidence in Five Continents (CIFC) [9]. Furthermore, we will take as geographical reference the set of the so-called Less Developed Regions (LDR) located in Africa, Asia (excluding Japan), Latin America and the Caribbean, and Melanesia [8]. We will consider some of the results of the RARECARE project realised in the European population [4].

2 The List and the Definition of Rare Cancers

The major challenges for management of rare cancers are clinical: scarce diagnostic expertise, difficulties in clinical making decision, few available treatment options, few or no clinical trials, and need of new methodologies for clinical studies. Therefore, the group of experts (pathologists, haematologists, clinicians, epidemiologists, and association of patients) that worked in the RARECARE project assumed the clinical relevance as the principal criterion for drawing a list of entities from which select rare tumours. The list, produced by the RARECARE group, was endorsed by the major European cancer societies/organisations, and its rationale is available at http://www.rarecarenet.eu. A synthetic grouping of the list is reported in Table 1. In brief, while cancer statistics are usually provided for broad cancer categories, based on the anatomic site of the malignancies as defined by the International Classification of Diseases (ICD) codes [10], rare tumour entities, because of their specific problems related to the health-care organisation and to the clinical management, might be more appropriately defined by a combination of topographical and morphological characteristics, as provided by the International Classification of Diseases for Oncology (ICD-O) [10]. Therefore, the first classification criterion separates epithelial cancers from sarcomas, neuroendocrine tumours (NET), germinal tumours, and haematological or other cancers arising from other tissues/cells. Such a sound use of morphology information was introduced by the RARECARE project and could be problematic to apply outside a specific project and without a centralised data check. The last two CIFC volumes, which provide most of data used in this analysis, while recognising the particular clinical and epidemiological relevance of the histological type of cancer [11], present incidence by broad morphological categories and only for some sites: for instance, squamous-, adeno-, large, and small cell carcinomas of lung cancer (C34) or seminoma, spermatocytic, and non-seminomatous tumours of the testis (C62).

The RARECARE list was hierarchically organised into three tiers. The first tier is based on patient referral purposes, i.e. it is relevant under the health-care organisation perspective. The second tier groups provide a list of cancer entities distinct

Table 1 European crude incidence rates, prevalence proportion of the RARECARE tumour entity (diagnoses 1995–1999)

Incidence (annual rate per 100,000)	Entity	Prevalence (per 100,000)
>50	Epithelial tumours of the breast	594
	Epithelial tumours of the lung	85
>20–50	Epithelial tumours of the skin	474
	Epithelial tumours of the prostate	474
	Epithelial tumours of the colon	233
	Lymphoid diseases	172
	Epithelial tumours of the bladder	133
>10–20	Epithelial tumours of the stomach	46
	Epithelial tumours of the rectum	102
	Malignant skin melanoma	135
	Epithelial tumours of the pancreas	8
	Epithelial tumours of the kidney	65
	Epithelial tumours of the corpus uteri	100
>7–10	Epithelial tumours of the ovary and fallopian tube	48
	Epithelial tumours of the oesophagus	8
>6–7	Epithelial tumours of the hypopharynx and larynx	36
	Epithelial tumours liver and intrahepatic bile tract (IBT)	9
	Epithelial tumours of the cervix uteri	58
	Tumours of central nervous system (including embryonal CNS tumours and meningiomas)	34
>4–5	Epithelial tumours of the oral cavity and lip	29
	Soft tissue sarcoma	43
	Epithelial tumours gallbladder and extrahepatic biliary duct	7
	Carcinomas of endocrine organs	41
>2–4	Acute myeloid leukaemia and related precursor neoplasms	8
	Tumours of the testis and paratestis	43
	Myeloproliferative neoplasms	29
	Epithelial tumours of the oropharynx	12
	Neuroendocrine tumours	19
>1–2	Epithelial tumours of the vulva and vagina	13
	Malignant mesothelioma	3
	Epithelial tumours of the pelvis ureter and urethra	10
	Myelodysplastic syndrome	4
	Epithelial tumours major salivary glands and salivary gland type tumours	10
	Epithelial tumours of the anal canal	7

(continued)

Table 1 (continued)

Incidence (annual rate per 100,000)	Entity	Prevalence (per 100,000)
≤1	Bone sarcoma	6
	Epithelial tumours of the small intestine	2
	Malignant melanoma of the uvea	5
	Epithelial tumours of the penis	5
	Malignant melanoma of the mucosa	2
	Epithelial tumours of the nasopharynx	2
	Epithelial tumours of the nasal cavity and sinuses	2
	Non-epithelial tumours of the ovary	3
	Kaposi sarcoma	2
	Embryonal neoplasms	4
	Myelodysplastic myeloproliferative diseases	1
	Adnexal carcinomas of the skin	3
	Epithelial tumours of the thymus	1
	Epithelial tumours of the eye and adnexa	1
	Epithelial tumours of the trachea	<1
	Extragonadic germ cell tumours	2
	Gastrointestinal stromal sarcoma (GIST)	<1
	Histiocytic and dendritic cell neoplasms	<1
	Epithelial tumours of the middle ear	<1
	Trophoblastic tumours of the placenta	<1

Table 2 The three-tier structure of the RARECARE list of cancers illustrated for epithelial cancers of the anal canal

Tier	Name
First	**Epithelial tumours of anal canal**
Second	**Squamous cell carcinoma and variants of anal canal**
Third	Verrucous carcinoma
Third	Undifferentiated carcinoma
Third	Basaloid carcinoma of anal canal
Second	**Adenocarcinoma and variants of anal canal**
First	Mucinous adenocarcinoma
Second	**Paget disease of anal canal**

with respect to clinical management and clinical research targets. The third tier includes all pathologically distinct entities defined by the WHO blue book entities. An example of this organisation is reported in Table 2.

As a final step, RARECARE defined rare cancers as those with an incidence of <6/100,000/year, corresponding to <30,000 new cases/year in Europe. A total of about 200 cancers were recognised as rare according to this definition.

In Europe rare cancers are officially defined according to the prevalence criterion (<50/100,000), in the same way as rare diseases in general. However, prevalence

has shortcomings as a measure of cancer rarity since some cancers with low incidence but good survival fall into the common cancer category as good survival pushes up prevalence; examples are squamous cell carcinoma of the uterine cervix and thyroid carcinoma. Similarly, some commonly occurring diseases for which survival is poor are considered rare because poor survival pushes prevalence down. Examples are adenocarcinoma of the stomach and lung and squamous cell carcinoma of the lung. These considerations suggest that incidence is better for defining rare cancers and is also in harmony with the sub-acute clinical course of most rare cancers, whereas most rare non-neoplastic diseases have a chronic course better measured by prevalence indicator. The RARECARE rarity threshold at <6/100,000 is of course arbitrary and was selected by pragmatic considerations. For example, a lower threshold of <3/100,000/year would be considered as common epithelial cancers of the oral cavity and lip, epithelial cancer of the oropharynx, epithelial cancers of the larynx, epithelial tumour of the gallbladder, soft tissue sarcomas, tumours of the testis and paratestis, carcinomas of the thyroid tumour of central nervous system, neuroendocrine tumours, myeloproliferative neoplasms and acute myeloid leukaemia. Yet these forms present all the characteristics of rare cancers, being often inadequately diagnosed and treated in relation both to lack of knowledge and lack of clinical expertise, clinical trials are rarely performed. They are best treated in specialised centres. Thus, the <6/100,000 threshold was selected to include all the forms with the problems typically present in rare cancers.

3 The Burden of Rare Cancers

In Europe, based on the above definition (incidence <6/100,000/year), 22 % of all cancers diagnosed in the EU27 each year are rare. In absolute terms, this is slightly more than half a million new rare cancer cases each year. About 4,300,000 patients are living today in the European Union with a diagnosis of a rare cancer, 24 % of the total cancer prevalence. Essentially, all childhood cancers and most cancers (sarcomas and lymphomas) in persons aged up to 39 years were rare. From age 40 on, the common cancers (breast, prostate, colon, rectum and lung) became increasingly prominent. Average age at diagnosis was 60 years for rare cancers and 67 for common cancers.

Rare cancers had, on average, worse relative survival than common cancers. Five-year relative survival was 47 and 65 % (Fig. 1) for rare and common cancers, respectively. Survival differences between rare and common cancers were small 1 year after diagnosis, but survival for rare cancers declined more markedly thereafter, suggesting that less effective treatment, and not later stage at diagnosis, is the main determinant of the poorer survival for rare cancers. Five-year survival was similarly high for both rare and common cancers in children and young adults (up to 39 years), but survival for rare cancers fell increasingly behind that of common cancers as age of diagnosis increased. Most cancers in children and young adults were rare embryonal or haematological types, for which effective treatments are

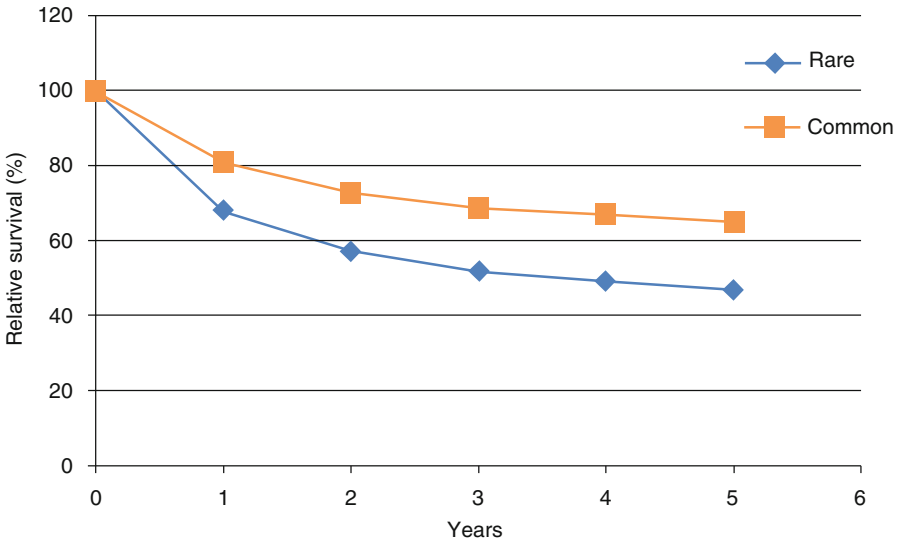

Fig. 1 Survival in Europe for rare and common cancers

available. In older patients, most of the rare cancers were rare epithelial forms, for which therapies are not as effective as for the rare paediatric cancers.

Since the definition of rare diseases is based on prevalence and the European Directive on Orphan Drugs provides incentives to foster research and development of orphan drugs for rare diseases, the availability of prevalence data for rare cancers should facilitate application of the EU orphan drug directive. Prevalence is not easy to estimate; only registries with more than 40 years of activity can directly calculate it. From the data of more recently established registries, prevalence can be only estimated by statistical modelling and a set of related assumptions, such as those used in RARECARE to made available prevalence of rare cancers [12]. Almost all cancers considered rare according to RARECARE are also rare according to the official prevalence criterion for rare diseases in Europe of <50/100,000. Six cancers are common according to the incidence criterion and rare according to the prevalence criterion including stomach adenocarcinoma, pancreatic adenocarcinoma, lung adenocarcinoma and lung squamous cell carcinoma. The explanation is that these are poor prognosis cancers which hence have low prevalence, even though incidence is high.

In the LDR, cancer incidence is a half of that observed in more developed countries (Table 3). However, it is an increasing challenge and has already become the second cause of death in these regions. According to the RARECARE threshold of <6 per 100,000/year, in LDR, the majority of cancers listed in Table 3 are rare. Only cancer of oesophagus, colon-rectum, liver, stomach, prostate, cervix uteri, lung and breast are common in LDR, as they all have incidence rates higher than 6. Among rare cancers in LDR, nasopharynx cancer and Kaposi sarcoma have a higher incidence than MDR (both 3.5 time higher). For most of the LDR rare cancers, as

Table 3 Incidence rates of 26 types of cancer and for all cancers together in LDR and MDR

Estimated cancer incidence, all ages: both sexes						
	Less developed regions (2012)			More developed regions (2012)		
Cancer	Numbers	Crude rate	ASR (W)	Numbers	Crude rate	ASR (W)
Hodgkin lymphoma	37,098	0.6	0.6	28,852	2.3	2.1
Kaposi sarcoma	40,874	0.7	0.7	3373	0.3	0.2
Melanoma of skin	41,064	0.7	0.8	191,066	15.3	9.6
Multiple myeloma	46,293	0.8	0.9	67,958	5.5	2.7
Testis	22,526	0.8	0.7	32,740	5.4	5.2
Nasopharynx	79,524	1.4	1.4	7167	0.6	0.4
Other pharynx	88,790	1.5	1.7	53,597	4.3	2.7
Larynx	99,133	1.7	1.9	57,744	4.6	2.7
Gallbladder	115,566	2	2.2	62,535	5	2.1
Kidney	137,869	2.4	2.6	199,991	16.1	9.2
Pancreas	150,407	2.6	2.8	187,465	15	7.2
Brain, nervous system	167,246	2.9	3	88,967	7.1	5.1
Bladder	175,950	3	3.3	253,843	20.4	9.5
Thyroid	175,326	3	3	122,776	9.9	7.4
Lip, oral cavity	199,550	3.4	3.7	100,823	8.1	4.7
Non-Hodgkin lymphoma	195,338	3.4	3.6	190,403	15.3	8.6
Leukaemia	210,691	3.6	3.8	141,274	11.3	7.2
Ovary	138,967	4.9	5	99,752	15.6	9.1
Corpus uteri	151,746	5.3	5.5	167,859	26.2	14.7
Oesophagus	369,640	6.4	7	86,144	6.9	3.6
Colorectum	623,735	10.7	11.7	736,867	59.2	29.2
Liver	648,149	11.2	12	134,302	10.8	5.4
Stomach	677,085	11.7	12.7	274,509	22	10.6
Prostate	352,950	12	14.5	758,739	125.2	69.5
Cervix uteri	444,546	15.6	15.7	83,078	13	9.9
Lung	1,066,487	18.4	20	758,214	60.9	30.8
Breast	882,949	30.9	31.3	793,684	124.1	74.1
All cancers excl. non-melanoma skin cancer	8,014,273	138	147.7	6,075,876	487.7	268.3

GLOBOCAN 2012, IARC −18.1.2015

Crude and age-standardised rates per 100,000

In bold: rare cancers for LDR, according to the RARECARE definition (incidence rate <6/100,000/year)

LDR less developed regions: all regions of Africa, Asia (excluding Japan), Latin America, and the Caribbean, Melanesia, Micronesia and Polynesia

MDR more developed regions: Europe plus Northern America, Australia/New Zealand and Japan

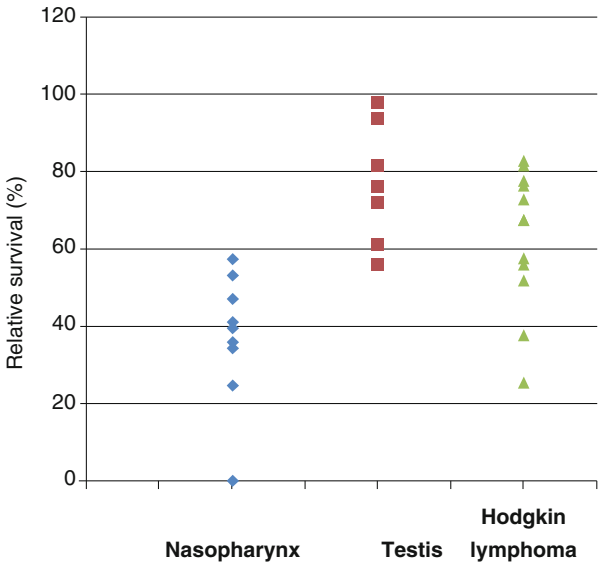

Fig. 2 Five-year survival in some rare cancers (nasopharynx, testis and HL) in LDR (0–74 aged)

		Nasopharynx	Testis	Hodgkin lymphoma
China	Qidong	36.4	–	–
	Shanghai	57.6	81.7	77.6
	Tianjin	57.6	76.4	81.9
Cuba	Cuba	–	–	57.5
Africa	Gambia	–	–	25.5
	Uganda	0	–	–
	Zimbabwe	–	–	46.5
India	Chennai	–	–	37.8
	Mumbai	24.7	56.2	52.2
Korea	Busan	53.2	72.2	76.9
	Incheon	53.6	98.3	82.8
	Seoul	47.1	93.9	76.3
Thailand	Chiang Mai	41.5	–	73.1
	KhonKaen	34.6	–	67.7
	Songkhla	39.9	61.1	56.4

1993–2000 registries in Sankaranarayanan et al.

skin melanoma, kidney, bladder, testis and corpus uteri, incidence is extremely low: less than 1 for melanoma and testis and 2 and 3 for kidney and bladder, respectively. Incidence rates were 5 for ovary and corpus uteri (Table 3). Rare cancers, mainly defined according to cancer site, account for 24 % of the all cancers listed in Table 3 in the LDR and only 6 % in the MDR.

Survival is another important indicator of burden of cancers in population, but this measure of outcome was rarely considered in comparative studies. The updated

CONCORD paper [13] includes survival for only one rare cancer: the childhood acute lymphoblastic leukaemia. The IARC scientific publication on survival in Africa, Asia, the Caribbean and Central America [14] included several rare cancers. Figure 2 shows 5-year survival for three of them: nasopharynx, testis and Hodgkin lymphoma (HL), and for a selection of registries from China, Korea, Thailand, Cuba and Africa. Differently with the majority of rare cancers, for testicular cancer and HL, a clear protocol of treatment exists for all the stages at diagnosis. Actually, they are curable tumours from the 1970s [15, 16]. For nasopharyngeal cancer, treatment is complex and there were no effective treatments for advanced cases [17]; therefore, early diagnosis is advisable. Outcome variation was large for testicular cancer and HL, indicating that access to appropriate treatment is still a main challenge. The African and Indian registries show the lowest survival. Similar results were from the CONCORD study for childhood leukaemia. Abandonment of treatment is a major reason of therapeutic failure in these resource poor countries [18].

4 Final Considerations

Most of cancers in the LDR, especially rare cancers, are associated with infectious causes. However, as largely recognised, poverty, low education and urbanisation facilitate such epidemics and make ineffective educational and preventive programme. Recently a review on the contribution of occupational exposure to rare cancers showed that several rare malignancies were consistently linked to occupational factors [19]. The transition from rural to industrialised civilisation which characterises several of LDR has to care about of exposition to new carcinogens and of the new risk factors which characterise western societies. In Europe and in general in the MDC, the research, the orphan drug regulations and the health-care organisation for rare cancers are in the agenda since several years. Furthermore, rare cancers benefit of the lobby of associations of rare diseases and rare cancer patients. Researchers and clinicians are facing the difficulties in gathering sufficient evidence on treatment efficacy and on clinical decision making. Several countries are dealing with the problem of identification of centres of reference. In some cases, discussion is ongoing on the best strategy to treat rare cancers, particularly if a network of centres or single centres of excellence may be more effective for treating these patients. In MDR primary prevention is not the principal issue, also because it does not recognise a fast economic profit. From patient associations and oncologic societies, the preferred reason for neglecting prevention in rare cancers is that ‘causes are unknown or little known’.

What to do in LDR? First of all, develop a surveillance system of the phenomenon, mainly through population-based cancer registries. Then, international collaborative research should be enhanced, allowing for more adequately powered epidemiological or clinical studies. Then, to believe on primary prevention, that remains the strongest chance to reduce the burden of rare cancers in these regions. Research in the primary prevention programmes has to be supported, and, if they are effective, governments have to apply them and make a follow-up of their impact. International collaboration

with twinning programmes has to be arranged to improve diagnosis and treatment. In particular, improving histological diagnosis is a vital prerequisite for a correct diagnosis and an effective treatment. The international cancer pathological societies have to intensify exchanges and training programmes. For lethal rare cancer treatment, palliation is the most important goal in all countries, mainly for those in poor socioeconomic conditions. Centralization and networking should be the solution for diagnosis and treatment when protocols or guidelines are available at the country level.

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Part V
Cancer Treatment in Tropical Areas

Cancer in Children

Mhamed Harif and Jamila El Houdzi

1 Introduction

Childhood cancer represents less than 3 % of human cancers. However, it is a leading cause of death of children in Western population and growing cause of morbidity and mortality in developing countries. During last decades, this group of diseases has been a fertile field of research and achievements. Research in childhood cancer shed light in various mechanisms of carcinogenesis and provided efficient models of diagnostic and therapeutic approaches. Seventy to 80 % of children with various cancers are now expected to be cured if appropriate diagnosis and treatment approach are provided.

Cancer in children differs from that of adults. It is often embryonic and fast-growing proliferation. It is also highly chemotherapy-sensitive tumor. This is related to the nature of the cancer but also the particular tolerance of chemotherapy at this age. High rates of treatment success led to approaches seeking to minimize the cost of cure represented by medium- and long-term sequelae and impact on quality of life, education, and socio-professional integration.

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2 Challenges of Care in Tropical Regions

Appropriate care of children with cancer requires however a high degree of organization of care and dedicated and accessible teams and facilities. This is not available in most of tropical area. This leads to the search for adapted approach in order to give these children the maximum chances of cure and reduce the risk related to treatment toxicity. Clinical skills and appropriate use of basic diagnosis and prognosis work-up are of great importance in this setting.

Significant improvement of care in this area and in other developing countries can be achieved through twinning and international collaboration [1]. This can help in creation of community of expert and young caregivers in these countries in order to improve their competence and help in putting into place the adapted diagnostic and treatment approaches. Besides the proper care in hospitals, no improvement can be achieved if proper information and some support to the family are not provided.

In this chapter, we will discuss the main features of childhood cancers in tropical regions focusing on the main adapted diagnostic and therapeutic options. Some aspects related to pediatric cancers in tropics are addressed elsewhere in this book.

3 Epidemiological Data

Incidence of childhood cancers varies according to the region and time reflecting the impact of environmental or genetic factors. Epidemiological data in tropical countries are often not reliable; they are primarily hospital based and in a context where access to care is low.

Lymphomas and in particular facial Burkitt's lymphomas are the most commonly reported cancer in tropical regions. These tumors are found to be associated with Epstein-Barr virus (EBV) infection. This virus has been associated with Burkitt's lymphomas but also with Hodgkin disease and immunosuppression-related lymphomas. Various markers in EBV infection are found in these patients and particularly virus gene in tumor tissue. Massively and early in life, EBV infection seems to induce uncontrolled B cell overgrowth resulting in lymphoma. In high prevalence human immunodeficiency virus (HIV) infection areas, Kaposi sarcoma is more frequently occurring. This is also reported to be related to EBV coinfection.

Retinoblastomas are also more frequently reported in the tropical areas. This increased incidence seems to be for unilateral non-hereditary cases and may be related to socioeconomic development [2].

4 Diagnostic Approach in Childhood Cancer

The mode of expression of the child cancer is often not specific. Epidemiological features of cancer and evaluable resources should be taken into account in patient evaluation. Age and site of the tumor have an important impact in clinical

manifestations. Diagnosis is usually more precocious in infants because of the special attention of the parents. The level of education of parents and especially mothers is also an important factor. Adolescents tend to not to discuss their problems with their parents. Thus, Wilms tumor and leukemia are typically early diagnosed, while neuroblastoma is often diagnosed in advanced stages. Finally, the quality of the training of the primary care physician and the organization of the sector of care are also factors impacting significantly the speed of diagnosis.

Symptoms and signs of cancer in childhood may be listed in four major groups:

- *General signs*, which are not specific and are rarely indicative of cancer in childhood. They become meaningful when they are associated with a mass or lymph nodes.
- *Tumor mass* is more evocative. Signs of compression are frequently found at the level of the thorax and head. Abdominal masses are usually revealed at late stages.
- *Metastases* may be revealed but are most often found in work-up. Bone metastases are among the most expressive metastases.
- In exceptionnal situation, paraneoplastic signs or symptoms may reveal or accompany the disease.

The diagnosis must be formally established before any specific treatment. In the vast majority of cases, a biopsy is necessary for diagnosis. However, in Burkitt's lymphoma, fine needle aspiration may be sufficient. In most cases, immunohistochemistry is not necessary, but a good clinical evaluation is needed. In urgent situations, treatment may be started while waiting for diagnosis confirmation. In the case of retinoblastoma, some brain tumors, and tumors of the kidney, the clinical and radiological diagnosis may be sufficient.

The evaluation of the disease spread usually includes chest x-ray and abdominal ultrasound and in NHL bone marrow aspiration and CSF analysis. The study of tumor markers in the event of suspicion of neuroblastoma, germ cell tumor, or hepatoblastoma should be considered for diagnosis and sometimes prognosis and therapeutic follow-up. In all steps, multidisciplinary approach should be preferred.

5 Heat and Neck Tumors

5.1 Burkitt's Lymphoma

Facial tumor is one of the most frequent clinical presentations of Burkitt's lymphoma in tropical areas and is sometimes called endemic Burkitt's lymphoma. The diagnosis is easily suspected in case of a fast-growing maxillary mass resulting in a fall of teeth and sometimes a contiguous extension of the orbit that may be causing exophthalmos. These tumors may be confused with dental abscesses and lead to a tooth extraction or antibiotic or anti-inflammatory treatment delaying diagnosis. The diagnosis in these cases may be done by fine needle aspiration or tumor biopsy. These tumors are frequently associated to abdominal mass that can be shown in clinical examination or only when abdominal ultrasound is done. For staging purpose, bone marrow and CSF examination should be performed.

There have been several reports showing possible cure of 30–50 % of these patients using cyclophosphamide monotherapy [3]. This is however confirmed only for localized tumors. More intensive treatment using other active drugs (vincristine, methotrexate, doxorubicin) should be proposed in late stages or bad responding tumors to initial cyclophosphamide.

5.2 Retinoblastoma

Retinoblastoma is the most common intraocular tumor of children. This tumor seems very frequent in tropical areas and comes in lots of hospital registries as the second most frequent. While leukocoria and strabismus are the usual clinical findings in developed countries, exophthalmos, buphthalmia, are extraorbital extension are the most commonly forms in tropical region. The prognosis is very bad in extraocular forms. Improving awareness of parents and health-care workers may have a great impact in survival of these patients. In intraocular retinoblastoma, enucleation is curative. For acceptance of enucleation, prosthesis should be proposed to the patients [4].

5.3 Central Nervous System Tumors

These tumors are very rarely reported in tropical regions. This is probably related to miss diagnosis for the patients because of the unavailability of CT scan and/or MRI in most parts of the tropics and also inappropriate referrals [5]. The symptoms may be misleading in children with atypical intracranial hypertension (ICHT) because of possibility of the opening of the cranial sutures and the fontanels and large brain plasticity. The tumor can reach volumes before the establishment of the diagnosis. The ICHT induces a macro-cranium, a bulging of the fontanels and sometimes Parinaud syndrome. Surgical resection is the only treatment approach in most tropic regions. In medulloblastoma cases, radiotherapy and chemotherapy when available should be considered.

6 Abdominal Primary Tumors

Abdominal mass is one of the most frequent childhood cancer presentations. Clinical examination must specify its mobility and consistency. A rectal exam must be systematic to search for a pelvic component and specify if it is pre- or retro-rectal.

Between 1 and 5 years, Wilms tumor and neuroblastoma are the most frequently encountered tumors. Malignant lymphoma (NHL B and in particular Burkitt) is expressed by several usually confluent masses associated with pain and diarrhea or vomiting. Sometimes acute intestinal intussusception can be the mode of expression of Burkitt's lymphoma.

Macroscopic or microscopic hematuria is suggestive of renal tumor, while aniridia, body hemi-hypertrophy, and genitourinary malformations suggest Wilms tumor. Subcutaneous nodules and orbital bruising are suggestive of neuroblastoma. Finally, a precocious puberty is in favor of gonadal tumors.

Ultrasound examination is the best first-line imaging approach for an abdominal mass. It may make the diagnosis or help in fine needle aspiration or biopsy.

6.1 Nephroblastoma

Also called Wilms tumor, this is the most common kidney tumor of children. The modern multidisciplinary approach achieves cure in more than 90 % of patients. In sub-Saharan Africa, preoperative chemotherapy approach proved to be pertinent in reducing tumor volume making surgery easier. Most patients can be cured with acceptable toxicity chemotherapy regimen associating vincristine and actinomycin D and addition of doxorubicin in cases of regional extrarenal involvement [6]. When possible, radiotherapy should be considered in locally extended tumors for better tumor control. Good coordination between pediatrician, surgeon, and pathologist is crucial.

6.2 Neuroblastoma

Neuroblastoma originates from the neural crest which gives rise to the adrenal medulla and the sympathetic ganglia. The abdominal locations are the most frequent. Most patients have an extended form and presents with anorexia, pallor, lethargy, weight loss, or irritability. At the level of the abdomen, the usual expression is a firm abdominal mass. At the level of the pelvis, the patients may complain of signs of compression (constipation, urinary retention). These tumors may also have posterior extension to the spinal cord with possible paralysis. Classical and very suggestive diagnostic manifestation is orbital metastases usually expressed as a periorbital hematoma. In most cases, metastases are found in the bone marrow. In cases of clinically suggestive features, the diagnosis can reasonably be accepted. In difficult cases, urinary catecholamines may help for establishment of the diagnosis. Because of the bad prognosis of metastatic neuroblastomas, in resource-constrained situation, only palliation therapy should be proposed. In localized cases of neuroblastoma, surgical treatment may cure most of the cases. Chemotherapy may help in reducing the tumor volume. Effective products are cyclophosphamide, etoposide, doxorubicin, cisplatin, and the carboplatin. In the case of patients less than 1 year old with localized primary tumor, with dissemination limited to the liver, skin, or bone marrow (stage IVs), spontaneous regression is the rule. The chemotherapy with short courses of cyclophosphamide monotherapy can control the disease in large tumors or massive hepatomegaly with respiratory or gastrointestinal compression.

7 Lymphadenopathies

Peripheral lymphadenopathies are a common cause of consultation. The difficulty often lies in the distinction between physiological lymph nodes not justifying any exploration and lymph nodes that may be related to a malignant pathological process. The site, the volume, and the associated signs are of major importance in the search for the etiology. Clear distinction should be localized and generalized lymphadenopathies. Generalized lymphadenopathies are considered when more than two non-contiguous territories are involved with or without splenomegaly. In the event of suspicious lymph nodes, a CBC, a chest x-ray, and viral serology and in particular a search for HIV infection should be considered. Antibiotic treatment test can be recommended for 1–2 weeks. In case of anemia, leukocytopenia, circulating blasts, or mediastinal lymphadenopathies, a bone marrow aspiration should be performed to rule out leukemia or lymphoma involvement. A fine needle aspiration can also help in the diagnosis, but often biopsy is required to bring the diagnosis.

7.1 Hodgkin Disease

Hodgkin disease is one of the most frequent causes of malignant lymphadenopathies. In developing countries, this disease seems to happen at earlier age and is usually EBV associated. Regarding staging work-up, chest x-ray, abdominal ultrasound, and bone marrow biopsy make a good evaluation in most cases. Treatment with chemotherapy alone has proved to be very efficient. The ABVD (Adriamycin, bleomycin, vinblastine, and DTIC) protocol for 4–6 cycles is one of the best regimen [7].

7.2 Leukemias

Leukemias seem not frequent in tropical regions. They are difficult to manage in resource-limited conditions. Diagnosis may be easy with fairly good hematology. Good facility and appropriate supportive care including IV antibiotics and transfusion products are needed. However, children with standard risk acute lymphoblastic leukemia can reach more than 50 % survival rate using steroids, vincristine, and asparaginase in induction; vincristine, 6MP, methotrexate, and steroids in consolidation; vincristine, doxorubicin, steroids, and asparaginase in intensification; and maintenance with 6MP and methotrexate. This treatment can be done at outpatient basis.

8 Bone Tumors

These tumors are mainly osteosarcoma and Ewing sarcoma. There are very rare reports on clinical features and survival of bone tumors in tropics. Ewing sarcoma seems very rare in black population. On standard x-rays, the lesions are usually mixed, lytic, and condensing. Cortical rupture, periosteal reaction, and infiltration

of the soft parts reflect the malignancy. CT scan and/or MRI allows a good analysis of the tumor process but may not be necessary if amputation is the only possible surgical treatment. As for search of pulmonary metastases, a chest x-ray is a good evaluation since there is a debate about the nature of small nodules shown only on CT scan. Open biopsy of the primary tumor is necessary for diagnosis. Appropriate treatment is a combination of chemotherapy and complete surgical resection for all patients. Chemotherapy should be used first to reduce the tumor volume. It should be also given after surgery. In Ewing sarcoma, a combination of cyclophosphamide, doxorubicin, vincristine, and actinomycin D is usually recommended. In osteosarcoma, the combination of cis-platinum and doxorubicin is also efficient. In Ewing sarcoma, axial tumors cannot usually be removed. Radiation therapy if evaluable should be proposed in these cases.

9 Other Cancers

9.1 Malignant Tumors of Soft Tissues

This is a heterogeneous group of malignant tumors that originate from the mesenchyme. Childhood rhabdomyosarcoma (RMS) is the most frequently encountered tumor. Nonmetastatic RMS can successfully be treated with complete surgical resection and short course of chemotherapy using vincristine, cyclophosphamide, and actinomycin D. Other soft part tumors are usually resistant to chemotherapy.

9.2 Malignant Germ Cell Tumors

These neoplasms originate from the primordial germ cells. These tumors are rare and can be found in the gonads but also throughout the axial region of the trunk and also in the brain. Alpha-fetoprotein and the subunit beta chorionic gonadotropin hormone are usually elevated and help in diagnosis. Complete surgical resection may cure localized forms. Most of the time, chemotherapy is necessary either before or after surgery. The main active drugs are vinblastine, bleomycin, cis-platinum, and etoposide. Survival rates exceed 90 %.

10 Conclusion

Though pediatric cancer care is a complex activity, it is possible even in less developed countries to treat and cure a significant number of children. Approaches should however be adapted to local resources. The team should however:

- Take into account the parents' needs of appropriate information and needs.
- Hold regular multidisciplinary meetings where documented observations should be discussed.

- Prevent and treat the immediate complications related to the disease and therapies and in particular the treatment of pain, lysis syndrome, and nutritional support.
- Finally adapting the support so as to reduce the length of hospital stay and try at least to maintain a social life of the child and in particular his schooling.

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Geriatric Oncology

Martine Extermann and Syed Akram Hussain

1 Relevance to Tropical Areas

At first glance, geriatric oncology might seem to be a problem limited to developed countries. Yet, as progresses have been made in sanitation, nutrition, and infectious disease prevention and treatment, life expectancy has markedly progressed in tropical countries. For example, the life expectancy at birth is now 65 years or more in 174 of 223 countries listed in the World Factbook, including countries such as India, Bangladesh, the Philippines, Indonesia, Brazil, or Egypt [1]. In fact in 2000, 59 % of the persons aged 65 and older lived in developing countries, and this proportion is projected to rise to 71 % by 2030 [2]. With this demographic trend comes an increased prevalence of chronic diseases, cancer being one of them. Therefore, medical teams training and planning for the management of cancer in the elderly will be a crucial component of good cancer care in tropical countries.

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2 Principles of an Integrated Approach

Aging is the main risk factor for cancer, with the incidence rising from 1/10,000/year at age 20 to 1 %/year at age 80. Therefore, a large number of cancers occur at an old age. A few key principles underlie the care of older cancer patients. One is population heterogeneity. Several of these patients have accompanying comorbidities or geriatric problems (Table 1). Therefore, a systematic approach will be needed to account for between patient variability in planning for cancer treatment. In an oncology setting, not all of the problems might need a comprehensive approach beyond what would be done in the general adult population. In our experience, about half of patients aged 70 and older screen positive for geriatric problems and will need multidisciplinary assessment/management, and half are functionally simply "old adults" and can be treated with a standard oncologic approach [3]. In countries with a shorter average life expectancy, the threshold should likely be adjusted down to 65 or even 60 years, as active life expectancy is correlated with overall life expectancy. A second principle is multimorbidity. In developed countries, a person in his/her 70s has an average of three comorbidities besides their cancer. In developing countries like Bangladesh, a recent study found hypertension in 30 % of lung cancer patients, diabetes mellitus in 22 %, and bronchial asthma in 8 % of their patients; 18 % of the patients were found to have both HTN and DM (Haque AA, Hussain SMA, Karim F (2014) Association of comorbidities with the survival of non-small cell lung cancer, unpublished data).

Comorbidity is a major influencer of remaining life expectancy (which is different from life expectancy at birth). This can vary by up to 10 years for older patients of the same age [4]. In addition to survival, comorbidity impacts relapse-free survival and risk of cancer [5]. The impact of comorbidity in general on toxicity from chemotherapy is less clear independently from functional status, but the associated polypharmacy does increase toxicities. As in younger patients, specific diseases can interfere with the use of specific chemotherapy drugs [6–8].

Another principle is the age-related decrease in functional reserve. Whereas baseline physical functioning changes little with age, the ability of patient and body systems to handle stress decreases. This plays an important role in treatment planning and management as we will discuss below. Older patients also frequently are

Table 1 Prevalence of problems in older cancer patients: outpatient oncology clinic setting

Problems	Prevalence (%)
ECOG PS ≥2	~20
ADL dependence	~20
IADL dependence	50–60
Comorbidity	>90
Severe comorbidity	30–40
Depression	20–40
Cognitive impairment	25–35
At risk of malnutrition/malnourished	30–50

vulnerable in their social support. This might vary considerably with culture and location, but with urbanization and the rise of the nuclear family, this can be a critical issue for city dwellers or displaced persons. Given this global picture, optimal treatment of older cancer patients requires a multidisciplinary approach.

3 Geriatric Screening and Assessment

A complete comprehensive geriatric assessment (CGA) can take hours to days. Furthermore, geriatricians are in short supply, in both developed and emerging countries. Therefore, geriatric oncology researchers have developed a two-step approach to identify patients needing a geriatric work-up. Patients are initially screened with a short instrument for geriatric problems. If they screen positive, they are referred to a multidisciplinary team or geriatrician for further evaluation (Fig. 1). One should note the importance of doing an early geriatric screening. This allows using the 2–4 weeks usually needed for an oncology work-up for a parallel geriatric work-up, if necessary. This two-step approach identifies roughly half of the patients as having geriatric issues. When cancer patients undergo a geriatric evaluation, this modifies the cancer management in ¼ to ½ of cases [9]. Several screening tools are available and were recently reviewed in detail by the International Society of Geriatric Oncology (SIOG) CGA task force [10]. The article also contains a copy of the instruments themselves. From a practical point of view, we suggest reviewing a few of the tested tools and choosing the one best adapted to your individual clinical setting. For example, if you want many clinics to test all older patients for referral to a multidisciplinary clinic, then a short, patient-filled tool, such as the G8, is

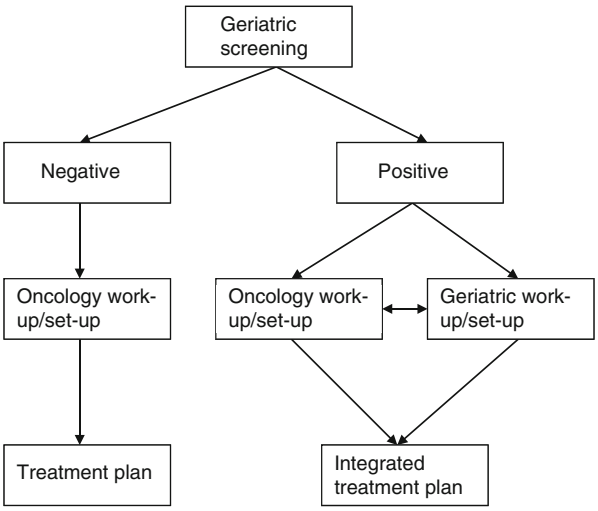

Fig. 1 General approach to treatment planning in an older cancer patient

likely best. On the other hand, if you have a multidisciplinary clinic where team members can assess the patients at first visit, a slightly more extensive tool such as the SAOP2 can help you identify more precisely which team members to involve. Most screenings can be patient answered or included in the initial nursing assessment.

3.1 Adaptation to a Sparse Resource Setting

A tropical oncologist might find himself/herself without an available consulting geriatrician or multidisciplinary team at hand. Although specific data are lacking, the advantages of running a geriatric screening are multiple. Firstly, this undeniably detects problems that otherwise would have been missed. Secondly, it identifies patients who will need a closer follow-up and coordination of care by at least the oncology team and the primary care physician or even a primary nurse practitioner in remote areas. We will detail some of these management considerations below. There is also an abundant general geriatric literature about nursing interventions that do not need an available physician. Sending a member of the oncology team for a short training in geriatric matters or an online course might prove very helpful.

4 Management Considerations

4.1 Decision Help Tools

An overall approach to treatment selection can use a three-tier model: healthy, vulnerable, and frail patients. Some tools have been developed that may assist in decision making. Several are available online (Table 2) and cover geriatric assessment, chemotherapy risk assessment, or life expectancy estimates. Standard oncology tools, such as Adjuvant! Online, can be suggestive, but should be used with caution, as their data estimates can be skewed in the elderly [11]. In addition, published predictive assessments are available, for example, for the risk of postsurgical complications: PACE/PREOP, Kristjansson [12, 13]. Some links provided in Table 2 are found very useful by the authors but in no way pretend to be an exhaustive list. Such lists evolve rapidly. With advancing age and comorbidity, patients may use increasingly diverse criteria to judge which treatment choice is "worth it," and subjective estimates by both patient and physician become increasingly imprecise as case complexity increases. Therefore, one of the main goals of these decision helps is to provide accurate estimates of the benefits and risks of cancer and its treatment alternatives for discussion with the patient and other stakeholders.

Table 2 Useful links to online resources (blank lines added for you to insert your own favorites)

Name	Type	Link
CARG score	Chemotoxicity risk prediction	http://www.mycarg.org/Chemo_Toxicity_Calculator
CRASH score	Chemotoxicity risk prediction (the page also contains a low neutropenia risk calculator, CIRS-G calculator, and SAOP2 questionnaires in several languages)	http://moffitt.org/cancer-types--treatment/cancers-we-treat/senior-adult-oncology-program-tools
ePROGNOSIS	General life expectancy	http://eprognosis.ucsf.edu/
NCCN older adult oncology	Consensus guidelines	http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
POGOe	Collection of free geriatric resources	http://www.pogoe.org/
SIOG	Geriatric assessment and cancer treatment guidelines for older patients	http://www.siog.org/

Of note, most of these tools and guidelines were developed for use in high-income countries. Adaptation to tropical setting might be needed
Links accessed on 10 November 2014
Abbreviations: *CARG* Cancer and Aging Research Group, *CRASH* Chemotherapy Risk Assessment Scale for High-Age Patients, *POGOe* Portal of Geriatric Online Education, *SIOG* International Society of Geriatric Oncology (Société internationale d'oncologie gériatrique)

4.2 Screening for Tropical Conditions

In tropical countries, parasitoses such as helminthiasis, kala azar, malaria, and filariasis are prevalent and should be treated prior to chemotherapy initiation. Vaccinations against viral diseases such hepatitis B and human papillomavirus have become available. Large vaccination campaigns such as those conducted against hepatitis B in Thailand appear to lead to a decrease in hepatocellular carcinoma. Data are sparse about the antitumoral effectiveness of vaccines in the elderly. On the other hand, the prevalence of chronic hepatitis B and C is a real issue. Lamivudine prophylaxis decreases the risk of reactivation of hepatitis B during chemotherapy [14]. At the present time, no prophylaxis is recommended for hepatitis C patients.

4.3 Surgery

Most surgical series highlight the fact that elective surgery in older patients has outcomes similar to those of younger patients with similar ASA scores, with only slightly higher morbidity/mortality [15]. A geriatric evaluation needs to be conducted to identify patients at risk of complications beyond a simple ASA score [12, 13]. Preoperative screening for risk of delirium is important, as it significantly increases the risk of functional dependence and mortality and prolongs hospitalization.

Furthermore, it can be prevented or reverted with mostly simple, non-medicamentous means if detected early [16]. On the other hand, because of the age-associated decrease in functional reserve, emergency surgery has a higher risk of morbidity and mortality in older patients than in younger ones [17, 18]. Therefore, every effort should be made to preempt emergency situations: public education, well-prepared elective interventions, and stabilization of an acute patient prior to surgery (e.g., endorectal stent). Discharge planning is also important. Older patients have higher transitional care needs, and home interventions can improve survival [19, 20].

4.4 Chemotherapy and Targeted Therapies

Several physiological changes of aging can affect the tolerance of an older person to chemotherapy. The most common ones are listed in Table 3. The most common (and cheap) implication for chemotherapy management is the need to calculate creatinine clearance in every patient. We recommend using the Cockroft-Gault formula. Although it tends to underestimate the creatinine clearance by about 5 % in the elderly, it tends to do so in a stable fashion, whereas other formulae are more erratic [21]. Furthermore, most chemotherapy adaptations are based on Cockroft-Gault.

Table 3 Age-related physiological changes that affect cancer treatment

Organ	Changes	Impact on treatment
Body composition	Sarcopenia, more rapid muscle loss with bed rest than young	Proactive and early PT/mobilization measures to prevent muscle and function loss
Bone marrow	Decreased functional reserve, higher hematologic toxicity	Use primary growth factors (if available) for NP fever risk >20–40 % above age 65
Gut/stomach	Decreased acute nausea, increased delayed nausea	Pay attention to delayed nausea prevention
	Decreased thirst reflex	Increased risk of dehydration with N/D/V
Heart	Subclinical injuries	Higher risk than young of CHF above 350 mg/m^2 of doxorubicin
Kidney	Decreased GFR, can be underestimated b/o sarcopenia	Systematically calculate creatinine clearance (Cockroft-Gault), even in patients with normal creatinine levels
Liver	Decreased volume and blood flow	Some drugs might be eliminated more slowly but data poor. Watch for CYP 450 interactions
Neurologic	Hearing loss	Check before giving neurotoxic agents (e.g., cisplatin) Check understanding of instructions, provide written material, have family members present
	Peripheral neuropathy	Caution with neurotoxic agents. Orthostatic hypotension can be a manifestation

Another common problem in the elderly is polypharmacy, whether prescribed drugs or over-the-counter medicines and herbs. Drug interactions can double or triple the risk of side effects from the chemotherapy [8]. Therefore, medications should be reviewed, e.g., using a drug interaction software, and the list pared down according to geriatric principles.

A key point in the management of chemotherapy is to be proactive with supportive care. Half of severe toxicities occur during the first cycle of treatment. Infection prevention is critical. Patient and family notions of hygiene vary a lot according to setting, and educational material might be needed. Growth factors are desirable if the risk of infection is >20–40 %, such as with CHOP-like regimens or most adjuvant breast cancer regimens. The risk calculators mentioned above can be used. Early aggressive diarrhea management is crucial to prevent dehydration, as well as proper antiemetic regimens covering well delayed nausea.

Some effects of chemotherapy are cumulative, notably fatigue. As older patients have less functional reserve, we tend to favor shorter regimens when feasible (e.g., docetaxel/cyclophosphamide (TC) × 4 (12 weeks) rather than a 4–6 months regimen for adjuvant breast cancer chemotherapy).

Although targeted therapies might tend to be as a group less toxic than chemotherapy, several of them can be associated with significant side effects, e.g., diarrhea on EGFR inhibitors, fatigue and nausea on tyrosine kinase inhibitors, and bleeding and thrombosis on VEGF inhibitors. The same general management rules apply as for chemotherapy.

Healthy older patients can usually be treated with regimens similar to younger patients. However, some drugs need adaptation. For example, high-dose Ara-C (3 g/m^2) should not be used in AML patients above the age of 60–65 years, as toxicity outweighs the benefits [22]. If irinotecan is used every 3 weeks, the starting dose should be reduced from 350 to 300 mg/m^2 [23]. There are also doubts on the additional benefits of using FOLFOX rather than simply 5-FU/leucovorin (preferably weekly, as the Mayo regimen is more toxic) in patients above the age of 70 [24].

4.5 Radiation

Radiation therapy series indicate that it is well tolerated by older patients. This is especially true if modern techniques such as conformational radiation and intensity-modulated radiation are available. Unfortunately, many tropical countries have an underdeveloped radiation facility network, as this requires reliable power sources, expensive machines, and the technicians and staff knowledgeable to operate them. Yet, even patients living a distance away might benefit from short duration treatment options. For example, short-course hypofractionated radiation rather than combined chemoradiation can be given as neoadjuvant treatment for rectal cancer. Adjuvant radiation for breast cancer can also be hypofractionated over 3 weeks or even a single week in small tumors. An excellent review of the available evidence in geriatric oncology was recently published by the SIOG radiation task force [25].

4.6 Supportive Care

Older patients are less prone to complaining than younger ones, so symptoms such as pain or distress should be systematically addressed. The WHO Step Ladder Model for pain control is easy to follow, but in poor settings, the availability of some synthetic opiates might be limited.

The metabolism of opiate medications can be very variable from individual to individual, so apply a "start low and go slow" rule to increasing the dose. Depression is frequent in all cancer patients. Simple grief (which will often resolve spontaneously or with supportive counseling) should be distinguished from clinical depression (which requires specific treatment to resolve). This should be done at all stages of the cancer course, including terminal. In the elderly, depression more frequently lacks positive signs (crying, expressed distress, agitation) and more frequently presents with negative signs (flat affect, lack of activity). Most geriatric screening instruments screen for it and follow-up should be initiated. Delirium prevention and management were discussed above. Patients with cognitive impairment can often receive cancer treatment, but their expected survival is roughly half that of patients without cognitive impairment [26]. Family education in symptom management can prove highly helpful.

4.7 Adaptation to a Sparse Resource Setting

Nurses, nurse auxiliaries, and families can be involved in delirium prevention, recognition, and management. Evidence-based cards can be created and distributed.

Patient and family education in infection prevention, hygiene, and dehydration management should be conducted prior to chemotherapy. If patients live a distance or in unsanitary conditions, consider housing them on or near the hospital compound during the first cycle of chemotherapy, as this is the period with the highest risk of complications.

Radiation facilities might be a long distance away for many patients in developing countries. Some countries might limit the use to curative intent. However, palliative radiation can be one the most effective pain control measures. Single-dose or very short courses of radiation can be used and are feasible for patients coming from a distance.

5 Public Health Considerations

Historically, tropical countries have placed a heavy emphasis on controlling infectious diseases and general sanitation measures. Recently, realization has come that chronic diseases, including cancer, are now outweighing infectious diseases as a

cause of morbidity/mortality. Yet in many cultures, cancer, especially in the elderly, is still synonymous with death. However, independent of age, early detection can allow cost-effective curative measures, such as surgery. While optimal management often involves multimodality therapy, surgery alone still cures 50 % of stage III colon cancers, 70 % of stage I lung cancers, 85 % of stage I breast cancers, and 70–75 % of stage II breast cancers. Therefore, accurate information targeting the older citizens and their family is a critical need and an early step in building a nationwide cancer management program. As resources and expertise increase, specialized centers can handle more treatment modalities and diffuse them progressively in the community.

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Surgery

Steve Kwon and T. Peter Kingham

1 Introduction

The International Agency for Research on Cancer predicts that the global burden of cancer incidence will reach 21.4 million by 2030 with the annual number of cancer deaths reaching 13.2 million [1]. The World Health Organization predicts approximately 60 % of all new cancer cases by 2020 will occur in low- and middle-income countries (LMIC) [2]. Yet, currently, there is a clear disparity in outcomes that correlate to the income level of countries [3]. The overall case fatality rate from cancer (percentage ratio of mortality to incidence) is around 75 % in low-income countries compared to 46 % in high-income countries [3]. The current challenge for us is to translate developments in cancer care from high-income countries (HIC) into LMIC, which will increasingly bear the world's cancer burden.

Surgery is a key component of all aspects of cancer care, ranging from diagnostic biopsies to therapeutic or palliative procedures. However, surgery is often overlooked in public health efforts to address cancer due to surgeon under-representation in the public health community [4]. Analysis using the WHO tool to look at surgical resources in LMICs revealed that 45 % of district hospitals did not have a functional anesthesia machine, and more than 52 % lacked a steady supply of sterile gloves [5]. Also, the extreme paucity of surgeons in LMICs is a significant barrier to surgical and thus cancer care. In a needs assessment of Sierra Leone, we found that in the ten government hospitals we surveyed, there were only ten fully trained Sierra Leonean surgeons to serve a population of 5.3 million [6].

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2 Role of Surgery/Surgeons in Diagnosis

A major and distinguishing challenge when making the diagnosis of cancer in LMICs is the limited availability of trained personnel and modern equipment. Lack of access to pathology services is a major barrier to the diagnosis and staging of cancers in LMICs. Malawi, for example, had a single pathologist in 2010 serving a population of 15 million. This led to an approximate wait time of 3 months for pathologic reporting [7]. With increasing Internet access, teleoncology initiatives are being implemented that may help improve access to pathology [8].

In HIC, cancer diagnosis and staging relies heavily on radiographic examinations. A combination of computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) is used. In comparison, physicians in LMIC rely on clinical examination, chest radiography, and ultrasound if available. Ultrasound can be especially useful for surgeons trying to make a diagnosis in resource-limited settings. In a large retrospective review from Cameroon, researchers looked at results from 1119 ultrasound examinations performed to make diagnoses ranging from gynecological to gastrointestinal. Abnormal findings were shown in 78 % of the ultrasound exams performed. In the 323 (28.8 %) patients where the diagnosis was certified, 67.8 % of the exams were deemed useful for diagnosis. Also in the certified group, ultrasound provided diagnosis in 31.6 % of the patients and allowed a differential diagnosis to be excluded in 36.2 % [9]. Although physicians in HICs rely on mammography and MRI for diagnosing breast cancer, it is possible that ultrasound could replace both in LMIC. Surgeons could be trained to use less expensive imaging tools such as ultrasonography to guide both radiologic diagnostics and biopsies [10].

Staging cancer patients is a significant problem in LMICs with no access to advanced equipment. For example, it was shown that Malawi's cancer registry had staging information for only 0.7 % of cancer cases [11]. Surgeons can use novel applications of technology, however, to help with staging. Examples are performing diagnostic laparoscopy to stage the abdomen and obtain tissue or capturing images via the use of smart phones to document cervical lesions.

Surgeons can play an important role in advocating for early diagnosis and developing low-cost, effective screening methodologies. For example, in cervical cancer, there has been a push to implement a screening procedure using visual inspection with acetic acid (VIA) and/or a low-cost rapid human papilloma virus (HPV) DNA-based test, rather than the more expensive Pap smear test [12, 13]. Such efforts are needed to avoid the late presentations that occur frequently in these countries because many common malignancies such as breast cancer, cervical cancer, gastrointestinal cancer, and Kaposi's sarcoma may be curable if detected and treated early. Surgeons also need to help build improved systems of educating communities about cancers and associated symptoms and also removing the fear that many in LMICs have of cancer being a death sentence [14]. Unfortunately, most available funds are spent on individual treatments and not in screening and diagnostic phases of cancer [3].

3 Role of Surgery in Treatment of Gastrointestinal Cancers

Many gastrointestinal cancers are curable with surgery. Despite this, surgery is rarely used. A retrospective study looking at characteristics of 206 patients diagnosed with hepatocellular carcinoma in Ghana showed that almost all patients received only supportive treatment and none received surgery, ablation, or transarterial chemoembolization. Further investigation revealed that less than 8 % had been eligible for resection, transplantation, or ablation, and up to 72 % had been eligible only for supportive care [15]. These results demonstrate the importance of performing further studies to estimate the contributions to lack of surgical use from both the presence of advanced disease and the lack of expertise. Distinguishing between the two will help focus efforts and more effectively manage these cancers in LMICs (i.e., screening and early detection vs. personnel training).

In colorectal cancers, surgery plays a crucial role because of the scarcity of adjunct treatments as well as the need to palliate symptoms (Table 1). However, there are certain limiting factors with surgery, especially with rectal cancers, due to lack of experience in sphincter-preserving rectal surgery, cost of certain stapling devices used for this surgery, and lack of neoadjuvant treatments to downstage these tumors [16, 17]. Perhaps due to these limiting factors, more than 40 % of patients with rectal cancer undergo abdominal perineal resection [16, 17], which is an important consideration in certain countries where stomas are not culturally accepted. A first step toward more sphincter-preserving rectal surgery may be further training of surgeons and better access to stapling devices that help facilitate these surgeries.

In gastric cancers, the morbidity and mortality rates are high. Major complications such as anastomotic leak and hemorrhage occur in as many as 30 % of the patients undergoing gastric resections [18], and operative mortality rates range from

Table 1 Availability of chemotherapies in sub-Saharan Africa

Available	Available by request, if patient can afford	Rarely available
Capecitabine	Bleomycin	Bevacizumab
Cisplatin	Carboplatin	Erlotinib
Cytarabine	Dacarbazine	Ibandronic acid
Dactinomycin	Epirubicin	Imatinib
Daunorubicin	Fludarabine	Rituximab
Doxorubicin	Gemcitabine	Sunitinib
Etoposide	Ifosfamide	Temozolomide
Fluorouracil	Interferon alfa	Trastuzumab
Folinic acid	Irinotecan	
Hydroxyurea	Oxaliplatin	
Melphalan	Pamidronic acid	
Mercaptopurine	Taxanes	
Methotrexate	Topotecan	
Thioguanine	Vinorelbine	
Vincristine	Zoledronic acid	

This table was adapted from Kingham et al. [33]

16 to 36 % [19]. The high complication and mortality rates are likely related to the fact that outcomes in gastric cancer surgery are closely associated with stage of disease at diagnosis. Early surgical intervention, before tumor enlargement and involvement of nearby structures, may improve these rates. Most patients, however, present with gastric outlet obstruction, hematemesis, or perforation. Access to surgeons trained in endoscopy is necessary when patients have persistent symptoms of dyspepsia, epigastric pain, or nausea to identify early gastric cancers and to lower these mortality and morbidity rates.

4 Role of Surgery in Treatment of Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer among men and the sixth leading cause of cancer death among men globally [1]. The treatment for prostate cancer in LMICs is limited by late presentation, advanced disease, and scarcity of urologists, pathologists, radiation treatment, and androgen-deprivation therapies. Compared to the 99 % 5-year survival rates in HIC for all stages of prostate cancer, a study from Nigeria showed that 16 % of patients died from this disease within a 3-year follow-up period [20, 21].

Currently, subcapsular orchiectomy and diethylstilbestrol are the two most widely used treatments in low-income countries [21]. Subcapsular orchiectomy is a good example of a cost-effective alternative treatment that can be performed surgically in place of a medical treatment (chemical castration). Unfortunately, due to lack of access and the high cost of prostate-specific antigen tests and transrectal ultrasonography, digital rectal examination alone remains for screening. The specificity, however, of digital rectal examination has been shown to be only 61 % [22]. Increasing access to diagnostic tools, such as transrectal ultrasound for earlier detection of prostate cancer, and increasing access to adjunct treatments, such as radiation therapy, hormone therapy, and chemotherapy, are key to improving survival in these patients.

5 Role of Surgery in Treatment of Cervical Cancer

Cervical cancer is the leading cause of cancer mortality in low-income countries [23]. For example, in Africa, 80,000 cases of cervical cancer are diagnosed per year in women older than 15 years. More than 50,000 of these women die from their disease. This is mostly due to late presentation, because cervical cancer is often curable when found in early stages. It is clear then that efforts should focus on cost-effective screening that is easily available.

As mentioned above, one approach to reducing costs is to replace the traditional screening tests, cytology, and colposcopy, with VIA and/or rapid HPV DNA-based

testing. These single-visit tests are appealing alternatives also because treatment, if needed, could be provided in the same day. Goldie et al., with data from five developing countries, demonstrated that if 35-year-old women were screened just once in their lives with VIA, their lifetime risk of invasive cervical cancer can decrease by 25 %. If screened twice with VIA, at ages 35 and 40, lifetime risk can decrease by 35 % [24]. HPV DNA-based testing was shown to be more effective at reducing the occurrence of advanced precancerous lesions over time. A study from India demonstrated that HPV DNA-based testing resulted in a greater mortality reduction than using VIA or Pap smear for screening [25]. However, HPV DNA-based testing is still relatively expensive and requires 7 h for laboratory processing. Therefore, a major focus should be on developing a low-cost screening test that would provide immediate and accurate results to enable screening, diagnosis, and treatment in the same visit. New, rapid HPV DNA-based testing is being developed for this purpose [26].

6 Role of Surgery in Treatment of Breast Cancer

Understanding how breast cancer in LMICs differs from breast cancer in high-income countries is crucial for surgeons. For example, patient characteristics in the high-risk groups are not identical from one region to the next. Notably, patients with breast cancer in sub-Saharan Africa tend to be premenopausal, multiparous, and have a history of protracted breastfeeding [27]. Such information can help clinicians target high-risk groups more effectively and reduce the current mean delay (11.2 months) from onset of symptoms to presentation [27].

Also, breast cancer biology in LMICs may differ from that in high-income countries. For example, in one study, researchers compared women with breast cancer in the United States to women with breast cancer in Ghana. Results showed that 76 % of the Ghanaian women had estrogen receptor-negative tumors in contrast with 22 % of the white American women. Also, 82 % of the Ghanaians had triple-negative disease in contrast with 16 % of the white Americans [28]. While such discrepancies may be in part due to inaccurate immunohistochemistry results, administering tamoxifen without confirming positive receptor status wastes valuable resources. Understanding the differences in tumor biology while also improving the accuracy of immunohistochemistry results may lead to more cost-effective interventions.

Lastly, it is important to realize that procedures that are offered in HICs may not be available in LMICs. For example, mastectomy is the most frequently offered breast cancer surgery in LMIC and is challenging culturally. It is estimated that 38.3 % of patients undergoing mastectomies are divorced within 3 years [29]. Surgeons should be attentive to this cultural barrier and work with the whole family in coming to an understanding of breast cancer and its treatments. Unfortunately, due to lack of resources, radiation therapy, chemotherapy, sentinel lymph node assessment, and breast-conserving surgery are rarely performed.

7 Chemotherapy and Radiation

Three major obstacles to delivery of appropriate multidisciplinary cancer care in LMIC are lack of personnel, high cost, and cultural beliefs. First, chemotherapy regimens are administered under direction of either surgeons or physicians, without specialized training in cancer care. With multidisciplinary cancer management adoption by tertiary hospitals, this will improve. Second, generic drugs are often used because the cost of patented drugs is prohibitive. This has negative effects because in the absence of regulatory bodies to control the influx of these medications, the bioequivalence, side-effect profile, and efficacy of generic drugs may differ from those of the originals. It is important for countries to identify which drugs are available (Table 1) and to calculate the cost to patients. It is also important to calculate the cost of chemotherapy maintenance as many drugs to treat chemotherapy-associated toxicities are either expensive or not readily available (Table 2). This information will help resource-limited LMICs to select the most cost-effective chemotherapy drugs. Cultural beliefs, patient denial, especially after complete surgical resection, and physician ignorance are all barriers to access. Also, traditional healers offer the promise of a cure without the side effects of chemotherapy such as hair loss, erectile dysfunction/infertility, or neuropathy.

Similarly, use of radiation therapy is limited due to its cost and lack of availability. In one study from Australia looking at the use of radiotherapy in LMICs, researchers showed that although 83 % of the breast cancer patients could be expected to have received radiotherapy, only 10.8 % received this treatment [30]. In Ethiopia alone, where it is estimated that 74 to 85 radiation machines are needed to meet patient requirements, there is only one machine available [30]. One way to reduce costs and improve access is to perform intraoperative radiotherapy. Researchers in South Africa studied the effectiveness of intraoperative radiation therapy. Baatjes et al. reported that after 7 years of follow-up, only one of 39 (2.6 %) women with breast cancer had a local recurrence, four (10.3 %) had regional recurrences, and three (7.7 %) had systemic relapses. The estimated cost of intraoperative radiotherapy was $1300 per patient, far less than $9000 per patient for standard external beam radiation therapy [31].

Table 2 Availability of supportive drugs to manage chemotherapy-associated toxicities in sub-Saharan Africa

Available by request, if patient can afford	Rarely available
Metoclopramide	Domperidone
Dexamethasone	Granisetron
Ondansetron	Erythropoietin
Lorazepam	Granulocyte colony-stimulating factor

This table was adapted from Kingham et al. [33]

8 Directions for the Future

Five key components that should be implemented in low-resource setting are improvements in the pathology services, access to surgery, radiology services, reliable data collection, and the modification of guidelines. The pathological and radiological components have been discussed in the Diagnosis section. Data collection is a difficult but crucial component to improve cancer management in low-income countries. A simple intervention can be introduction of patient data cards containing information on a patient's age, sex, date of diagnosis, presenting symptoms, significant family history and social habits, studies performed, estimate of tumor stage, treatment to date, and pathological stage when possible. A similar approach has been used to improve adherence to childhood vaccinations [32]. Lastly, development and implementation of modified guidelines are important because there are regions where surgery may be the only therapeutic option.

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Radiotherapy

Mei Ling Yap and Michael Barton

1 Introduction

The global burden of cancer is increasing, with the incidence projected to rise to 23 million cancer cases worldwide in 2030 [5]. Radiotherapy (or radiation therapy), the medical use of ionising radiation, is a vital component of a cancer care service. Radiotherapy uses high-energy ionising radiations (x-rays, γ-rays or particles) which cause cancer cells to die by inflicting damage on the DNA.

2 Indications for Radiotherapy

Radiotherapy can be used to cure many cancers that occur in tropical countries. It can be used as primary curative treatment for cancers such as prostate cancer and to preserve function for larynx cancer and breast cancer. It is also used concurrently with chemotherapy to cure cancers such as cervix cancer and head and neck cancer. Radiotherapy may also be applied prior to or following surgery, to reduce the risk of

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locoregional recurrence and/or improve survival for cancers such as breast and rectal cancer.

In patients with incurable disease, radiotherapy provides cost-effective relief of distressing symptoms such as pain and bleeding. Palliative radiotherapy for bone metastases will result in significant reduction in pain in over 2/3 of patients [16].

Using the best available evidence, the proportion of Australian cancer patients who should receive radiotherapy at least once in their treatment course is 48.3 % [3]. The proportions of patients with a specific cancer subsite who would benefit from radiotherapy are listed in Table 1. In many tropical countries, cancer patients may present at more advanced stages of disease. The optimal proportion of patients who should receive radiotherapy in such countries is likely to be higher than that of Australia, given that there are more indications for radiotherapy in the setting of locally advanced and metastatic disease.

Table 1 Optimal radiotherapy utilisation rates per cancer subsite

Site	Optimal radiotherapy utilisation rate (%)
Bladder	47
Brain	80
Breast	87
Cervix	71
Colon	4
Gall bladder	17
Head and neck	74
Kidney	15
Leukaemia	4
Liver	0
Lung	77
Lymphoma	73
Melanoma	21
Myeloma	45
Oesophagus	71
Other	19
Ovary	4
Pancreas	49
Prostate	58
Rectum	60
Stomach	27
Testis	7
Thyroid	4
Unknown primary	61
Uterus	38
Vagina	94
Vulva	39

3 Radiotherapy Equipment

Radiotherapy can be delivered by a radiotherapy machine (external beam radiotherapy or teletherapy) or using radioactive sources (brachytherapy). There are two main types of radiotherapy machines available in tropical countries: cobalt-60 machines and linear accelerators (linacs).

Cobalt machines are able to deliver simple, effective radiotherapy plans through a cobalt-60 source housed in the radiotherapy machine. The first functioning cobalt-60 machine was developed in London, Ontario, Canada in 1961, but in high-income countries, there are now few machines remaining. According to the International Atomic Energy Agency (IAEA)'s DIrectory of RAdiotherapy Centres (DIRAC) database [7], in 2013, only 17 % of world's external beam radiotherapy machines were cobalt. However, in many tropical countries, cobalt-60 machines account for a higher proportion of radiotherapy machines, e.g. in Colombia, just under half of its 70 external beam machines are cobalt. Overall, the proportion of cobalt machines available worldwide is decreasing, consisting of 32 % of 288 machines in African continent in 2013 compared to 60 % of the 155 machines available in 1998 [1].

The advantages of cobalt-60 machines include less dependent on a constant power supply, simpler installation, less maintenance and quality assurance programmes and repairs. The initial cost of cobalt-60 machines is also lower at approximately 1/3 to ½ of the cost of a linac [18]. However, cobalt-60 sources should be replaced every 5–7 years which significantly increases their lifetime costs.

A linear accelerator (Fig. 1) accelerates electrons via a wave guide onto a tungsten target, generating x-rays, also called photons, which are then aimed at the tumour. The advantages of linacs include their increased versatility, with the ability to deliver a range of different beam energies, electron beams as well as photons and the potential to deliver complex treatments. As well, the absence of a cobalt source

Fig. 1 Linear accelerator (Photo credits: Thomas Tran)

removes the potential issues of source theft, slow dose rate associated with decaying cobalt sources and the complex radiation safety concerns associated with a radioactive radiation source [12]. The disadvantages of linacs are the requirement for expert quality assurance to ensure that the machine is producing a safe beam and the ongoing maintenance costs which are usually equivalent to 10 % of the purchase cost per annum. Replacement parts may be expensive and difficult to procure in low-income countries (Fig. 1).

Brachytherapy units use radioactive sources such as iridium-192 to provide temporary intracavitary, interstitial or intraluminal irradiation to tumours. This technique is able to deliver a high dose of radiotherapy to tumours, with a rapid dose fall-off to reduce dose to critical structures ('brachy' comes from a Greek word meaning 'close'). In combination with external beam radiotherapy, brachytherapy is the only curative treatment for advanced cervix cancer. Cervix cancer is common in many tropical countries such as Tanzania where it accounts for 30 % of all cancer cases (http://GLOBOCAN.iarc.fr).

4 Service Delivery: Resources and Staffing

The delivery of radiotherapy requires both specialised equipment and staff:

- The *radiation oncologist* is a doctor who has specialised in the treatment of cancer and selected benign conditions with radiation.
- The *radiation therapist* is a technical person skilled in the planning and delivery from the radiation source or machine of the prescribed dose.
- The *radiation physicist* helps to ensure that the dose prescribed is actually delivered by dose verification measurements and plays a major role in radiation safety issues.

Access to radiotherapy in many tropical countries is limited. As seen in Fig. 2, some countries have no radiotherapy services available at all. In many tropical countries where radiotherapy is available, the ratio of patients to radiotherapy machines is higher than the recommended standard of 400–450 patients per year [15]. Another factor limiting the provision of radiotherapy services is the lack of trained, specialised staff. The ESTRO-QUARTZ project recommends workforce planning of one radiation oncologist per 200–250 patients per year and one physicist per 450–500 patients per year.

5 Radiation Safety and Quality

Radiation safety is paramount in order for radiotherapy to effectively improve outcomes for cancer patients IAEA [8]. The radiotherapy process is complex, and strict controls are needed to minimise the risks of errors [19]. Departments should also

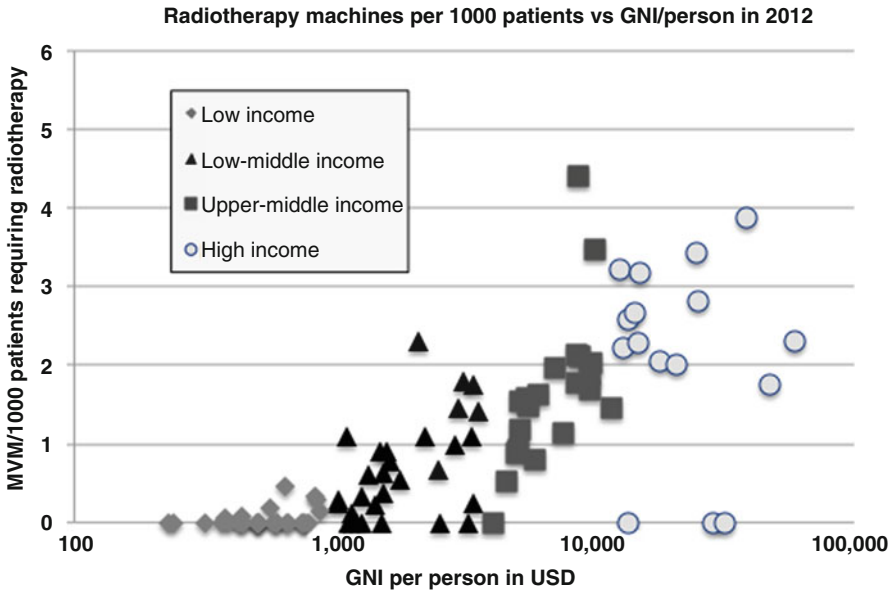

Fig. 2 Availability of radiotherapy machines in tropical countries ($N = 94$)

utilise protocol-based treatment and ensure quality assurance practices are conducted through all aspects of radiotherapy planning and delivery.

6 Education

In order to ensure adequate staffing and a quality radiotherapy service, education is imperative. Many tropical countries lack comprehensive teaching programmes in oncology. The role of distance learning, such as the IAEA course [4] and twinning partnerships [14] is very important. Another significant challenge is the retention of staff once they have been educated in order to prevent 'brain drain'.

7 Costing

Radiotherapy costing is complex and varies from country to country. Given the number of complex activities involved in the process of radiotherapy, an activity-based method has been favoured [10]. Costs include equipment costs, space costs, overhead material costs and wage costs, the latter comprising majority of costs in high-income countries in particular. Equipment costs required include that of the radiotherapy simulator, treatment planning system and radiotherapy machine.

Material costs include use of blocks, shielding and immobilisation equipment. In high-income countries, wages are the largest proportion of costs, but in low-income countries, capital and equipment costs dominate.

8 Treatment Complexity

The complexity of radiotherapy treatment also varies between countries. In most low-income tropical countries, two-dimensional radiotherapy, using one or two simple radiotherapy fields planned with an x-ray simulator, is frequently employed. Three-dimensional conformal radiotherapy is used routinely in most high-income countries, where radiotherapy plans using multiple beams are generated on computed tomography (CT)-based data in order to achieve a conformal radiation dose. Intensity-modulated radiotherapy (IMRT) is the use of multiple, highly conformal beamlets through the use of tungsten multileaf collimator leaves, allowing for the creation of concave shapes (Fig. 3). IMRT is commonly employed in sites such as head and neck cancer, where high doses are required for tumour kill, but nearby critical structures such as the brain stem must be spared [11]. Image-guided radiotherapy is the use of imaging, such as x-ray, CT or magnetic resonance imaging (MRI) to verify the position of tumour and/or organ at risk prior to or during radiotherapy delivery. The use of these newer technologies is associated with higher costs [17] and potentially longer radiotherapy planning and/or treatment times and requires stringent quality assurance so it is likely to take some time before it is widely available in many tropical countries (Fig. 3).

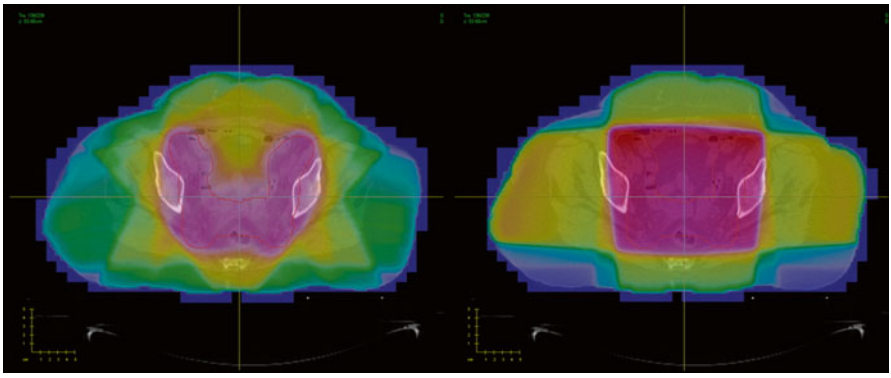

Fig. 3 Comparison of postoperative endometrial cancer IMRT (*left*) and 3D conformal radiotherapy (*right*) plan. The IMRT plan provides a more conformal radiation dose, allowing sparing of the small bowel (Image credits: Dr Michael Jameson)

9 Other Barriers to Radiotherapy Delivery in Tropical Countries

There are a number of other barriers to meeting the radiotherapy demand globally. Cultural perceptions of cancer remain a challenge, with cancer in many countries associated with significant social stigma [6]. Radiotherapy and its benefits are unknown by many members of the medical and general community in some tropical countries. Advocacy websites such as globalrt.org are important in attempting to overcome some of these challenges [13]. As well, there are many competing issues in tropical countries, such as communicable disease, poverty and political instability. Initiatives such as the Global Task Force in Radiotherapy for Cancer Control (GTFRCC) aim to address the issue of global radiotherapy deficit through an international, collaborative and evidence-based approach [9]. It is important for radiotherapy to be included as a major component in a comprehensive cancer plan, given that it has proven to be a beneficial, cost-effective treatment [2, 18].

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Medical of Cancer Treatments

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1 Chemotherapy, Hormonal Therapy, Targeted Therapy and Supportive Therapy in Low-Resource Settings

1.1 Introduction

Extrapolation of epidemiological studies indicates that LMIC will suffer the consequences of a cancer epidemic within the next decade as a result of lack of preparedness to deal with prevention and management of cancers leading to high morbidity and mortality. Cancer drugs are expensive worldwide, and availability in each country depends on the economic strength and commitment to the health of its population. Generic substitutes have improved the spectrum of drugs available to LMIC but concerns arise about their efficacy. Very few generic substitutes are available for targeted therapies and are restricted for use in specific populations. Results of well-conducted phase 3 clinical trials back the evidence of the effectiveness of cancer therapies in national guidelines but underserved populations such as minority ethnic groups including Africans, and older patients are underrepresented. In the absence of a strong health budget, it is difficult to recommend regional evidence-based

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guidelines based on results of stringently conducted national clinical trials. It is therefore not unusual to find that most countries adopt western protocols without validating their appropriateness or applicability.

Countries with limited resources have older drugs which are not included in new recommendations as alternatives even though they are still effective and may not have the required targeted therapies and supportive measures required in newer protocols. Skilled oncology personnel are best at adapting protocols to local conditions; however, we find that many patients are managed by general practitioners who tend to ignore the basic principles of oncology resulting in over or undertreatment of patients.

The complexity of delivery of chemotherapy and management of its side effects require that these therapies be administered in hospitals with wide spectra of specialties including pharmacists, nurses and clinicians with oncology backgrounds. In view of the medical complications from treatment and the compounding effects of preexisting medical conditions, medical oncologist preferably or clinical oncologist (a rapidly declining speciality of combined medical and radiation oncology) should direct managements where available. Radiation oncologist has a strong background in the multidisplinary management of cancer including knowledge of cancer medicines and toxicities and therefore can direct management in the absence of medical or clinical oncologist. LMIC should encourage training of clinical oncologists to meet their needs. University and private oncology dedicated hospitals are best suited followed by regional hospitals, and referrals to these centres are ideal. Unfortunately, these institutions are inaccessible to rural patients. Clinicians and nurses with oncology experience can administer drugs under guidance of an oncology specialist by phone or the Internet and must have the ability to recognise and manage side effects. In oncology, treatment outcomes directly correlate with experience of treating clinician.

Oncology-trained nurses are in short supply in most LMIC and this should be strongly addressed. Their contribution to successful cancer treatments is underestimated. Short-term hands-on trainings and online module teachings are recommended in the absence of a structured certifying training programme.

Chemotherapy is commonly delivered via peripheral access intravenously. PORT-A-CATH is recommended when there is poor peripheral access and for highly vesicant drugs but is not readily available, expensive to obtain and insert and difficult to maintain, and the idea of a permanent catheter is not readily acceptable to patients. Peripherally inserted central catheters (PICC lines) are temporary and cheaper alternatives to PORT-A-CATH but only recommended for up to 12 weeks.

Oral medications are attractive and more acceptable alternatives to intravenous medications; however, they are not common where indicated, and there are genuine concerns about their absorption and bioavailability as studied factors such as diet, enzymatic activity in gastrointestinal tract, inheritable genes and environmental influences are known to affect the efficacies of these drugs. Compliance is also a major problem, and patients need to be educated about benefits of adherence to prescriptions, and prescribers should ensure that enough medication is available till next clinical visit.

Tolerability of medications depends on gender and ethnicity due to genetic polymorphisms or environmental factors, and this may explain why certain anticancer drug may cause more toxicity in certain ethnic populations, gender or individuals. Example is the increased specific toxicities of 5FU related to the levels of dihydropyrimidine dehydrogenase enzyme in females, people with African decent and the Chinese,

increased gastrointestinal toxicity in patients with UGTIA1 enzyme deficiency receiving irinotecan, TPMT enzyme deficiency and increased 6-mercaptopurine toxicity.

Response to medications can also be influenced by somatic mutations as in KRAS and BRAF reducing response to EGFR-targeted monoclonal antibodies, and EML4-ALK fusion required for response to crizotinib to treat NSCLC. Biomarker testing is therefore recommended prior to treatment but this facility is limited in many LMIC. Receptor testing for hormone treatments is the most widely available biomarker test but still considered suboptimal. Her2/neu receptor testing is not widely available even though highly recommended to guide management even in the absence of targeted therapies.

1.2 Chemotherapy

The use of chemotherapy depends on availability, cost, convenience and expertise of treating physicians in delivery and management of toxicities. The choice a specific protocol depends on availability of drugs, complexity of delivery, required supportive care and most importantly the cost of treatments. General physicians are more likely to under- or overestimate the impact of chemotherapy for their patients. The medical complications associated with chemotherapy limit their adoptability in less developed area. Educating physicians about premedication, baseline test and monitoring of organ function, prevention, grading and management of side effects, and contraindications may encourage the use of chemotherapy in the less resourced setting.

1.3 Hormonal Therapy

Tamoxifen for breast cancer is the most commonly prescribed and cheapest hormonal therapy but should be limited to receptor-positive cases. Aromatase inhibitors are indicated in specific cases and as at now relatively expensive with compliance issues related to musculoskeletal-related toxicities.

Oral antihormonal therapies for prostate cancer are cheaper alternatives but have increased toxicities.

Injectable hormonal therapies for prostate cancer are expensive, and the long duration of treatment is also a setback to affordability, but they are more culturally acceptable than orchiectomy.

1.4 Targeted Therapy

Their use is limited to higher-resource regions and where available on national insurance schemes. Availability is also a major issue as companies are unwilling to stock medications requiring large monetary investment but slow turnover and short lifespans. Procurement is per request making it expensive and not cost-effective.

Biomarker testing is expensive and limited in most LMIC limiting applicability. Cure is achieved in few haematological and solid tumours, and the main indication is for metastatic disease with marginal overall benefit. Toxicities and their management are another limitation to their use. The clinical benefit and expected toxicity of each targeted drug as well as the entire cost should be discussed with every patient thoroughly. Targeted drugs for haematological malignancies are the most commonly available. Anti-VEGF drug bevacizumab does not require biomarker testing, and it is indicated in advanced ovarian, cervical and colorectal cancers in combination with chemotherapy. Trastuzumab for her2/neu overexpressing breast cancer is the other frequently used targeted therapy, but cost and protracted duration of treatment are the major limiting factors. Unpublished data from a survey of breast cancer management practices in Africa indicate that less than 5 % of patients can afford this medication; majority were prescribed with the shorter 9-week schedule in lower-resource countries compared to majority in Northern and Southern Africa receiving the 1-year protocol.

1.5 Supportive Therapy

GCSF is expensive and rarely required with adequate dose calculations, monitoring, dose reductions (not more than twice) and switching to less myelosuppressive protocols. Emesis can be controlled with combination of dexamethasone, anxiolytics and commonly available antiemetic for up to 4 days in the absence of expensive but effective antiemetic such as granisetron. Premedication for hypersensitivity reactions includes dexamethasone starting 1 day prior and the day after. Musculoskeletal pain can be alleviated with anti-inflammatory drugs. Broad spectrum beta-lactam antibiotics should be available to manage febrile neutropenia.

Table 1 depicts availability of drugs, and Table 2 summarises drugs to avoid and monitor or that are associated with certain medical conditions.

Table 1 Availability of common anticancer drugs in public facilities

	Common	Upon request	Special request	Rarely available
Solid cancers	Doxorubicin Cisplatin Folinic acid 5FU Steroids Dactinomycin Methotrexate Cyclophosphamide Vincristine Etoposide Tamoxifen LHRH/GnRH Flutamide	Paclitaxel Docetaxel Capecitabine Trastuzumab Bevacizumab Epirubicin Aromatase inhibitors Dacarbazine Fludarabine Stilbestrol Bicalutamide	Mitoxantrone Irinotecan Oxaliplatin Trastuzumab Lapatinib Temsirolimus Carboplatin Gemcitabine Vinorelbine Vinblastine Gemcitabine Ifosfamide Estramustine	Abiraterone Enzalutamide Epothilones Pertuzumab Sorafenib Cetuximab Panitumumab Temozolomide Cabazitaxel Erlotinib Liposomal doxorubicin Nab-paclitaxel S1
Haematological cancers	Melphalan Mercaptopurine L-asparaginase Hydroxyurea Daunorubicin Thioguanine Bleomycin Ara-C	Rituximab Interferon Carmustine Idarubicin ATRA Procarbazine	Imatinib Thalidomide Interleukin Gemtuzumab Bendamustine	Lenalidomide Bortezomib Pomalidomide Carfilzomib
Supportive medications	Metoclopramide Prochlorperazines Domperidone Amoxicillin/clavulanic acid Aminoglycosides Fluconazole Ketoconazole Nystatin Allopurinol	Zoledronic acid Erythropoietin Granisetron Ondansetron Lorazepam Itraconazole 3rd-generation cephalosporins	Ibandronate Vancomycin Amphotericin B 4th-generation cephalosporins	Palonosetron Aprepitant Denosumab

Table 2 Drugs associated with major organ toxicities which require caution or monitoring

Renal dysfunction	Liver dysfunction	Cardiac dysfunction	Neuropathy
Cisplatin	Ifosfamide	Herceptin	Paclitaxel
Topotecan	Cyclophosphamides	Anthracyclines	Docetaxel
Capecitabine	Temozolomide	Paclitaxel	Vinorelbine
Ifosfamide	5-Fluorouracil	5-Fluorouracil	Platins
Zoledronic acid	Gemcitabine	Capecitabine	Etoposide
	Methotrexate	Mitoxantrone	
	Anthracyclines	LHRH/GnRH	
		Aromatase inhibitors	

2 Non-Hodgkin's Lymphomas

2.1 Follicular (Indolent Subtypes)

2.1.1 Chemotherapy

For follicular indolent types which are asymptomatic but advanced stage (stages III and IV) cases, watchful waiting can be applied. For symptomatic advanced stage patients, options are (a) single alkylating agent therapy such as chlorambucil 0.8 mg/kg orally every 3 weeks, cyclophosphamide at 1200–1500 mg intravenously every 3 weeks, 300–500 mg intravenously weekly or 60–100 mg orally daily and (b) combination chemotherapy such as chlorambucil, cyclophosphamide, vincristine, prednisone (LOP, COP), or doxorubicin added to the COP regimen (CHOP), or just an alkylating agent with prednisone, combination of fludarabine, mitoxantrone and high-dose dexamethasone (FND).

2.1.2 Targeted Therapy

Anti-CD20 monoclonal antibody (rituximab) in combination chemotherapy in indolent types of B-cell lymphoma or bortezomib, lenalidomide and bendamustine are useful with better overall survival compared to chemotherapy alone but are quite expensive.

2.2 Aggressive Subtypes

2.2.1 Chemotherapy and Targeted Therapy

Options include:

1. Stage IA cases are preferably treated with limited chemotherapy, e.g. CHOP × 3 courses followed by involved-field irradiation.
2. Advanced disease should be treated with aggressive combination chemotherapy till complete remission, possibly with a view to giving consolidating irradiation to areas of initially bulky disease.

CHOP remains the standard of care for most cases. The others include MACOP-B or hyper-CVAD with high-dose methotrexate and high-dose cytosine arabinoside when feasible.

For the B-cell-derived aggressive phenotype NHLs, R-CHOP is also not readily available in resource-poor settings; hence, CHOP remains the preferred treatment.

Precursor B-cell and precursor T-cell lymphoblastic leukaemia/lymphoma, Burkitt' s lymphoma and some variants of diffuse large B-cell lymphoma and adult T-cell leukaemia/lymphoma (ATL) should be managed by physicians well versed with acute leukaemia therapy. The optimal treatment for peripheral, aggressive T-cell lymphomas excluding anaplastic large cell lymphoma is not clearly defined. CHOP is still the standard combination but with disappointing disease-free and overall survivals. Several other combinations have been tried with different results reported for various subcategories.

For CD30 expressing types, brentuximab in combination with combination chemotherapy appears promising.

B-cell subtypes associated with HIV/AIDS can be preferentially managed with concomitant rituximab, and chemotherapy is useful if affordable otherwise with chemotherapy alone.

3 Plasma Cell Myeloma

3.1 Treatment

1. Supportive measures
2. Specific antineoplastic agents

3.1.1 Supportive Measures

Supportive measures include correcting anaemia, pathological fractures (both established and impending), hypercalcemia, hyperuricemia, hyperviscosity, renal failure, dehydration and pain. The haemoglobin should be raised to 10 g/dl before starting specific anti-myeloma therapy, and likewise, any preexisting infection must be controlled. Bisphosphonates are recommended prophylactically in patients with significant myeloma bone disease.

3.1.2 Chemotherapy

Melphalan combined with prednisone is the most basic and effective treatment; however, new guidelines show additional benefit including thalidomide in the management of multiple myeloma as it is more efficacious compared to melphalan and prednisone alone. Because of their relatively low side effect profile especially to haematopoietic tissue, thalidomide and high-dose dexamethasone are recommended

to be used up front in treatment of multiple myeloma. Thalidomide may be unavailable in certain situations. Other treatments include cyclophosphamide orally for 14 days followed by 14-day rest after which the same is repeated or intravenously 1,000 mg/m^2 on day 1 plus prednisone 60 mg/m^2/day on days 1–4 and a combination of vincristine and doxorubicin at 9 mg/m^2/day, both by continuous infusion day 1–4 in combination with high intermediate doses of dexamethasone (VAD regimen). Oral idarubicin may be substituted for doxorubicin and appears to be equally effective and convenient.

3.1.3 Targeted Therapy

Where resources are available, targeted therapies include bortezomib in combination with doxorubicin and dexamethasone (VAD2); bortezomib and dexamethasone; bortezomib, melphalan, and prednisone (VMP); bortezomib, thalidomide and dexamethasone (VTD); or lenalidomide and dexamethasone. Lenalidomide is combined with liposomal doxorubicin.

More recent additions include carfilzomib, a novel proteasome inhibitor, and pomalidomide, a novel IMiD currently approved for third-line use.

3.1.4 Bone Marrow Transplant

This innovative method of treatment has been available for many years but is not accessible to many in LMIC except in academic institutions. Allogeneic haematopoietic progenitor cell transplantation is so far the only curative treatment for multiple myeloma, albeit in a very small minority. Autologous transplantation, especially of peripheral blood progenitor cells, is currently the standard of care for multiple myeloma. Melphalan should be avoided as much as possible in patients who are eligible for autologous transplant.

4 Hepatocellular Cancer

4.1 Chemotherapy

Most patients present with advanced tumours which can be treated with local ablative therapies including percutaneous chemoembolisation or ethanol embolisation, radiofrequency ablation or external beam irradiation. As a word of caution, HCC with attendant liver cirrhosis, especially Child-Pugh class C, has poor outcomes whatever the therapeutic intervention.

Various chemotherapeutic agents with modest influence on the course of the disease include doxorubicin, cisplatin, 5-fluorouracil and gemcitabine as single agents or in combination. The benefit versus the toxicity needs to be thoroughly discussed.

4.2 Targeted Therapy

Antiangiogenic agent bevacizumab has been used, with mixed and unimpressive results. Multikinase inhibitor, sorafenib, is the current standard of care, but again, its role is not universally accepted as it does not significantly improve disease-free or overall survival.

5 Breast Cancer

5.1 Hormone Therapy

Controversial reports of hormone receptor positivity rate in Africa are a limitation to the appropriate application of hormonal therapies in breast cancer management. Receptor testing is highly recommended where feasible as it gives important prognostic information. Receptor-positive patients invariably have high clinical response and survival rates with hormone therapies and poor clinical response to chemotherapies in general. Hormonal therapy is recommended as the first-line therapy for strong receptor-positive disease in the absence of severe symptomatic disease and is more acceptable to the patient. Even though hormonal therapy may be detrimental in hormone-negative subtypes, empirical use is unavoidable when patient does not respond to chemotherapy or cannot afford these medications. Aromatase inhibitors are considered more effective compared to tamoxifen in the postmenopausal setting however, without a survival advantage. Recent evidence points to increased efficacy when aromatase inhibitors are combined with ovarian suppression in the premenopausal state compared to tamoxifen with or without ovarian suppression. The high cost of aromatase inhibitors and the associated musculoskeletal side effects make it relatively unattractive leading to high rate of noncompliance. Tamoxifen is indicated in the pre- and postmenopausal woman and is readily available, relatively cheap and therefore highly recommended. Sequential treatment of aromatase inhibitors and tamoxifen may be another means of reducing overall cost without compromising effectiveness compared with tamoxifen alone in the postmenopausal woman.

5.2 Chemotherapy

The choice of chemotherapy depends of tumour biology, comorbidities, prior therapies and most importantly cost and convenience of administration. The cheapest and readily available regimens are the old regimens containing Adriamycin, 5FU, cyclophosphamide and methotrexate. They are still very effective in most breast cancer patients. Additional small but significant benefits are realised when Adriamycin in combination with taxanes is used for more aggressive-type tumours

such as node-positive, triple-negative and her2-positive. Neoadjuvant chemotherapy is used frequently due to high representation of locally advanced cancers and long theatre waiting list. To date, there is no overall survival advantage compared to adjuvant therapies, and notably due to cultural influences, patients do not return for mastectomy especially following complete clinical responses. However, neoadjuvant chemotherapy approach may spare patients the use of medications that may not have worked. CMF is less commonly prescribed as it is considered suboptimal for aggressive tumour types. Classical CMF may have less compliance rates due to the multiple clinic visits and poor adherence with oral medication. Newer drugs such as gemcitabine, vinorelbine, capecitabine and epothilones used in combination with other drugs or as single agents have improved response and survival rates for recurrent and metastatic disease but are expensive and not readily available. Problems associated with weekly schedule drugs are neutropenia, cost of granulocyte colony-stimulating factors and inconvenience in administration, and therefore best administered in specialised centres. Triple-negative subgroups may have additional benefit if taxanes and/or platinum are included in first-line or subsequent lines of therapy, but CMF is an option when patient fails initial anthracyclines. Patients with metastatic disease can be managed with single agent sequentially without compromising overall survival which is less toxic, thereby reducing treatment-related morbidity and invariably a cost-saving measure. Clinical exam, tumour markers or radiological test where available should be used to access treatment response every 2–3 cycles and change regimen if there is no significant response.

5.3 Targeted Therapy

Advanced techniques for receptor testing are neither readily available nor affordable in low-resource settings. Lack of stringent quality assurance in the few testing laboratories has questioned the relevance of testing in such situations. Nevertheless, if done properly, it guides appropriate care. Her2-targeted therapies are expensive and not covered by national insurance policies. The benefits of her2/neu-targeted therapies where indicated are profound (up to 50 % reduction in recurrence rates and 37 % improvement survival). It is quite unfortunate that 20 % of women with breast cancer who are her2/neu positive in these parts of the world will not realise these benefits. Affordable generic substitutes should be widely available to these populations as a humanitarian gesture. The recommended 1-year duration of treatment is another limiting factor driving most oncologists to prescribe shorter regimes of 9 weeks to 6 months whose benefits even though inferior to longer treatment durations were better compared to those who did not receive her2-targeted therapy at all. Needless to say, second-line and dual targeting is completely beyond the scope of practice in most public institutions. Other therapies are being developed for triple-negative breast cancer but all at prohibitive cost. Tables 3, 4 and 5 summarise some common chemotherapy and hormonal and targeted therapies indicated for breast cancer management.

Table 3 Early breast cancer

Common neoadjuvant/adjuvant therapies	Advanced adjuvant/neoadjuvant regimens
CAF or *CEF*: cyclophosphamide, doxorubicin, epirubicin,5FU *AC*: doxorubicin, cyclophosphamide *CMF*: cyclophosphamide, methotrexate, 5FU *E* or *A* → *CMF*: epirubicin or Adriamycin × 4 followed by CMFX6	*AC* → *paclitaxel or docetaxel*: doxorubicin, cyclophosphamide followed by paclitaxel or docetaxel *TC*: docetaxel, cyclophosphamide *Dose-dense AC* → *T*: Q2w doxorubicin, Cyclophosphamide followed by paclitaxel, may require filgrastim support *FEC* → : 5FU, epirubicin, cyclophosphamide followed by docetaxel *TAC* Q3w: docetaxel, doxorubicin, cyclophosphamide, may require filgrastim support

Table 4 Her2/neu positive *therapies*

First line	Recurrent or persistent disease
AC → *TH*: doxorubicin, cyclophosphamide followed by paclitaxel and trastuzumab	Trastuzumab with paclitaxel or docetaxel or capecitabine or lapatinib
Dose-dense AC → *TH* : doxorubicin, cyclophosphamide followed by paclitaxel with trastuzumab	Pertuzumab + herceptin + docetaxel
Chemotherapy → *H*: trastuzumab after completion of chemotherapy q3 weekly × 1 year	Lapatinib + capecitabine
DH → *FEC*: docetaxel with trastuzumab followed by 5FU, epirubicin, cyclophosphamide	Lapatinib

Table 5 Hormonal therapies

	Available	Advanced
Premenopausal	Tamoxifen	Exemestane + ovarian suppression (surgery, pelvic radiation or chemical castration)
Postmenopausal	Tamoxifen	Aromatase inhibitors

6 Carcinoma of the Cervix

6.1 Chemotherapy

Neoadjuvant and adjuvant therapies have not shown reproducible benefit in the management of cervical cancer. However, concurrent chemoradiation with cisplatin with or without 5FU has significantly improved local control and survival rates. The benefit is more pronounced in the less advanced stages. Patients in low-resource settings are more likely to present with locally advanced disease involving the pelvic side walls (stages 3 and 4), renal compromise and chronic anaemia; therefore, the morbidity and additional cost of chemotherapy need to be weighed against the expected benefit. Weekly schedules of cisplatin for 5–6 weeks are less toxic and more tolerable but may be more expensive and increase the workload of limited staff. Three-weekly schedules

(2 cycles) may be cheaper and easier to administer but are less tolerable and result in alopecia. Radiation alone in cervical cancer (delivered within 8 weeks) as practised in Japan has shown comparable results to concurrent chemoradiation protocols. Unfortunately, many patients in LMIC do not have access to radiation therapy and are managed with surgery with or without neo- or adjuvant chemotherapy.

Recurrent and metastatic cervical cancer benefits from palliative systemic therapies. Cisplatin is used in combination with other agents or alone. Addition of taxanes or topotecan results in higher response rates and a modest survival benefit but is associated with higher cost and morbidity. Other active drugs include 5FU, carboplatin, hydroxyurea, anthracyclines and, in more advanced settings, ifosfamide, irinotecan, vinorelbine and gemcitabine.

6.2 Targeted Therapy

The role of vascular endothelial growth factor-targeted therapy (bevacizumab) in combination with chemotherapy is now defined in the management of persistent, recurrent or metastatic cervical cancer resulting in improvements of 3.7 months in median overall survival compared with chemotherapy alone. These therapies are currently unaffordable to most and require clinical expertise in monitoring and managing life-threatening toxicity that may arise.

7 Prostate Cancer

7.1 Chemotherapy

Patients with metastatic prostate cancer are living longer compared to a few decades ago, and this can be attributed to new and effective anticancer agents.

Hormone-refractory prostate cancer patients benefited minimally from estramustine, mitoxantrone and prednisolone (few weeks). Subsequently, docetaxel and prednisolone chemotherapy resulted in modest improvements in survival and PSA control but is associated with neutropenia and gastrointestinal toxicity which may be of concern in older-aged men. New nonhormonal agents such as abiraterone and enzalutamide included in international guidelines are beyond the financial means of patients and are not routinely stocked. Clinicians are more likely to try older medications like stilbestrol at lower doses of 1 to 2.5 mg daily, ketoconazole, cyproterone acetate, oral cyclophosphamide and prednisolone. These agents control disease on average for 3 months, and sequential administration leads to some minimal but reasonable extension of life and control of disease and defers the need for more expensive drugs including docetaxel. Since the spectrum of effective drugs for managing such patients is limited, abbreviated cycles of docetaxel, i.e. 4 instead 6–8 are given to achieve PSA and symptom control and reintroduced when there is progression.

7.2 Hormonal Therapy

Hormone suppression in any form leads to improvement in biochemical control and survival for locally advanced and metastatic prostate cancer and is therefore highly recommended. Short-term concomitant androgen suppression therapy and radical radiotherapy significantly improve biochemical control compared to radiotherapy alone for patients with intermediate-risk prostate cancer. Patients should be screened for predisposing factors which may worsen toxicity, and the prescribing physicians should be conversant with the severe morbidities associated with these medications to prevent unnecessary and premature deaths. It is not recommended for low- to-risk groups due to toxicities. Orchiectomy is the simplest and most cost-effective means of achieving hormone suppression; however, male clinicians and patients both old and young prefer chemical castration in spite of the exorbitant cost and unfavourable toxicity profile. Stilbestrol, a synthetic non-steroidal estrogen, even though banned in some countries because of associated increase in cardiac-related deaths, is the cheapest, readily available and highly patronised form of hormone suppression.

As the benefits of complete androgen suppression versus monotherapy are not that significant, as a cost-saving measure, monotherapy with either antioestrogen or LHRH/GnRH is frequently prescribed for hormone-sensitive disease, with the latter preferred. Non-castrate patients with local disease and biochemical failure can be managed with intermittent versus continuous androgen suppression without compromising overall survival while reducing cost and morbidity. However, intermittent androgen deprivation is inferior to continuous therapy in terms of survival in the metastatic setting but still an option where cost or toxicity is an issue. Patients should have baseline and periodic cardiac evaluation and placed on calcium supplements.

7.3 Targeted Therapy

Sipuleucel-T targets dendritic cells developed from individual patients and indicated in metastatic patients with minimal symptoms and low burden of disease. It is resource intensive and not available in LMIC.

Table 6 summarises available therapies for the management of hormone-refractory prostate cancer.

Table 6 Systemic therapies for hormone-refractory prostate cancer

	Chemotherapy	Antiandrogens	Antioestrogens	Nonhormonal
Commonly available	Oral cyclophosphamide Estramustine Mitoxantrone Oral etoposide 5FU	Flutamide Prednisone	Stilbestrol Tamoxifen	Cyproterone acetate Ketoconazole
Advanced settings	Taxanes	Bicalutamide enzalutamide		Abiraterone

8 Ovarian Cancer

8.1 Chemotherapy

Cisplatin and carboplatin have equal efficacy and are important components of therapy. Single-agent platinum has better response rates compared to observation for early and advanced stage disease and is recommended in limited-resource settings. However, the addition of taxanes to platins improves survival with a hazard ratio of 1.28 versus 1.16 for single-agent platinum and has an 11 % overall survival advantage over the addition of cyclophosphamide. Taxanes are not readily available and are relatively expensive in LMIC. A literature review shows no differences in the response and survival results of cyclophosphamide and Adriamycin and cisplatin compared to cisplatin and paclitaxel except the latter has a more favourable toxicity profile. Most patients have large residual disease after surgery and therefore do not derive maximum benefit from chemotherapy. Neoadjuvant chemotherapy improves down staging and the chances of achieving optimal tumour clearance at surgery without compromising local control and survival outcomes in locally advanced disease compared to adjuvant therapies. The choice of salvage therapies is guided by availability, improvement in quality of life and financial implications to family. Table 7 depicts various anticancer agents recommended for ovarian cancer treatments.

8.2 Hormonal Therapy

Tamoxifen and aromatase inhibitors are indicated for maintenance or salvage therapy when chemotherapy fails. Response rates however are low.

8.3 Targeted Therapy

The cost, availability and toxicities of targeted therapies in LMIC limit its use. Bevacizumab with chemotherapy improves disease-free survival by 6 months and significantly improves median survival by greater than 1 year versus chemotherapy alone in platinum-resistant ovarian cancer. Olaparib, a recently approved targeted drug, improves disease-free survival by 7 months but does not improve overall survival for BRCA 1 and 2 with locally advanced disease and is currently either unavailable or unaffordable in our settings.

Table 7 Systemic therapies for ovarian cancer

A. Epithelial ovarian tumours				
	Adjuvant therapy	**Recurrent or metastatic**	**Hormonal**	**Target**
Commonly available	Cisplatin + cyclophosphamide Cisplatin + Adriamycin + cyclophosphamide	Oral etoposide 5FU + LV Capecitabine Oxaliplatin Melphalan	Tamoxifen	–
Advanced settings	Carboplatin + paclitaxel Cisplatin + paclitaxel	Carboplatin + gemcitabine Liposomal doxorubicin Vinorelbine Topotecan Ifosfamide Paclitaxel Docetaxel Gemcitabine	Aromatase inhibitors	Bevacizumab Olaparib
B. Germ cell and sex cord stromal tumours				
	Adjuvant	**Recurrent or metastatic**	**Hormones**	
Commonly available	Etoposide + cisplatin	Vincristine + dactinomycin + cyclophosphamide	Tamoxifen	
Advanced settings	Bleomycin + etoposide + cisplatin	Taxanes Ifosfamide	Aromatase inhibitors	

9 Colorectal Cancer

9.1 Chemotherapy

Local control and survival of colorectal cancer patients have improved with a doubling of survival benefit every decade even for metastatic colorectal cancer. Unfortunately, patients in less developed parts of the world do not have access to newer drugs including targeted therapies and local radiotherapy for rectal cancers. Neoadjuvant 5FU-based chemoradiation has become the standard of care for localised rectal cancer followed by surgery with good local control without a survival advantage. This treatment is practised in some teaching institutions, but surgery remains the most common initial therapy as surgeons are the first point of call and may not be adequately educated in recent advances or most commonly because access to radiotherapy is limited. Surgical expertise is directly correlated with outcomes, and delays in initiating adjuvant therapy (> 4 weeks delay results in 15 % reduction survival chances) could be compounding factors why we have poor local control and survival rates. High-risk stage 2 colon cancer which includes resection of less than 10–12 lymph nodes may derive a small but significant benefit from adjuvant chemotherapy with 5FU/LV or capecitabine. Very few patients undergo adequate lymphadenectomy which leads to unnecessary burden on the patient and the overstretched health resources. Omission of surgery for complete responders to chemoradiation is a recent option which may suit our circumstances as most patients default surgery from fear of being ostracised as well as the cost and inconvenience of using colostomy bags. 5FU or other oral 5FU analogues, e.g. capecitabine, are the drugs used in the chemoradiation protocols with the latter being the favourite as it negates the need for expensive infusion pumps and hospital admissions for protocols requiring continuous infusion. Bolus infusion of 5FU/leucovorin is substituted for capecitabine if unaffordable or unavailable. Oxaliplatin combinations with 5FU/leucovorin are the preferred choice in the adjuvant setting except that benefit is not realised in patients more than 70 years old and high-risk stage 2 disease. Irinotecan is inferior to oxaliplatin in the adjuvant setting but may be used when oxaliplatin is unavailable. The treating physician must be aware of irinotecan-induced severe life-threatening diarrhoea and febrile neutropenia. Genetic testing for susceptibility to gastroenteritis is not available and atropine premedication is recommended. Recurrent and metastatic diseases are difficult to manage as the barrage of active drugs is unavailable. For this reason, most patients are surgically managed. Recurrence can be diagnosed early with serial tumour marker measurements. Oxaliplatin failures are managed with irinotecan combinations and vice versa where available. Continuous infusion of 5FU and high-dose leucovorin is expensive and is frequently substituted with oral 5FU or daily 5-day bolus 5FU and low-dose leucovorin. There is no significant difference in response rates for high- versus low-dose leucovorin. Single-agent 5FU is a reasonable option if LV is unavailable, but dose increments are recommended if well tolerated. A 6-month median survival benefit is achieved when 5FU/LV is compared with observation only. A 12–18-month median survival is achievable when patients receive all active chemotherapy

drugs sequentially, and a 24-month median survival is achievable when all drugs are combined concurrently. A median survival of greater than 24 months is achievable with the addition of targeted therapies. Nonetheless, multi-agent concurrent chemotherapy is associated with severe toxicities and therefore advisable only for patients with good performance status under the supervision of clinicians experienced in these protocols. Many of our patients are either old, have several comorbidities and do not have access to these drugs or supporting medical systems precluding the use of aggressive protocols. Sequential monotherapy is much more tolerable and affordable and associated with improvements in quality of life. Management strategies such as maintenance chemotherapy and rechallenge with previously effective chemotherapies should be tailored to individual patients and available resources; many patients with metastases end up with unnecessary invasive procedures as the only available option. The expertise for liver resections and intra-arterial chemotherapy administration is sparse; therefore, conventional chemotherapy alone remains the only option for good prognosis to patients leading to suboptimal survival rates (5–10 months OS) compared to those who undergo liver resections (5 years 40 % overall survival).

9.2 Targeted Therapy

Targeted drugs in combination with chemotherapy have resulted in longer survival rates for patients with metastatic colorectal cancer. However, they are not without severe life-threatening toxicities. The cost and mandatory requirement for EGFR, RAS mutations and other biomarker testing limits its applications in LMIC. There is some data showing high rate of RAS mutations and BRAF in West African countries, for example. Bevacizumab on the other hand does not require molecular profiling and therefore the most commonly used targeted agent. New drugs such as aflibercept and regorafenib increase median survival by less than 2 months and therefore not recommended in countries with very low GDP on account of the cost and unavailability. Where these drugs are available, patients must explicitly understand the goals and duration of treatment as well as the severity of toxicities that may occur.

10 Managing Common Side Effects and Oncological Emergencies

10.1 Neutropeina

In resource sparing settings, granulocyte colony-stimulating factor (GCSF) is unaffordable; therefore, many patients with low white cell count require a dose reduction or delay of chemotherapy when neutrophil count is below 1.0.

10.1.1 Afebrile Neutropenia

Afebrile neutropenic patients are managed on the outpatient bases and are discouraged from taking antipyretics. They are to report immediately to the hospital when they have a fever or feel unwell. Precautions such as strictly eating only cooked meals and avoiding pets and fresh flowers are currently disputed. Prophylactic antibiotic use promotes resistant strains and limits the spectrum of antibiotics available for management. If neutropenia persists to the day of next cycle of chemotherapy, a 25 % dose reduction of the chemotherapeutic drug is given when neutrophil count corrects.

10.1.2 Febrile Neutropenia

Febrile neutropenic patients (>38 °C) are admitted to isolation wards and examined to determine the source of infection. Laboratory test including blood, urine, sputum or wound cultures is taken. Antibiotic therapy is not delayed in lieu of blood cultures or laboratory test being unavailable. As soon as possible, IV ceftriaxone and gentamicin as broad-spectrum antibiotics are administered as they are cheaper options. However, for very ill patients or those nonresponsive to this combination, carbapenem with or without aminoglycoside (depending on renal function) is administered. In the presence of diarrhoea, metronidazole is added. Patients considered stable are managed on outpatient basis with levofloxacin or ciprofloxacin with amoxicillin/clavulanic acid as IV stat doses followed by oral administration for week. Patients presenting with oral thrush are treated with antifungals in combination with antibiotics. Fluconazole is effective for oral thrush. Antibiotics and antifungals are reviewed every 48 hr and adjusted based on culture and sensitivity reports and continued even in the absence of any isolated organism. Consider treating for MSRA after 96 hr of continuous fever. Fever in a patient receiving chemotherapy with low neutrophil count should be managed as febrile neutropenia concomitantly with any other endemic disease entity such as malaria. Vital signs are monitored 4 hr and the use of antipyretics is discouraged to avoid masking of the temperature. Discharge if temperature settles for at least 24 hr.

10.2 Hypercalcemia

Hypercalcaemic patients are immediately hydrated with IV normal saline with the first litre running over 30 min to 1 hr. Once hypovolaemia is corrected, give loop diuretics usually 40 mg furosemide 12–24 hr and dexamethasone 10–20 mg

IV stat followed by oral 8 mg twice a day and then tapered down for 5–7 days to help drop the serum calcium. Bisphosphonates (zoledronic acid 4 mg or pamidronate) are very effective and are administered where available but are expensive. Gallium nitrate, mithramycin and calcitonin are other options but may not be available.

10.3 Extravasation of Chemotherapy

Occasionally, unintended leakage of the chemotherapy drug into the extravascular space occurs during chemotherapy administration.

Chemotherapeutic agents such as the vinca alkaloids, mitomycin C and anthracyclines induce tissue necrosis resulting in disfigurement and functional impairment. Others such as the platinum compounds, taxanes and topoisomerase I inhibitors cause an inflammatory reaction and not tissue necrosis.

Patients with extravasation may present with induration at the site of the extravasation, pain, discolouration and later ulceration at that site. Once suspected, the infusion is discontinued immediately, and the affected limb elevated. The IV cannula device is not removed, but used to attempt to aspirate fluid from the extravasation area.

With the exception of epipodophyllotoxins and vinca alkaloids which require warm packs, ice packs are applied to the affected area as this causes vasoconstriction and reduces the extent of local injury. Topical corticosteroid creams are applied. In the advanced settings, dexrazoxane is administered IV as a 1- to 2-hr infusion through a separate venous is for the treatment of extravasation resulting from anthracycline therapy.

10.4 Mucositis

Oral candidiasis is managed with oral fluconazole 150 mg daily for a week with excellent results. The recommended drug itraconazole is not readily available and not affordable to the majority of our patients. In addition to the fluconazole, a mixture of Maalox, Phenergan and plain 1 % Xylocaine gel as a swish and swallow solution as well as adequate pain medication should be prescribed. Diarrhoea is managed by oral rehydration, antidiarrheal, metronidazole or cephalosporins (Table 8).

Table 8 Management guidelines for some common chemotherapy toxicities

Side effects	Mild to moderate	Moderate	Severe
Neutropenia (neutrophil <1)	Hold till recovery, 25 % dose reduction next cycle	As in grade 2, GCSF or change meds	Stop drugs or GCSF
Febrile neutropenia Fever >38 °C		Intravenous cephalosporin ± aminoglycoside (renal function) ± antifungal + metronidazole for diarrhoea	As grade 3, needs intensive care support and consider vancomycin, GCSF if available
Thrombocytopenia	–	Hold till recovery with 25 % dose reduction for next cycle	Hold till recovery and change drug or stop
Anaemia	Increase HB by oral haematinics and hold drug if HB <8 g/dl	Hold drug, transfuse with blood 25 % dose reduction on next cycle	Hold, transfuse and consider changing drug
Diarrhoea	Hold drug till grade 1 and reintroduce at same dose	Hold drug till grade one, correct electrolyte and rehydrate, 25 % dose reduction on next dose	Discontinue or use atropine and Imodium to control symptoms
Oral mucositis	Hold drug till alleviated Pain medication, anaesthetic oral rinses and antifungal for 2 weeks	Hold drug, fluid replacement, pain medication, antifungal and antibiotic rinses, 25 % dose next cycle	Admit to intensive care Antifungal and antibiotics Discontinue or switch drug
Hypersensitivity	Hold, antihistamine, IV or topical steroids, reintroduce at slower rate	Stop medication, antihistamine and steroids Recommend premedication with steroids and antihistamine, 25 % reduction for next cycle	Admit and manage as appropriate, discontinue or switch drug
Peripheral neuropathy	Hold till grade 1, 25 % reduction in dose for next cycle	Hold till grade 1, then 15 % reduction next cycle or change drug	Discontinue
Renal impairment	Rehydrate and improve urine output with IVF and diuretics, 25 % reduction next cycle	Rehydrate and improve urine output and change drug Refer to nephrologist	Discontinue drug Dialysis may be required
Liver impairment	Continue with 25 % dose reduction except for preexisting conditions where hepatotoxic drugs are avoided	Discontinue all hepatotoxic drugs Capecitabine does not require dose adjustments	Discontinue and refer to prevent liver failure
Tinnitus	Baseline hearing test and 25 % dose reduction	Discontinue	Discontinue

Table 8 (continued)

Side effects	Mild to moderate	Moderate	Severe
Cardiotoxicity	Echocardiograph baseline, repeat after each cycle; if there is a decline in ejection fraction, hold the drug	Discontinue cardiotoxic drugs if ejection fraction is <52 % and refer for physician support	Discontinue
Hand and foot syndrome	Hold drug till grade 1 and reintroduce at same dose. vitamin B6 supplements and moisturise	Hold till grade 1 Pain medications and moisturise Antibiotics where indicated, 25 % dose reduction next cycle	Manage symptoms to prevent cellulitis and discontinue drug

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Cancer and HIV Treatments

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1 Introduction

Since 1996 and the introduction of the highly active antiretroviral therapy (HAART), we observe an increasing life expectancy in persons living with HIV (PLHIV) worldwide [1] with a changing in death profile causes.

Indeed, both AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma and, since 1993, cervical cancer) and non-AIDS-defining cancers (NADC) such as anal cancer, Hodgkin disease, skin cancers, and lung cancer represent an increased cause of death among PLHIV, in both high-income and low-middle income countries [2–6].

In comparison with persons nonliving with HIV (PNLHIV), PLHIV have an increased risk of cancer [7]. The explanation is not clear, and many causes are suspected such as the usual main risk factors (alcohol, tobacco) and coinfections.

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So, it could be more relevant to distinguish cancers in PLHIV into virus-induced cancers (HPV, HBV, HCV, EBV, HHV8) and nonvirus-induced cancers [8].

Concerning the HIV infection, the World Health Organization (WHO) recommends the use of HAART. However, some disparities exist between countries, because of treatment access and local recommendations. The WHO recommends to start HAART when CD4 lymphocytes count is under 500/mm^3 [9], although, as an example, French learned societies recommend to start the HAART as soon as the patient is diagnosed [10].

No specific references exist for the cancer treatments in PLHIV, while this is a fragile population with morbidities requiring more attention.

In this chapter, we will develop malignancies and HIV treatments references in high-income countries (the United States, Europe, Australia) and then on how to apply them in low-middle income countries (LMICs), to help physicians to improve patient care.

2 HIV and Cancer Treatments in High-Income Countries

2.1 Epidemiology

Nowadays, cancer is a leading cause of death in PLHIV, counting for 33 % of all death causes in France in 2010. Although NADC proportion has increased from 11 to 22 % between 2000 and 2010 [11], non-Hodgkin lymphoma (NHL) is still the most frequent cancer encountered among these patients [12].

Cancers in PLHIV are frequently associated with a late diagnosis, a more aggressive pathology, and morbidities such as immunosuppression, leading to poorer outcomes.

2.2 When to Start HIV Treatment?

The aim of an antiretroviral treatment is to prevent death and AIDS stage, with a CD4 lymphocyte count higher than 500/mm^3 and an undetectable viral load (<50 copies/ml).

Several studies have shown an improvement in survival and a decreased AIDS status when HAART is started with CD4 lymphocytes count between 350 and 500/mm^3 instead of CD4 counts lower than 350/mm^3 [13, 14].

Moreover, the benefit to start a treatment of patients with CD4 lymphocyte higher than 500/mm^3 was demonstrated in some cohort [14].

Indeed, these studies have shown a decreased morbidity in HIV patients coinfected with the hepatitis B virus (HBV) or the hepatitis C virus (HCV), cardiovascular diseases, or cancer [15].

Moreover, HAART reduces the risk of HIV transmission about 92 % [16].

Therefore, French learning societies recommend to start HAART among all PLHIV regardless of CD4 lymphocyte count [10].

However, according to international recommendations, HAART should be introduced as soon as CD4 lymphocytes count are less than 500/mm^3. Hence, introducing precociously, a HAART should be discussed first because of potential adverse effects, then impact in quality of life, and finally treatment costs.

In 2013, HAART is composed by 2 nucleoside reverse-transcriptase inhibitors (NRTIs) with a third added agent, which is a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) [9].

The choice of these agents depends on the virus mutational profile and patient comorbidities.

2.3 Cancer Treatments in PLHIV

More than classic cancer risk factors, the increase in cancer rate in PLHIV depends on the immunosuppression status, HIV replication [17], the oncogene virus exposure (HPV, HBV, HCV, EBV, HHV8), and the prevalence of other risk factors, such as tobacco use, environmental exposures, and aging [18].

Therefore, prevention is essential to fight against general cancer risk factors and control HIV infection.

We should always remember that cancer can reveal an HIV infection. Testing HIV in cancer-diagnosed population could be an opportunity to improve patient care. Indeed, these patients could benefit of a coordinated and combined HIV and cancer care [19].

So, Morlat report in France recommends systematically an HIV test among people with a new diagnosed cancer since 2013 [15].

The management of cancers in the PLVIH is unclear, and guidelines are lacking. PLHIV are usually excluded from clinical trials, and the treatment is generally the same that in PNLHIV.

In fact, several studies found that PLHIV are less likely to receive specific cancer treatment that the PNLHIV, which could affect the survival rate [20].

Patient cancer care program is composed by several points:

First, it is recommended to start the HAART, for all the different cancer types and regardless of CD4 rate. The aim is to control the HIV infection and restore the immune system. This is an important way to increase outcomes [21], and this can be enough to completely heal some cancers, as it is observed in low stages Kaposi sarcoma [22]. Physicians have to be aware about the immune reconstitution inflammatory syndrome. This phenomenon corresponds to a clinical deterioration despite the immunity recovery with an increasing CD4 lymphocyte count and a decreasing HIV viral load. This is a frequent issue with an incidence from 7 to 31 % in Kaposi's sarcoma [23].

Then, drug interactions between antiretroviral therapy (ARV) and chemotherapy must be estimated and discussed by a multidisciplinary team composed of

oncologists and infection disease specialists [24] to prevent toxicities and maintain an optimum efficiency in therapeutics. This is a key point for patient management.

Indeed, the pharmacokinetics of both ARV and chemotherapy are using the same cytochromes [4], leading to possible drug interaction risk with a more important toxicity or inefficacy for the HIV and cancer treatments in PLHIV (Table 1).

In addition, these drug interactions also concern supportive care treatment and the use of analgesics, antiemetics, and corticoids that are possibly needed in cancer treatments.

Third, opportunist infections, such as pneumocystosis and toxoplasmosis, and their preventive treatments should be considered.

Finally, treatment compliance and follow-up should be adapted to each patient, so multidisciplinary staff such as CANCER VIH group in France, consultation, and supportive care are essential [24].

3 HIV and Cancer Treatments in Low- and Middle-Income Countries

3.1 Epidemiology

Based on the WHO data, 24.7 million people live with HIV in sub-Saharan Africa (SSA) in 2013. 70 % of new HIV infection in the world is in SSA.

In 2013, more than 12.9 million people with HIV are treated by a HAART worldwide of which 11.7 million in LMICs.

We can obviously consider HIV like a worldwide public health problem. So by referring causes of death in PLHIV in high-income countries, cancer in LMICs must be considered as a priority in HIV patients care.

3.2 HIV and Cancer

Many data concern epidemiology of HIV-associated cancers from high-income countries. Our knowledge of the epidemiology of HIV-associated cancers in LMICs is limited. The reasons include weaknesses in healthcare infrastructure for diagnosing malignancies and limited epidemiological expertise in these countries. Moreover, many cancers are probably undiagnosed or untreated, so comprehensive information from cancer registries cannot be obtained [6].

Thus, we rely on high-income countries epidemiological profile and evolution in HIV-associated malignancies to assume evolution in low-middle income countries.

By significantly increasing the access of PLHIV in low- and middle-income countries to HAART [25], life expectancy and incidence of selected malignancies in an older population have increased [26, 27], and mortality due to infectious complications of HIV has decreased.

Table 1 Major cancer and HIV drug interactions

Molecule	Indication	ARV	Cytochrome	Effect	Action
All		PI	3A4/5		Specialist advise
Cyclophosphamide	Breast	NNRTIs	2B6, 2C9, 3A4	Increase toxicity and efficacy	Monitoring
Docetaxel	Breast, prostate	NNRTIs	3A4	Increasing toxicity	To avoid – change taxane
Erlotinib/gefitinib	Lung	NNRTIs	3A4	Toxicity	Avoid/monitoring
Etoposide	Lung, neuroendocrine	NNRTIs	3A4, UGT1A1	Toxicity	Monitoring
Everolimus	Renal, breast	NNRTIs	3A4	Toxicity	Avoid
Ifosfamide	Sarcoma	NNRTIs	3A4, 2B6	Decreasing efficacy	–
Imatinib	LMC, GIST	NNRTIs	3A4, 1A2, 2D6, 2C9, and 2C19	Toxicity	Monitoring
Irinotecan	Colorectal	NNRTIs	3A4	Toxicity	Monitoring
Lapatinib	Breast	NNRTIs	3A4	Toxicity	Monitoring
Methotrexate	Leukemia	NNRTIs NRTIs			Contraindicated/ monitoring
Paclitaxel	Breast, ovarian, lung, cervical, Kaposi sarcoma	NNRTIs	2C8, 3A4	Toxicity	Monitoring
Tamoxifen	Breast	NNRTIs	2D6, 3A4	Decreasing efficacy	Monitoring
Vinblastine	Lymphoma	NNRTIs	3A4	Toxicity	Monitoring
Capecitabine/5Fluorouracil	Breast, colorectal	NRTIs		Toxicity	Monitoring
Platine	Lymphoma, lung, cervical, ovarian	NRTIs		Neurotoxicity	Monitoring

PI protease inhibitors, *NNRTIs* non-nucleoside reverse-transcriptase inhibitors, *NRTIs* nucleoside reverse-transcriptase inhibitors

3.3 Treatment in HIV-Associated Cancer

Treatment of PLHIV must be optimal in controlling HIV with a low viral replication and a higher number of CD4 cells, such as recommended in the WHO guidelines [9].

Cancer treatment will depend on tumor type and international recommendation guidelines such as described in the previous chapters.

Problems of drug interactions are the same as in high-income countries, and a special care is needed. The challenge will be in accessibility in specific treatments and their costs.

Because of a higher incidence of associated infections, it is important to test and treat them, particularly for HBV and tuberculosis, and to prevent the strongyloïdes hyperinfection with ivermectin under corticosteroid therapy, commonly used in cancer treatments.

Hence, developing prevention, early diagnoses, and cancer infrastructure might be a key to develop a better patient care. Unfortunately, cancer infrastructures are underdeveloped particularly in SSA [28]. Adebamowo et al. study suggests that the infrastructure for cancer should comprise four elements: physical infrastructure, qualified staff, supportive policies, and supportive laws [6]. Established HIV care infrastructure in SSA would be a base to support the training of cancer care professionals, but efforts are needed to increase the human capacity for patients care with HIV-associated malignancies. Partnerships between international and US institutions have already begun and must be continued to address this need [29].

4 Conclusion

Because of the high incidence of HIV and the improvement of HAART access in tropical countries, both HIV-related and non-HIV-related malignancies will become a major public issue in these countries. Specific features are important to deal with, such as the eventual coinfections often associated (HBV, HCV, tuberculosis).

Specific cancer infrastructures are insufficient, and an integrative approach is necessary to improve both HIV and cancer-specific patient care. So, this care strategy needs partnerships between high- and low-middle income countries to improve the infrastructure and to help physicians. Interactions between cancer and HIV treatments must be estimate to ensure the efficacy and the minimal toxicity of each treatment.

A multidisciplinary approach could allow competencies mutualization and the development of a personalized patient care.

Cancer prevention and screening in PLHIV should not be forgotten. Indeed, it is a good option to decrease cancer incidence and improve outcomes with an acceptable cost.

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Supportive Care

Matti Aapro

1 Introduction

In order to improve cancer treatment tolerance and thus the quality of life of the cancer patient, one needs supportive care measures. This chapter highlights some of the key supportive care topics, such as prevention of nausea and vomiting, febrile neutropenia, bone health, and anemia. Another chapter in this book deals with palliative care. It is important to understand that these two areas form a continuum and that there is evidence that early supportive/palliative care can have an impact on patient survival and on the treatment of the older cancer patients [1, 2]. Furthermore this chapter includes for each topic recommendations for countries with limited resources, as developed by a group of the Breast Health Global Initiative (BHGI) [3]. This group has divided resource allocation into four groups: basic level, limited level, enhanced level, and maximal level, with basic level representing countries with minimal healthcare budgets, while enhanced and maximal levels representing areas or countries with little restrictions.

2 Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) can lead to dehydration and low blood pressure and affect renal function and induce a dramatic drop in quality of life which can lead to treatment refusal. Depending on the emetogenic potential of chemotherapy, specific considerations are needed (see Table 1). Evidence-based

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Table 1 MASCC/ESMO Antiemetic Guideline. Summary of acute and delayed prevention

Emetic risk group	Risk (% pts.)	Acute prevention	Delayed prevention
High	>90 %	5-HT_3 RA	DEX + aprepitant
		+ DEX + (fos)aprepitant	
AC combinations	–	5-HT_3 RA[a]	Aprepitant
		+ DEX + (fos)aprepitant	
Moderate	30–90 %	Palonosetron + DEX	DEX
Low	10–30 %	Single agent (DEX, 5-HT_3 DRA)	No routine prophylaxis
Minimal	<10 %	No routine prophylaxis	No routine prophylaxis

Updated from Ref. [4]
Recommended 5-HT3 RAs: palonosetron, granisetron, ondansetron, dolasetron oral, tropisetron, *DEX* dexamethasone, *AC* anthracycline-cyclophosphamide, *DRA* dopamine receptor antagonist. Aprepitant in delayed phase depends on (fos)apretitant use in acute phase
[a]If an NK-1 RA is not available then palonosetron is the preferred 5-HT3 RA also in AC regimens

guidelines recommend that patients who receive anthracycline-cyclophosphamide or any highly emetogenic agents (cisplatin, DTIC) should receive a 5-HT3 receptor antagonist, dexamethasone (or another corticosteroid at adapted doses, i.e., a multiplying factor of 6 is suggested if prednisone is available), and a neurokinin 1 (NK1) receptor antagonist. While these guidelines indicate preferential use of palonosetron, this agent is very expensive. Several 5-HT3 receptor antagonists (but not palonosetron) carry warnings about potential prolongation of the QTc electrocardiographic interval which can lead to severe arrhythmias. Guidelines may change as there is growing evidence that the use of corticosteroids may be decreased on the days after the chemotherapy (delayed phase) without loss of antiemetic efficacy, at least when the longer-acting 5-HT3 receptor antagonist palonosetron is used. This is particularly relevant for patients who have diabetes which can become more difficult to control when corticosteroids are used. The potential interactions of the antiemetic aprepitant, a neurokinin-1 receptor antagonist, which is a moderate inhibitor of cytochrome P-450 isoenzyme 3A4 (CYP3A4), lead to an increase of the area under the curve of dexamethasone (which therefore should be used at lower doses) and can influence warfarin-like anticoagulants. However, no clinically relevant interaction exists with most chemotherapeutic agents, and it seems that the concern of negative interactions remains largely theoretical [4, 5].

The above recommendations can often not be applied. As indicated by the BHGI group [3], at *basic levels* of resource allocation, hydration therapy should be available (oral and IV hydration and electrolyte replacement). Available antiemetics should include corticosteroids, prokinetic, nonselective serotonin antagonists, and dopamine receptor antagonists. At *limited levels*, antiemetics should include selective serotonin (5-HT3) antagonists. H2 antagonists could be considered to counteract steroid side effects. At *enhanced levels,* newer effective antiemetics, such as NK-1 antagonists, may be used with highly emetogenic chemotherapy. Proton pump inhibitors (PPIs) may be considered to counteract steroid side effects.

3 Febrile Neutropenia

Prevention of febrile neutropenia is essential as this complication can lead to death, especially in patients with comorbidities. Furthermore, in curative settings, maintenance of adequate dose intensity of chemotherapy leads to better chances of patient survival. Febrile neutropenia (FN) is defined as an oral temperature >38.5 C or two consecutive readings of >38.0 C for 2 h and an absolute neutrophil count <0.5 * 10^9/l, or expected to fall below 0.5 * 10^9/l [3]. Evidence-based guidelines identify a risk of more than 20 % of febrile neutropenia as a reason to use primary prophylaxis with G-CSF and indicate that in cases where a predicted FN risk varies around 10–20 %, other risk factors have to be considered, with age more than 65 clearly increasing the risk of FN [6].

There are various forms of G-CSF available: originators and biosimilars, from short acting like filgrastim or lenograstim to longer acting (needing only one injection) like pegfilgrastim and lipegfilgrastim. One should pay attention to the quality of these agents, and guidelines suggest to use those recognized by EMA or FDA and according to the label, i.e., beyond the day of nadir of white blood cell counts in case of short-acting agents. The European Organisation for Research and Treatment of Cancer (EORTC) guidelines, and others, indicate that the use of antibiotic prophylaxis (fluoroquinolones) to prevent infections in cancer patients at risk of neutropenia is generally not recommended and carries the risk of development of bacterial resistance. Of note, the UK National Institute for Health and Clinical Excellence has issued a position which considers this as an alternative to G-CSF usage [7]. There is no evidence specifically for or against this practice, but the development of antibiotic resistance, side effects, and drug interactions may be of concern.

It is suggested to identify patients at risk for complications if febrile neutropenia appears using risk indices such as those developed by the Multinational Association for Supportive Care in Cancer (See Table 2). This MASCC score, which has not been validated in a tropical environment, indicates that patients with a score of 21 or more points are considered at low risk and might be treated as outpatients in some conditions, while all other patients should be admitted to a clinical facility [8]. The type of antibiotic to be initially used is obviously related to the patient's infectious disease history and prior antibiotic usage, and one has to take into account the particular strains of possibly resistant bacteria that the patient may have been exposed to. In stable patients, combinations (quinolone with amoxicillin plus clavulanic acid) are preferred over single-agent quinolones because most centers have seen a rise in Gram-positive FN episodes [9]. In high-risk cases, like those who will have prolonged neutropenia and those with proven bacteremia, intravenous combinations of a beta-lactam antibiotic with an aminoglycoside are preferable. In other high-risk patients, an anti-pseudomonal cephalosporin like ceftazidime or a carbapenem can be used initially.

However, many countries have had to restrict access to G-CSFs, even though their cost is decreasing with the advent of biosimilars. These are the BHGI recommendations: At *basic levels* of resource allocation, broad-spectrum antibiotics

Table 2 MASCC (Multinational Association for Supportive Care in Cancer) risk index

Score	Characteristic
	Burden of illness
5	No or mild symptoms
3	Moderate symptoms
5	No hypotension
4	No chronic obstructive pulmonary disease
4	Solid tumor/lymphoma or no previous fungal infection
3	No dehydration
3	Outpatient status at onset of fever
2	Age <60 years

A score of 21 or more indicates a modest risk of complications related to febrile neutropenia modified from

should be available. At *limited levels*, antifungal agents should be available. Red blood cell transfusion may be needed in case of acute anemia or bleeding, and consultation with a specialist regarding febrile neutropenia should be considered. At *enhanced levels*, additional therapies include and granulocyte growth factors.

4 Bone Health

Bone loss (osteoporosis) and associated fractures increase with patient age, for both sexes, and are also related to malnutrition, in particular lack of vitamin D which is frequent also among populations in sunny countries [10].

The World Health Organization indicates the following risk factors (other than low bone mineral density) for bone loss: age, gender (female), smoking, personal history of fracture after 50+ years, parental history of hip fracture, low body mass index (<20 kg/m^2), consumption of more than three units of alcohol per day, corticosteroid use, and having other diseases (such as rheumatoid arthritis or vitamin D deficiency [11].

Aromatase inhibitors (AIs), both steroidal and nonsteroidal, provoke significant bone mineral density (BMD) decreases and they increase the fracture rate. Androgen deprivation therapy (ADT) is an important treatment approach in most men with prostate cancer. Definitive ADT can be achieved by orchiectomy, but is more commonly accomplished through the use of a gonadotropin-releasing hormone agonist (GnRH). This results in a reduction of both serum testosterone and estradiol, which in turn accelerates bone loss and significantly increases risk of fracture [12]

The effect of lifestyle management on bone loss is difficult to assess. Exercise, smoking cessation, and the reduction of alcohol consumption could all positively affect bone metabolism and turnover and are recommended on the basis of expert opinion. Vitamin D and calcium are also important in preventing bone loss in

patients with cancer, and supplementation has been shown to improve BMD and reduce the risk of fracture [13, 14].

For bone loss associated with cancer therapy-induced menopause/andropause or for prevention of skeletal-related events in patients with solid tumors that are metastatic to the bone, agents such as zoledronic acid and denosumab seem to be needed.

Clinical trials have demonstrated the benefit of bisphosphonates such as zoledronic acid with positive effect on bone mineral density as well as a reduction in skeletal-related events in breast cancer, prostate cancer, and other solid malignancies. A new targeted agent, denosumab, is a fully human monoclonal antibody designed to inhibit rank ligand which is a protein in the signaling pathway for bone removal. The FDA approved this drug for use both to prevent osteoporosis (under trade name Prolia) and to prevent skeletal-related events in patients with solid tumors metastatic to the bone (under the trade name Xgeva). Although several clinical trials have shown denosumab to be superior to zoledronic acid, the cost-effectiveness between the treatment options still requires analysis [15].

A recent meta-analysis suggests an important role for bisphosphonates [16] Among 11,306 postmenopausal women receiving adjuvant treatment for breast cancer (including women age > 55 if menopausal status unknown), bisphosphonates achieved a highly significant difference in distant recurrence, with rates of 18.4 % in women on bisphosponates vs 21.9 % in those taking no bisphosphonates ($P = .0003$), and in bone recurrence, with rates of 5.9 and 8.8 %, respectively ($P < .00001$). No significant effect of bisphosphonates was observed on non-bone recurrence. Among postmenopausal women, the rate of breast cancer mortality was 15.2 % for those treated with bisphosphonates vs 18.3 % for those not receiving bisphosphonates ($P = .004$), and the rate of all-cause mortality was 21.5 % vs 23.8 %, respectively ($P = .007$) . Such data suggest that bisphosphonates should be added routinely in the treatment of postmenopausal women with breast cancer.

The BHGI regrettably did not discuss weight-bearing exercise, cessation of smoking, and vitamin D as well as calcium supplements as a means to decrease the risk of osteopenia/osteoporosis [14]. At *enhanced levels*, the BHGI mentions bone mineral density assessment for at-risk patients and that bone-modifying agents should be available.

5 Anemia

The incidence and prevalence of anemia of different origins vary in various conditions and countries. Anemia is a common complication of cancer and its treatment. The World Health Organization (WHO) defines anemia as hemoglobin concentrations less than 13.5 g/dl for men and 12.0 g/dl for women [17]. These values may be too low for patients living in high altitude.

In more than 50 % of cases, anemia has a recognizable and treatable cause, which may include iron and cobalamin deficiency [17, 18]. In a third of the cases, the

cause of anemia is not apparent, and it may include early myelodysplasia, renal insufficiency [17, 18], and rare causes.

Iron deficiency mainly related to iron malabsorption is due to inflammatory diseases (also metastatic cancer),atrophic gastritis, *H. pylori* infection, and celiac disease. The main causes of cobalamin deficiency include atrophic gastritis and medications (proton pump inhibitors and metformin).

Anemia is a risk factor for mortality, functional dependence, postoperative delirium, congestive heart failure, and falls and increased risk of cognitive impairment and dementia.

In addition, anemia has been associated with decreased response to radiotherapy and increased risk of myelotoxicity from cytotoxic chemotherapy. As the majority of antineoplastic agents are bound to red blood cells, one may expect that the concentration of free drug in the circulation and the risk of toxicity may increase with anemia. Anemia may also be a cause of fatigue, the most common complication of cancer that may lead to functional dependence.

Before therapy, the actual causes of anemia should be investigated, and reversible etiologies promptly treated. The diagnosis of iron deficiency in the presence of inflammation may represent a challenge.

Absolute iron deficiency is then defined at a ferritin level below 100 ng/ml and a transferrin saturation less than 20 %. Functional iron deficiency is defined as ferritin above 100 ng/ml with a transferrin saturation less than 20 %. Patients with cancer and iron deficiency may need intravenous iron as they may not be able to absorb iron normally because of the inflammatory reaction [19]. Intravenous iron should be used to a maximum dose of one gram, taking into account product characteristics. Blood transfusion should be used sparingly in cancer patients. In the absence of symptoms due to anemia, it is currently recommended that blood transfusions be not used unless the hemoglobin levels are between 7 and 8 g/dl [17, 18].

The use of erythropoietin-stimulating agents (ESA) such as epoetin α or β, theta, and zeta and darbepoetin α should follow guidelines. Most country regulatory agencies have issued specific rules for the use of ESAs. These agents are effective in improving the fatigue and the quality of life of cancer patients, but a number of recent studies suggested that they may cause deep vein thrombosis (DVT), and there are no guidelines for the prevention of DVT which is also a side effect of transfusions [17, 18]. The use of ESA for hemoglobin levels lower than 12 g/dl appears safe in virtually all studies [20].

The BHGI considers red blood cell transfusion in case of acute anemia or bleeding at *limited levels* and suggests at *enhanced levels* additional therapies for low blood cell count including iron therapy and growth factors.

6 Conclusion

Management of the cancer patient requires careful assessment and close monitoring, in order to obtain significant improvements in prognosis. In addition to traditional outcomes, such as survival and disease response, other important goals

include at least maintenance of quality of life and performance status improvement if possible. Supportive care is an essential component to ensuring such good results. Prevention of nausea and vomiting, avoidance of febrile neutropenia, maintenance of bone health, and treatment of anemia are important areas of focus since they affect not only patient's quality of life but can interfere with treatment in addition to adding complexity to patients with multiple comorbid conditions. The best management of these issues is their recognition and prevention, adapting the approach to the local realities as discussed above and by the BHGI. There is a great need and opportunity for supportive care trials in cancer patients in tropical areas.

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Palliative Care for People with Haematological Cancers

Richard Harding and Emmanuelle Luyirika

1 Recognising the Need for Palliative Care

In 2014, the World Health Assembly passed the first resolution on palliative care. This important step recognised that palliative care is an essential component of the patient's treatment and care in the face of progressive and incurable disease. The resolution requires each member state to ensure that it provides a conducive policy and legislative environment as well as resources for palliative care education and training, research care and support to patients and families in order to receive quality palliative care.

The resolution was passed in light of a strong body of evidence that palliative care improves patient and family outcomes [1–3], and there are benefits to health systems in that palliative care saves costs due to reduced use of futile interventions and admissions [4–7]. Within an African hospital setting, a palliative care service reduced admissions and length of stay and increased the proportion of patients who achieved home death [5]. The provision of palliative care is an ethical duty for health systems [8].

With respect to haematological malignancies, GLOBOCAN have estimated the numbers of people dying in the world's regions during 2012 [9]. Within sub-Saharan Africa, estimates are as follows: Hodgkin's lymphoma $n = 3130$, non-Hodgkin's lymphoma n18923, multiple myeloma $n = 3457$ and leukaemia $n = 13{,}746$. In South East Asia, the numbers are 819, 10,350, 1843 and 11,694, respectively. Globally,

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for less developed regions the figures are 11,891, 74,547, 200,759 and 100,003, respectively. Relatively poorer access to healthcare and fewer curative options make palliative care even more important in low- and middle-income countries.

2 Health Systems and Palliative Care

"Palliative care as defined by the WHO is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical". Importantly, recent evidence has demonstrated that palliative care introduced early in the disease course further improves costs and outcomes [10], which underlines the WHO guidance that palliative care should be provided alongside treatment where appropriate.

Palliative care is by its nature multiprofessional to ensure that the physical, psychological, social and spiritual needs associated with progressive incurable and life-limiting disease are met. The ability to meet needs irrespective of treatment use and disease stage is crucial.

The WHO framework for a public health approach to cancer palliative care identifies the necessary activities [11]. These are identified as policy, medicines availability and education. Policies to ensure that palliative care is recognised and promoted as part of a national health plan are key – indeed Uganda was the first African country to achieve this when in 2004 it introduced a statute that allowed nurses and medical assistants (clinical officers) other than just doctors to prescribe oral morphine for pain control in the palliative care context. Policy can be directly influenced and measured to determine success in facilitating palliative care and drug availability. Drug availability is the next WHO public health strategic component. Although drugs for pain and symptom relief are named on the WHO essential drugs list, opioid consumption for pain relief is woefully inadequate in many low- and middle-income countries. The inadequate availability of opioids and the phenomenon of "opiophobia" as well as the limited number of legally allowed prescribers have led to poor supply and demand, underprescribing and patient fears of consumption. Uganda has been a model country in promoting the safe use of opioids, developing and implementing programmatic approaches [12] that have shown to result in no reported diversion [13]. Lastly, education is essential. Within many parts of the world, palliative care forms a clinical specialty or subspecialty. The availability of specialists in palliative care offers the possibility for these specialists to take referrals of complex cases while performing education and mentorship roles for generalists. This enables all healthcare professionals to integrate palliative care principles into their daily practice.

3 Availability of Palliative Care

Palliative care, as defined by the WHO, is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual".

The WHO/WPCA global palliative care atlas has revealed enormous disparity in the availability of palliative care services [14, 15]. This disparity in availability impacts not only on access to care but on the capacity of specialists to provide education, training and lobbying/advocacy activities. Sadly, almost half of the world's countries had no identifiable palliative care service. Those countries with the lowest human development index were more often categorised into having no identifiable palliative care service.

4 Needs and Preferences in Palliative Care

An important goal of palliative care is to identify the patient and family's preferences for advanced care. The variability of preferences reflects the nature of palliative care as a global health clinical and research topic [16]. While palliative care often focuses on "advance directives" and "advance care planning", most research and guidance have been generated within high-income countries. Research from South Africa has revealed important cultural dimensions of such decision making [17]. In more communal (rather than individualistic) societies, with fewer economic resources, the processes of making and meeting choices may vary greatly [18].

Global evidence also suggests a preference for home death [19]. However, the vast majority of studies have been conducted in high-income countries, and many factors may influence choices. As described above, availability and coverage are far more patchy in low-income countries, and the availability of services to provide appropriate and effective palliative care in the community may greatly influence this choice. Studies from southern and eastern Africa have indeed shown a preference to die in hospital in a scenario of serious illness [20, 21].

While the vast majority of evidence on needs has been generated in high-income countries, recent evidence has identified the high prevalence of life-limiting illness in African referral hospitals [22, 23], the high prevalence of both physical and psychological problems in advanced cancer and the patient/family preference for better communication and information [24].

One population that is particularly neglected in the evidence is children and young people. Despite the relatively high proportion of children facing life-limiting/

life-threatening illness (compared to high-income countries), very little is known about their needs, models of care and outcomes [25]. Low-income countries have particularly poor coverage of paediatric palliative care. More research is urgently need to ensure that models of cancer palliative care are developed that are appropriate to health systems and their resources, responsive to cultural preferences and expectations and adequate to scale up to population-level need [26].

5 Unique Palliative Care Needs in Haematological Cancers

The haematological cancers are often diagnosed late because of the various nonspecific symptoms which in turn complicate the patient's experience. They often present with unique needs which include pancytopenia or decline in all blood cells which in turn result into signs and symptoms associated with haemorrhage, anaemias, infections due to reduced immunity and enlargement of lymph nodes and other internal organs [27]. The care of such patients may require administration of blood products, and therefore the palliative and oncological teams face challenging decisions to make as to when such interventions should be stopped while addressing the other care needs. This calls for evidence-based, patient-centred and ethical considerations as such as decisions are taken to maintain the quality of life while minimising suffering.

6 Directing Care Through Tool Use

The key skills of assessment and holistic care delivery form the core of palliative care.

The availability of simple, brief tools to measure the problems and concerns of patients and families with progressive illness is key to improving care. The Palliative Outcome Scale (POS, www.pos-pal.org) is a family of global tools to measure and improve care, is freely available and has a global community of registered users. Within LMIC, POS is being embedded into practice to improve assessment, care planning, research and evaluation, management, resource allocation and education [28]. The use of such tools enables healthcare professionals to ensure that they address all the potential domains of concern and that they are able to monitor response to care strategies.

7 Resources

There are a number of resources available in terms of further reading, clinical guidelines, strategic documents, tools and research.

E cancer offers an online module for palliative care in Africa: http://ecancer.org/education/course/1-palliative-care-e-learning-course-for-healthcare-professionals-in-africa.php.

The World Hospice Palliative Care Alliance will identify your national palliative care association and has free resources such as the Palliative Care Toolkit www.thwwhpca.org.

The POS resources are freely downloadable here, with guidance on interpretation and analysis www.pos-pal.org.

The Cicely Saunders Institute offers postgraduate education, research and links to global partners www.csi.kcl.ac.uk.

St Christopher's Hospice offers the "Multiprofessional+" course to healthcare professional around the world www.stchristophers.org.uk.

eHospice provides a global community of information sharing www.ehospice.com.

The International Association of Hospice and Palliative Care offers resources, a global community of care providers and advocates, membership with journal access and an information gateway www.hospicecare.com.

The African Palliative Care Association offers free resources, clinical guides, advocacy plans and strategies for education and drug availability www.africanpalliativecare.org.

Hospice Africa Uganda provides the free "Blue Book", a clinical guide on palliative care delivery for all levels of care providers from lay family member to medical doctor www.hospiceafrica.or.ug.

Latin American Association for Palliative Care is a membership organisation with links to national associations, an information gateway and resources in Spanish www.cuidadospaliativos.org

Asia Pacific Hospice Palliative Care Network is a membership organisation that provides national linkages, education opportunities and free resources www.aphn.org.

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Erratum to: Adult T-Cell Leukaemia/ Lymphoma (ATL)

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Erratum to:

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The Table 1 is incorrect. It should read as follows:

Table 1 Shimoyama classification defining four ATL subtypes

	Smouldering	Chronic	Lymphoma	Acute
Lymphocyte count ($\times 10^3$/L)	**<4**	**≥4**	**<4**	↑
% flower cells	**<5 %**	**≥5 %**	**≤1 %**	↑
LDH	≤1.5 N	<2.5 N	↑	↑
Ca^{2+}	Normal	Normal	↑	↑
Skin and/or lung involvement	±	±	±	±
Lymph node involvement	No	±	Yes	±
Spleen/liver involvement	No	±	±	±
Central nervous system/bone/pleural/ascites	No	No	±	±

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