Chapter 81

Indian Guidelines and Protocols in Oncology: Solid Tumors and Hematological Malignancies

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INTRODUCTION

Currently we are in the era of the so-called evidence-based medicine. Management of patients follows internationally acceptable guidelines and recommendations. This is to ensure that we are able to provide the optimal therapy and maximize outcome. At the same time, we are also surrounded by publications that talk about personalized therapy. This is to ensure that taking into consideration all the variables (patient, disease, tumor, host and environment), the treatment most likely to work is selected from the standard options available.

Are these seemingly opposite ends of the spectrum? Nothing could be further from the truth. Since medicine is not mathematics, it is as much a science as it is an art. And both these approaches have the same primary objective, the best interest of the patient.

In order to make this possible, a judicious use of guidelines, protocols, common sense and compassion are necessary. This is particularly important for oncology—be it solid tumors or hematological malignancies.

EPIDEMIOLOGICAL BACKGROUND

World Health Organization (WHO) says that by the year 2020, a total of 10 million deaths will occur annually in the world, of which 3 million will be in industrialized nations and 7 million in developing countries. Disparity also exists in outcome (survival). This is not only when comparing the industrialized to developing countries but also for western Europe as compared to central/eastern Europe as well as for different ethnic groups within a developed country (USA—Hispanics, Blacks and Caucasians).

This is primarily due to the disparity in the infrastructure and human resource available in various countries. This spectrum has been elegantly demonstrated by Noronha et al. in the South Asian Journal of Cancer **(Table 1)**.

In the 12th 5-year plan, Ministry of Health, Government of India is focusing on four non-communicable diseases [cancer, diabetes mellitus (DM), hypertension and stroke]. This is because currently more than 10 lakh new patients are confirmed to have cancer on biopsy every year and our citizens are facing a tremendous increase in the projected incidence of various cancers. For instance the population based cancer registry run by Indian Cancer Society indicates that the prevalence of breast cancer in the state of Maharashtra will increase to a staggering 43,468 by the year 2021 **(Table 2)**.

Cancers are a group of disorders that are strongly related to lifestyle. Tobacco, obesity, lack of exercise, alcohol and environmental toxins are well known. For this manuscript, the authors would like to revisit infectious causes, since a novel intervention has

TABLE 1 | Insight into oncology status of South Asian Association for Regional Cooperation (SAARC) countries

Sr No	Question	Bhutan	Pakistan	India	Bangladesh	Sri Lanka	Nepal
1.	Number of qualified oncologists in the country	2	125	1,500	150	18	40
2.	Number of cancer centers in the country	1	20	27	18	06	5
3.	Number of other hospitals treating cancer patients in the country	1	50	300	30	04	5
4.	Number of new cancer patients diagnosed every year in the country	300	150,000	1,000,000	100,000	15,000	30,000
5.	Number of medical oncology journals brought out by the country	Nil	0	5	3	None	None
6.	Number of oncology conferences and CMEs conducted in the country every year	Only once in 2011	6	55	20	05	30
7.	Number of radiotherapy machines currently available in working condition in the country	Nil	25	300	19	11	6
8.	Number of scientific societies/associations dedicated to oncology in the country	Nil now, going to set-up soon	2	5	3	01	10
9.	Is there degree training in oncology (any branch) available in the country?	No	Yes	Yes	Yes	Yes	Yes
10.	Is there an official national health care policy for cancer in the country (of any nature)?	Yes	No	Yes	No	Yes	Yes

TABLE 2 | Breast cancer trends in Maharashtra (based on data from the Indian Cancer Society's population-based cancer registry)

	2001	2011	2021
Incidence	9,121	11,401	14,252
Mortality	4,652	5,815	7,268
Prevalence	27,819	34,774	43,468

become recently with far-reaching potential implications. Human papillomavirus (HPV) infection is clearly the most common sexually transmitted disease (STD) globally affecting approximately 6 million people annually. As many as 80% of women will acquire an HPV infection during their lifetime. Even with a single sexual partner, almost half the women will get this infection within 3 years. They have direct correlation with precancerous lesions as well as full blown cancers of the cervix (100% association), anus (80%) vagina, vulva, penis (40–60%). Globally 530,000 women are diagnosed with cervical cancer every year, and about 275,000 women die from the disease. In rural India, cervical cancer still ranks as the most common cancer in females affecting 132,000 women annually and causing 74,000 deaths. Seventy nine studies from 18 countries were identified that confirmed the correlation between HPV and cervical cancer. Persistent HPV infection may lead to the entire spectrum of the disease from cervical intraepithelial neoplasia (CIN) to invasive cervical cancer the natural history of such progression varying from 7 years to 20 years (invasive cervical cancer).

Human papillomavirus infection therefore becomes the logical target and prototype for a preventive vaccine strategy, especially since cervical cancer remains a major cause of morbidity and mortality in India as well as other developing countries. It is now clearly documented that vaccine-induced immunity is stronger, develops faster and lasts longer than the response following infection. In addition it also benefits by partial cross-protection against other HPV serotypes.

CONCEPT ABOUT INDIAN GUIDELINES

Medical science is progressing so rapidly that it is almost impossible to keep up with the thousands of articles published every year. In fact, each doctor would have to read 17 articles to be abreast with all phase III clinical trials data published in the English language alone. With significant number of unmet medical needs, continuous development of new treatment options and the current preference for personalized evidence-based medicine, need for guidelines have been well established.

Guidelines, consensus statements, position papers and recommendations are names that are commonly used in an interchangeable manner while referring to such documents. They are made after careful and systematic considerations of available evidence by a team of experts. This group usually consists of those who have vast experience, proven academic interest and have reputation respected by peers making them key thought leaders.

Such guidelines are most useful to health care professionals who work in the community and deal infrequently with the disease under consideration. Usually it is therefore most useful to a physician from an ancillary speciality (e.g. chest physician faced by a lung cancer patient) or one who is a generalist oncologist/hematologist dealing with few cases of everything. Guidelines filter and provide a distillation of the entire evidence-based medicine database with clear idea about essential next steps. Following the algorithm from a reputed guideline also protects the health care professional in case of a medicolegal challenge. Managing a patient as per accepted guidelines would back up a statement that due diligence was followed while imparting treatment—risk of "acts of omission" become attenuated.

At the same time we must remember that guidelines are just that—guidelines. They provide a rule-of-thumb. In each individual case, there could be the need to go beyond these guidelines. Such deviations are not uncommon, especially when trained, qualified and experienced oncologists decide about personalized medicine. This is the reason even the best of international guidelines are followed only in a minority of cases. Each addition beyond such guidelines needs to be documented with the specific rational for the same.

Numerous international guidelines exist. Commonly used ones in oncology include those from American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) (USA). Most of them are updated regularly—usually annually or at least once in 2 years. Several countries have their own guidelines (Asian, Japanese, Chinese, etc). Most of them have minor changes or specific additions for features to their ethnic population [e.g. gefitinib in lung cancer since epidermal growth factor receptor (EGFR) mutations are higher among Asians]. Comorbidities influence the development and implementation of guidelines. Since cancer is a disease common in the elderly, this becomes crucial for chronic illnesses (DM, hypertension, arthritis, renal impairment).

In India, the Indian Society of Medical and Pediatric Oncology (ISMPO), Indian Cooperative Oncology Network (ICON) as well as the Indian Society of Hematology and Transfusion Medicine (ISHTM) have been at the forefront of developing guidelines, consensus statements, position papers and recommendations. More recently the Indian Council for Medical Research (ICMR) has set up a committee for developing guidelines for specific cancers. Several of the subcommittees have already submitted their recommendations and such guidelines are available on the ICMR website.

The authors will now take three examples to have a snapshot of guidelines and management protocols in oncology and hematology in India.

Lung Cancer

In the 4th edition of Principles and Practices of Cancer edited by DeVita et al. Canadian medical oncologists were asked whether they would take chemotherapy for metastatic non-small cell lung cancer (NSCLC). Almost all of them declined. This was because the limited chemotherapy drugs available at that time had minimal efficacy, natural history was short and the outcome uniformly poor. We have come a long way since. Today platinum-based doublet chemotherapy is the standard of care for metastatic NSCLC **(Tables 3 and 4)**.

It is important to maintain dose intensity in oncology. The first chance is usually the best chance. Optimal outcome occurs only when

TABLE 3 | Treatment decision in metastatic non-small cell lung cancer (NSCLC)

- Cytological or histological confirmation of small cell lung cancer v/s NSCLC.
- Subclassify NSCLC into squamous cell v/s nonsquamous cell.
- For nonsquamous cell, epidermal growth factor receptor (EGFR) mutation testing (wild type vs mutated type).
- For EGFR mutated tumors, treatment offered is oral small molecule tyrosine kinase inhibitors [tyrosine kinase inhibitors (TKIs) like gefitinib and erlotinib].
- For EGFR wild type tumors, treatment offered is intravenous platinum doublet chemotherapy **(Table 4)** with or without monoclonal antibodies (like cetuximab, nimotuzumab and bevacizumab).

TABLE 4 | First-line doublet chemotherapy for metastatic non-small cell lung cancer (NSCLC)

- Platinum drug: Cisplatin, carboplatin, oxaliplatin
- Non platinum drug: Gemcitabine, pemetrexed, paclitaxel, docetaxel, nanoparticle paclitaxel, albumin bound paclitaxel, vinorelbine, etoposide, vinblastine, and irinotecan.
- Pemetrexed should not be used for squamous cell tumors.
- Performance status, stage, weight loss and gender are prognostic markers.
- The two drug combination to be selected for a particular patient is based on the toxicity that needs to be avoided and the combination that potentially offers the maximum benefit.
- The schedule selected can be weekly, three weekly or day one plus eight of three weekly cycles.
- No of cycles of chemotherapy are usually between 4–6 cycles.
- Maintenance therapy is given in selected cases. This can be continuation maintenance or switch maintenance.
- Patients who relapse or progress are to be considered for second-line and third-line cancer directed systemic therapy.

the planned treatment is implemented correctly. And dose reduction or delay in cycles has significant adverse impact on response rate and overall survival **(Table 5)**. The authors have previously shown that outcome in NSCLC is best when the chemotherapy is administered under the direct supervision of trained, qualified and experienced medical oncologists as compared to other doctors **(Table 5)**.

In India, we are also striving to provide our patients with the most cost-effective regimen possible. We have developed an innovative scheduling of gemcitabine and carboplatin combination that is one third of the cost but even more effective than the standard schedule. This is possible by prolonging the infusion time of gemcitabine from the standard 30 minutes to 4 hours. Since gemcitabine is a prodrug, it needs to be converted to the active form in the body. This requires an enzyme called deoxycytidine kinase. This is a rate-limiting step that gets saturated at 30 minutes. Taking advantage of this fact, we were able to get superior results (response rate as well as overall survival) by simply increasing the duration of the infusion to 4 hours. The equivalent dose of gemticabine to maintain the same area under the curve (AUC) was 350 mg/m^2 as compared to the standard 1,000 mg/m^2 **(Table 6)**. This results in upto 66% reduction in cost of chemotherapy, a significant saving for Indian patients.

TABLE 6 | Prolonged infusion gemcitabine doublet combination chemotherapy that saves up to 66% of chemotherapy cost in nonsmall cell lung cancer (NSCLC)

Sr No.	Drug	Dose	Route	Duration
1.	Injections Gemcitabine	350 mg/m^2	IV infusion	4 hours
2.	Injections Carboplatin	AUC 5	IV infusion	2 hours

TABLE 7 | Avoiding unnecessary use and minimizing wastage of blood

- Transfuse only when necessary
- Prevention, early diagnosis and effective treatment of anemia
- Use good anesthetic and surgical techniques to reduce blood loss
- Use pharmacological options to reduce blood loss
- Avoid preoperative transfusion to raise hemoglobin
- Avoid transfusion for a misconception of early discharge from hospital
- Judge the need based on clinical condition of the patient and not solely the laboratory results
- Use only the component that is needed
- Use replacement fluids to maintain normovolemia
- Use only the amount required

TABLE 8 | Selection of ABO compatible donor red cells

Recipient ABO group	Donor ABO group			
	First choice	Second choice	Third choice	Fourth choice
O	O	None	None	None
A	A	O	None	None
B	B	O	None	None
AB	AB	A	B	O
Oh (Bombay Group)	Oh	None	None	None

55% of blood collected is O group in Male.

Blood Transfusion

Transfusion of blood and blood components must be approached like the use of medicines. They must be used only after weighing the benefits against the risks as well as in the right dose and schedule. It must always be remembered that improper use has led to significant morbidity and even mortality. The right decision for transfusion is the use of right product for the right patient in the right dose at the right time for the right indication **(Table 7)**. In case the same ABO blood group is not available, the selection of ABO compatible donor red cells should follow the guidelines shown in **Table 8**.

In special circumstances, washed red cells (WRC) are to be used. Washed red cells are prepared by washing with sterile normal saline. This makes it an open system and the blood unit needs to be transfused within 6 hours.

The indications for transfusion of WRC are:

- Multitransfused patients with recurrent febrile reactions
- Urticarial reactions
- Anaphylactic reactions in patients with IgA deficiency with IgA antibodies
- Paroxysmal nocturnal hemoglobinuria
- Patients with T-activated cells who require transfusion.

Platelet concentrates are an important component of today's medical management. They may be made from a single unit of collected whole blood (platelet-rich plasma or buffy coat) or as platelet concentrates [random donor platelets (RDPs) or single

TABLE 5 | Importance of dose intensity in treatment of advanced nonsmall cell lung cancer (NSCLC)

Variable	Comparison	Median overall survival (months)	P value
Chemotherapy completion	6 cycles versus < 6 cycles	14 vs 4	0.000
Dose reduction	Dose reduction versus no reduction	18 vs 7	0.000
Best response to treatment	PR + SD versus PD	15 vs 5	0.000
Chemotherapy administration	Medical oncologists versus other doctors	13 vs 6	0.004

donor platelets (SDPs)]. Typically 1 unit of RDP prepared from 450 mL whole blood should have at least 50 × 109 platelets in a volume of approximately 50 mL. Platelet concentrate made from one donor being apheresed using a cell separator machine is called SDP. Typically 1 unit of SDP should have 300×10^9 platelets (equivalent to approximately 6 units RDP) in a volume of 200–350 mL.

Platelet transfusions should also be used judiciously. The guidelines for when to use platelet transfusions are shown in **Table 9**. Likewise there are contraindications to the use of platelets **(Table 10)**. Please note that these contraindications are usually relative and the treating physician must use his clinical judgment on a case to case basis.

Leukocyte depletion filters remove leukocytes from cellular blood products like red cells and platelets. Currently available filters achieve more than 3 log (at least 99.9%) depletion of leukocytes. The residual leukocyte count of filtered product is less than 5×10^6. Filtration can be done either in the blood bank laboratory or by the bedside. Blood bank filtration permits quality control of the leukocyte depleted product. Prestorage filtration is more effective than poststorage or bedside filtration, as it prevents collection of cytokines.

Leukocyte depleted cells can be used to prevent febrile reactions, human leukocyte antigen (HLA) alloimmunization and refractoriness to platelet transfusions. It also prevents cytomegalovirus (CMV) transmission in immunosuppressed seronegative recipients as it is difficult to find CMV seronegative donors. It does not prevent transfusion-associated graft-versus-host disease (TA-GVHD).

In the current scenario, it is important to emphasize the correct use of blood component therapy for the treatment of dengue fever/dengue hemorrhagic fever. This is particularly important for cases in Grade III-IV. According to the WHO guidelines for such treatment in small/community hospitals, patients with profound shock, undetectable pulse and blood pressure should be given blood components as follows:

- If shock still persists and the hematocrit level continues declining:
  - Give fresh whole blood 10 mL/kg as a bolus
  - Monitor vital signs every 30–60 minutes
- In case of severe bleeding:
  - Give fresh whole blood 20 mL/kg
  - Give platelet rich plasma transfusion exceptionally when platelet counts are below 5,000–10,000/mm^3
  - After blood transfusion, continue fluid therapy at 10 mL/kg/h and reduce it stepwise to bring it down to 3 mL/kg/h and maintain it for 24–48 hours.

A topic often neglected is the storage conditions of blood components. Guidelines on how to ensure proper storage are specified in **Table 11**.

Finally, safe blood transfusion is everyone's responsibility. The last opportunity is at the bedside of the patient. This checklist is outlined in **Table 12**.

TABLE 9 | Trigger for platelet transfusions

• Asymptomatic patient: (prophylactic)	10,000/ml (or even below 5,000/μL)
• Febrile neutropenia/uncomplicated BMT	20,000/ml
• Bleeding other than petechiae and bruises, mucocutaneous bleeds DIC	50,000/ml
• BMT with complications like fever/septicemia/infection/disseminated intravascular coagulation (DIC)/bleeding/(graft-versus-host disease) GVHD Uncontrolled hypertension	
• Elective invasive procedures like central venous line insertion or surgery	> 50 and < 75,000/ml
• Major Surgery	50,000/μL
• Surgery on vital organs e.g. eye or brain	100,000/μL

TABLE 10 | Contraindications to platelet transfusions (absolute and/or relative)

- Thrombotic thrombocytopenic purpura (TTP)
- Heparin induced thrombocytopenia (HIT)
- Idiopathic thrombocytopenic purpura (ITP)
- Post-transfusion purpura

Cervical Cancer Vaccine

The two prophylactic HPV vaccines currently available are prepared from purified L1 structural proteins that induce a protective immunity. Gardasil® is a quadrivalent vaccine (HPV types 6, 11, 16 and 18) whereas Cervarix™ is a bivalent vaccine (HPV types 16 and 18). The vaccine is a sterile suspension in single-use glass vials/prefilled syringes to be stored using cold chain (2–8°C; not to be frozen). The cost of each dose of Gardasil® and Cervarix™ is approximately Rs 2,800 and Rs 3,300 respectively in India. They are recommended for use in females 10–26 years of age, for the prevention of cervical, vulvar, vaginal cancers, intraepithelial neoplasia and condyloma acuminata, and recently vaccination in boys and men 9–26 years of age for the prevention of anogenital warts. In India, both vaccines have been licensed for use in females (primary vaccination at 10–12 years, catch-up up to 26 years). Each baseline and subsequent dose is 0.5 ml administered intramuscularly. The quadrivalent vaccine is repeated between 2 months and 6 months and the bivalent vaccine given between 1 month and 6 months. The minimum interval between successive doses should be 4 weeks (first and second dose) and 12 weeks (second and third dose). If the vaccination is delayed, the remaining doses should be given as close to the original plan as possible. After complete vaccination, almost all the recipients develop an antibody response. The antibody titers peak after the third dose, decline gradually and then level off at 24 months (remaining higher than following a natural infection).

Both vaccines are safe and well tolerated with no statistically significant difference in the risk for vaccine-related serious adverse events (AEs) between vaccine and control groups. Pain and erythema at injection site (83–93.4%), headache and fatigue (50–60%) are the most common vaccine-related systemic AEs. HPV vaccines are contraindicated in those with history of severe allergic reactions to vaccine components. In individuals who are currently suffering an acute illness, HPV vaccination should be delayed till complete recovery. Vaccination is not recommended for women who are known to be pregnant. Breast-feeding is not generally a contraindication for vaccination.

Such vaccination has shown good efficacy rates for condyloma, low and high-grade CIN. The overall HPV vaccine type-related

TABLE 11 | Optimum storage conditions for blood components

Component	Storage temperature (°C)	Shelf life
Whole blood	2–6	35 days
Red cell concentrate	2–6	35 days
Leukoreduced red cell concentrate with AS	2–6	42 days
	20–24; with agitation	5 days
	20–24	
Platelet concentrate (RDP/SDP)	<-30	24 hours
	<-30	1 year
Granulocyte concentrate/buffy coat	<-30	1 year
		1 year
Fresh frozen plasma		
Cryo poor plasma/plasma		
Cryoprecipitate		

TABLE 12 | Patient bedside safety check list for safe blood transfusion

Before	During	After
• Check patient identity: Name, date of birth, hospital registration no. • Check compatibility report with product identity: Blood group, unit no., expiry date • Check product integrity • Document date and time of starting • Check temperature, pulse, respiration (TPR) • Check if correct set is used • Check if specific needs are provided e.g. warming, irradiation, LD filter • If transfusion is delayed store the product at correct temperature • Start transfusion • Check there is no air bubble in the line, filter is wet and drip chamber is not more than half full	• Observe closely for first 15–30 minutes • Monitor TPR • Monitor rate of flow–maintain slow rate for first 30 minutes • Observe the clinical status of the patient • Check venepuncture site • Change set if required • If any adverse reaction occurs • Take immediate action • Stop the transfusion • Inform clinician • Record • Inform Blood bank	• Document time and volume • Check TPR and record • Dispose bag/set/needle • Observe patient for half hour • Look for any delayed reaction • Look for evidence of improved clinical status

CIN efficacy has ranged from 89.2–100%. The protective efficacy of the vaccines is well documented throughout the study (5 years for Gardasil® and 8.4 years for Cervarix™). Muñoz et al. vaccinated 3,819 older women (24–45 years old) and found 90% efficacy against combined incidence of vaccine HPV-related 6 months persistent infection, CIN 1–3 or external genital warts.

A recent observer-blind head-to-head randomized controlled trial sponsored by GlaxoSmithKline (GSK) showed that the mean titers of serum neutralizing antibodies ranged from 2.3–4.8 folds higher for HPV 16 and 6.8–9.1 folds higher for HPV 18 after vaccination with Cervarix™ compared with Gardasil®, across all age strata. The incidence of AEs was comparable between groups. It is also estimated that antibody levels will remain detectable near lifelong in 99% of vaccinated females. However, since the immunity does tend to drop after several years, a booster dose might be recommended in the future.

Vaccinating males also has the potential to prevent HPV related disease [anogenital warts, anal intraepithelial neoplasia (AIN) and anal cancer]. Giuliano et al. have reported an efficacy of 90.4% against external genital lesion and 85.6% against persistent infection by HPV 6/11/16/18 among 4,065 vaccinated healthy, predominantly heterosexual males 16–26 years of age. Men are at a higher risk than women of developing oropharyngeal cancers, 50% of which may be HPV related. Men who have sex with men (MSM) and those with immunodeficiency are also at higher risk and will benefit from HPV vaccination. In addition, vaccinating boys has the potential advantage of reduction cervical cancer through "herd immunity".

Based on the present vaccine protocol, we can anticipate that approximately 70% of cervical cancers are preventable by vaccination. This percentage might be slightly higher because there also exist cross-reactivity with types 31, 33 and 45 of the HPV 16 and 18 antigens.

Human papillomavirus vaccine can be safely given to human immunodeficiency virus (HIV) positive and other immunocompromised individuals. Though its efficacy is significantly lesser, (seroconversion rates of upto 98%, 99%, 100% and 95% were observed for HPV types 6, 11, 16 and 18 respectively) evidence suggests that such vaccination should be offered to all irrespective of their immunocompetence status.

In April 2009, WHO confirmed its value by issuing a position statement recommending that routine HPV vaccination of females be included in national immunization programs **(Table 13)** provided that (1) cervical cancer and/or HPV related diseases constitute a public health priority; (2) vaccine introduction is programmatically feasible; (3) sustainable financing can be secured; and (4) cost-effectiveness of vaccination strategies in the country or region is considered. Also, cervical cancer screening in national programs for vaccinated females should remain the same as for non-vaccinated females. Both the Indian Academy of Pediatrics (IAP) and the Federation of Obstetric and Gynaecological Societies of India (FOGSI) support these recommendations.

A well-known HPV vaccination projects had started in India (school and community based vaccination in Khammam district, Andhra Pradesh with Gardasil® and Vadodara, Gujarat with Cervarix™). Unfortunately media allegations of "vaccine-induced" deaths led to these studies being suspended. Even though the allegations were found to be unsubstantiated and the deaths confirmed as unrelated to the vaccine, these studies remain in a limbo.

A cross-sectional survey in 2009, done by Di Angi et al. in Botswana throws light on the acceptability of this vaccine in the community. Although only 9% (32/376) of their respondents had heard of HPV vaccine prior to the survey, 88% (329/376) said they definitely will have their adolescent daughters receive HPV vaccine. In fact respondents were more likely to get HPV vaccine for their daughters if they had less education or lived more than 30 km from their capital city, indicating good acceptance among the poor socioeconomic strata (which are also the ones needing this vaccine the most).

Thus, like research on hepatitis B vaccination, HPV vaccines have significantly changed the field of prevention of cancer. Currently available HPV vaccines are safe and effective. They are applicable to both women and men. They prevent HPV-induced anogenital warts, precancerous lesions, cervical cancer oropharyngeal cancer

TABLE 13 | Human papilloma virus vaccination as part of national immunization programs in Americas (2006–2010)

Country	Year of implementation	Target population	Geographic scope
United States	2006	Females, 11–12 years	National
Canada	2007	Females, 9–15 years	National
Panama	2008	Females, 10 years	National
Mexico	2008	Females, 9–12 years	Partial (5%)

and anorectal cancers. This has led to the recent expansion of United States Food and Drug Administration (USFDA) approval of the quadrivalent HPV virus-like particle vaccine to include men and boys. The vaccines are best given before the onset of sexual activity and provide long-term protection.

BIBLIOGRAPHY

1. Centers for disease control and prevention. Progress toward implementation of human papillomavirus vaccination the Americas, 2006–2010. Morbidity and Mortality Weekly Report (MMWR). 2011;60(40);1382-4.
2. McKeage K, Romanowski B. AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix™): a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. Drugs. 2011;71:465-88.
3. Noronha V, Tsomo U, Jamshed A, et al. A fresh look at oncology facts on South Central Asia and SAARC Countries. South Asian J Cancer. 2012;1:1-5.
4. Pandhi D, Sonthalia S. Human papilloma virus vaccines: current scenario. Indian J Sex Transm Dis. 2011;32(2):75-85.
5. Parikh PM, Patel MH, Goyal NR. Blood and blood components. In: Jain PK (Ed). Principle and Practice of Critical Care, UK: Anshan limited; 1996.
6. Parikh PM. Practical Hematology Oncology. 2nd edition. 1999.
7. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
8. Prasad N, Bakshi A, Deshmukh C, et al. Importance of dose intensity in treatment of advanced non small cell lung cancer in the elderly. South Asian J Cancer. 2012;1:9-15.
9. Trim K, Nagji N, Elit L, et al. Parental knowledge, attitudes and behaviors toward human papillomavirus vaccination for their children: a systematic review from 2001–2011. Obstet Gynecol Int. 2012;(2012):921236
10. World Health Organization (2011). Vaccines against human papillomavirus. [online] Available from www.who.int/vaccines/en/hpvrd.shtml/shtml/shtml. [Accessed December, 2012].