LEADership Training Programme

MANUAL

for Medical Professionals in Cancer Prevention and Control

2019-'20

Regional Cancer Centre, Thiruvananthapuram

Editors

Dr. Gigi Thomas
Additional Professor & Head
Division of Community Oncology
Regional Cancer Centre, Thiruvananthapuram

Dr. R. Jayakrishnan
Associate Professor
Division of Community Oncology
Regional Cancer Centre, Thiruvananthapuram

Acknowledgements

Dr. Meenakshi. V
Additional Director of Health Services (Public Health) ,Kerala State

Dr. Bipin K. Gopal
Nodal Officer, State NCD ,Kerala State

Dr. Geetha N
Additional Director ,Regional Cancer Centre ,Thiruvananthapuram.

Dr. Sajeed. A
Medical Superintendent ,Regional Cancer Centre ,Thiruvananthapuram

Dr. Madhu Muralee
Deputy Superintendent ,Regional Cancer Centre ,Thiruvananthapuram

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Design: smartdocposters@gmail.com

Foreword

We are happy to know that the Regional Cancer Centre is taking the initiative to organise leadership training programmes to enhance the capacity of medical professionals to identify common cancers at an early stage. These training programmes are being conducted with the support of the National Health Mission, Kerala and the State Health Services Department. The LEAD 2019-2020 training programmes will help augment cancer prevention and control activities in the State. Needless to say, the training programmes will equip medical professionals in setting standards for prevention, early cancer detection and prompt referral particularly at a time when the State Government is gearing up for scaling the Aardram Mission Campaign to newer heights in the State. We are confident that this training manual for clinicians prepared by the Regional Cancer Centre , Thiruvananthapuram would come handy to the medical professionals to serve as a valuable information booklet in their busy practice in cancer prevention and control activities.

Shri. Keshvendra Kumar IAS
State Mission Director
National Health Mission, Kerala

Dr. Saritha R.L.
Director of Health services
Kerala

LEAD 2020

Our Faculty Members
Of The Training Programe

1.Dr. Ramadas. K
Professor & Head, Radiation Oncology

2.Dr. Beela Sarah Mathew
Professor, Radiation Oncology

3.Dr. Paul Augustine
Additional Professor & Head Surgical Oncology

4.Dr. Chandramohan. K
Additional Professor, Surgical Oncology

5.Dr. P.Rema
Additional Professor, Surgical Oncology

6.Dr. Madhu Muralee
Additional Professor, Surgical Oncology

7.Dr. Arun Peter
Additional Professor, Surgical Oncology

8.Dr. Gigi Thomas
Additional Professor & Head, Community Oncology

9.Dr. Suchetha. S
Additional Professor, Surgical Oncology

10.Dr. Kainickal Cessal Thommachan
Additional Professor, Radiation Oncology

11. Dr. Kalavathy M.C
Associate Professor, Community Oncology

12.Dr. R. Jayakrishnan
Associate Professor, Community Oncology

13.Dr. Wagh Mira Sudham
Associate Professor, Surgical Oncology

14.Dr. Arun Sankar
Associate Professor, Radiation Oncology

15.Dr. Rexeena Bhargavan
Associate Professor, Surgical Oncology

16.Dr. Siva Ranjith
Assistant Professor, Surgical Oncology

17. Dr.Dhanya Dinesh
Assistant Professor, Surgical Oncology

18.Dr. Aswathy G. Nath
Division of Gynec Oncology

19.Dr. Naveen Kumar
Division of Radiation Oncology

Foreword

The emergence of cancer as a major public health problem in Kerala is a matter of concern for oncologists and policy makers considering the sharp increase in patient load in tertiary cancer centres. In addition to this, clinical presentation of the disease mostly in the advanced stages adds to the disease burden in terms of the quality of life being compromised in such situations. In this scenario, prevention and early detection of common cancers holds the key to reducing the cancer burden in the state. Primary prevention strategies coupled with early detection measures may have greater impact to reduce the morbidity and mortality associated with common cancers in the society.

The LEADership Training Programme (LEAD 2019-2020) is an attempt by the Regional Cancer Centre to enhance capacity building of medical professionals of the State Health services Department working in primary health care settings and in areas where cancer prevention and control activities are in the sub optimal stage. The training programmes are being organised with the support of the National Health Mission and the State Health Services department. The curriculum of this training programme is designed in such a way that the diagnostic capabilities of medical professionals to detect cancers at an early stage could be enhanced through lectures and active case discussions. Considering the cost and time incurred to attend training programmes at RCC, a proactive approach would be undertaken by the RCC to undertake 14 such programmes in all the 14 districts of the State by the year 2020. This clinician's hand book would act as a quick reference manual towards primary prevention strategies and early detection measures. I hope the training programmes would be a major step to enhance the capacity of medical professionals to strengthen cancer prevention and control activities and thereby reduce the cancer burden in the State of Kerala.

02-11-2019

Dr. Rekha A. Nair
Director
Regional Cancer Centre
Thiruvananthapuram

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Understanding Primary Prevention of Cancer - A Provider's Perspective

Dr. R. Jayakrishnan
Associate Professor, Community Oncology,
Regional Cancer Centre, Thiruvananthapuram

"An ounce of prevention Is worth a pound of cure ."

Benjamin Franklin

Background

One of the most frequently discussed topics in public health yet to receive recognition and gain momentum, particularly in developing countries is 'primary prevention'. The term often regarded as 'ambiguous' because of the indistinct understanding of the concept among health care providers, underestimates its true potential resulting in a sense of 'deja vu' among the community. The result has taken a toll in developing countries where the most cost effective and practically possible methods are waiting to gain traction to compliment the broader concept of prevention and control.

In simple terms, primary prevention implies preventing the occurrence of outcome (Example: disease) by various measures or interventions against those factors that are deemed to be causal or at risk with reference to the outcome. While secondary prevention aims to protect a person who has the tendency to develop a disease, or, a disease that has started but not blown to its full potential. (Example: pragmatic efforts for early detection of oral, cervix and breast cancers)

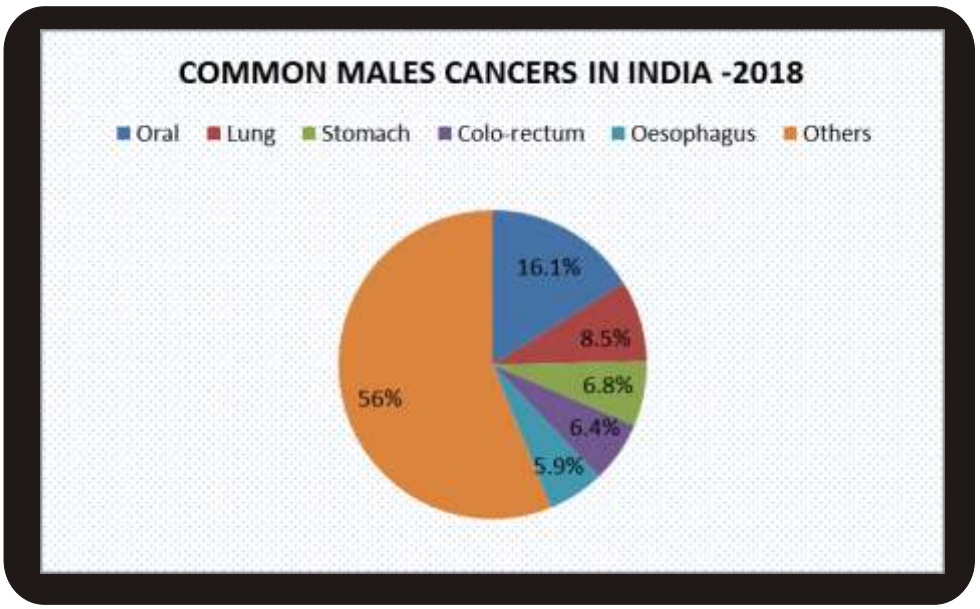
CANCER FACT SHEET- GLOBOCAN 2018[1, 2]

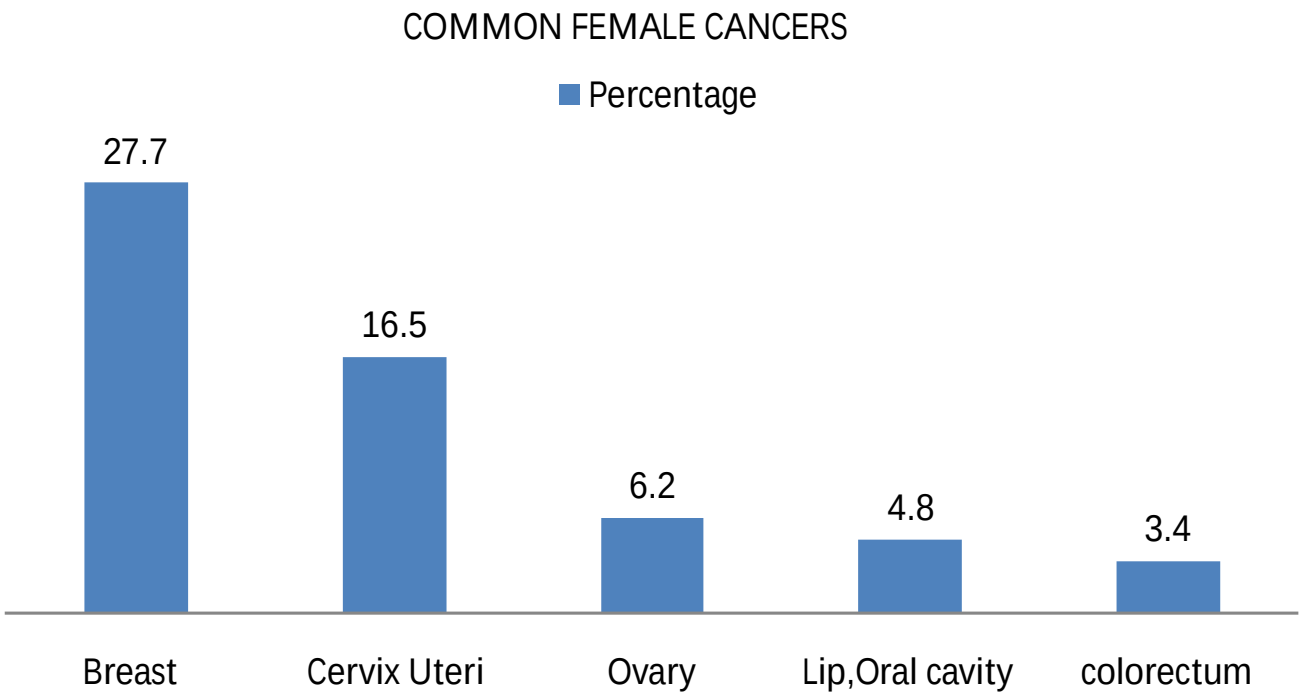
Global

18.1 million new cases, 9.6 million cancer deaths annually

Common cancers lung (11.6%), breast (11.6%), colo-rectum (10.2%), Prostate (7.1%), Stomach (5.7%), liver (4.7%)

COMMON CANCERS IN INDIA





* A closer look at these figures point to the need of primary and secondary prevention to deal with some of the common cancers in India

RISK FACTORS

While discussing primary prevention, the two terms that often appear in deliberations and articles are '*cause*' and '*risk*', sometimes used interchangeably. In primary prevention, the two terms are perceived in the epidemiological concept and not in colloquial expressions, hence to be used judiciously. Risk factors are those that could increase the likelihood of developing a disease. A risk factor may not always be a causal factor. However, it may be associated with the outcome. An example is lower socioeconomic status (SES) and oral cancer. Here, lower SES is a factor that contributes to the occurrence of oral cancer, but it is not a causal factor. The living standards of people residing in the lower socioeconomic strata differ compared to that of higher SES groups which is mainly reflected in low education, low wage pattern compared to white collar jobs, resulting in nutritional deficiencies and low standard of living. Due to less education, the nature of the work they are engaged in could be exhausting such as in the case of a manual labourer. These social disparities could be frustrating and may trigger the person to take up tobacco and alcohol habits. All these factors could have a cascade effect on the outcome.

To substantiate the meaning of 'risk', let us take the fictional example of a next door neighbour who has placed a warning on the gate of the house that says ...

How are we going to analyse this sentence? The house owner had not written emphatically saying that the dog will definitely bite those who enter the house. All bite marks on a person who enter the house would not have been caused by the dog and not all persons entering the house will be bitten by the dog. Here the word used is 'risk', which says there is a possibility/likelihood of getting bit by the dog, but may not always be possible in the strict sense if the dog is familiar with the person entering the house or the dog is relaxed after having a good meal. In short, this example was meant to say the importance of using the word 'risk' in discussions related to cancer incidence.

CAUSAL FACTOR

Causation or causality is more of a complex process, a judgement made by collective consensus based on a plethora of evidence.

To understand the concept, let us take the example of a person affected with infectious conjunctivitis, which is a contagious disease, and no other household was affected with the disease at present. We also assume that the cause was identified and clinical examination conducted by the Ophthalmologists lead to the treatment of the disease. Thereafter necessary instructions were given to the patient and household members to prevent the spread of disease. Here the cause of the disease was identified that lead to interventions and good prognosis. In this example, there is a one to one effect between the cause and outcome. That means the cause preceded the outcome and effective treatment by the doctor and precautions taken by the households had resulted in restricting the disease to one person alone, though it is a contagious one.

Criteria for causation

In short, a factor can be said to be causal, taking into consideration a variety of factors mainly temporality (cause should precede the effect), biological gradient (dose- response), plausibility (to justify the biological mechanism) and notwithstanding the fact that interventions to remove the cause could avert/reduce the occurrence of outcome.)

In addition to this, other factors viz. strength of the association, consistency, specificity (one cause for one outcome) and analogy also have to be looked upon (Hills criteria of causation[3])

However, while discussing the link between 'cause and effect' with reference to non-communicable diseases, a section of the public health fraternity argue for usage of the term 'probabilistic cause' (example: smokers have higher likelihood of developing lung cancer compared to non-smokers) rather than a 'deterministic' causal mechanism linked to the effect (example: all individuals who smoke develop lung cancer).

Hence, 'cause and effect' are arguably being linked more towards infectious disease epidemiology. While for non communicable diseases, risk factor is the term commonly used and not to forget that some causal factors (example: smoking and lung cancer; oncogenic HPV infection and cervical cancer) have also got a profound impact on the outcome of disease. However to think in a causal way or to put this in 'high risk' category is often debatable. This is mainly due to the fact that certain cofactors (example: age, gene-environment interactions) also play a prominent role in the occurrence of disease.

In a nutshell, we have been confined by the fact that CANCER IS NOT A SINGLE ENTITY, BUT A DISEASE OF MULTIFACTORIAL ORIGIN

Based on the available information, more than a third of the cancers occurring in our country are preventable and a similar proportion of cases are treatable through early detection (secondary prevention) which reiterates the fact that preventive programmes must have a prominent role in cancer prevention.

RISK FACTORS FOR CANCER

While discussing disease prevention, two types of risk factors have to be considered viz. modifiable and non-modifiable risk factors. Life style and environmental risk factors occupy the slot of modifiable risk factors. Individual behavioural characteristics such as ...

- Tobacco
- Poor diet
- Physical inactivity
- Alcohol use
- Infections

are those risk factors mainly considered under life style risk factors.

There is confirming evidence on the role of the above risk factors on cancer occurrence based on large population based epidemiological studies. Environmental risk factors (Example: environmental pollution, radiation) contain carcinogenic agents and here, an individual's role to prevent exposure is limited. On the other hand, age, sex, genetic inheritances are known as non modifiable (fixed) risk factors.

The best estimates to understand population based disease prevention comes from 'attributable risk' estimates which give us the possibility to understand how much risk of the disease could be averted in a population, if we get the chance to eliminate the risk factor that we are probing on. Here the estimates reported by Doll and Peto in the year 1981[4] throws light on the fact that 25- 40% of cancer related deaths (best estimate 30%) could be attributed to tobacco. In simple terms, it says that 30% of tobacco related deaths could be averted given the fact that effective policy measures to curtail tobacco use was enforced in the population, whereas more than a third of the cancer cases (best estimate 35%) was attributed to poor diet, while a smaller percentage could be attributed to occupation (4%), pollution (2%) and other risk factors. Another report also claimed of similar findings with a change in attributed risk related to poor diet, where instead of pointedly attributing the risk of 35% to diet alone, it was split upon into a combination of diet and obesity contributing 30% and sedentary life style (5%)[5]. However there are differences of opinion among public health scientists particularly environmental health scientists questioning the way of quantifying environmental health hazards that lead to a smaller proportion of risk factors

For the sake of our understanding and to convey the message in the community, the following discussion will elaborate on life style related risk factors alone.

Tobacco

Annually 8 million deaths worldwide, 1.3 million in India; contains 7000 chemicals (nicotine, tar, hydrogen cyanide, carbon monoxide...to name a few),60 are carcinogenic, second hand smoke, a reason for 1.2 million deaths globally[6]

The only legally available commercial product which kills people when it is used entirely as intended
- The Oxford Medical Companion 1994

Ever since the association between smoking and lung cancer has been proved way back in the 1950s, tobacco menace continues to pose a major threat to humanity even in the 21st century. India has the second largest number of tobacco users in the world, where 266 million (26.6 crore) people[7] aged 15 years or above use tobacco in some form or the other. It is alarming to see that this figure is comparable to the population of Indonesia which is the fourth most populated nation in the world. Overall tobacco related cancers are the leading cancers in India, though the rates have varied from one state to another. In Kerala, the prevalence of tobacco use in any form at present is 12.7%. This shows that Kerala has leaped forward in tobacco control from a reasonable high prevalence of 21.6% reported in the year 2009-10. The relatively low percentage of tobacco prevalence compared to other states in many parts of the country has happened because of the untiring efforts of various governmental and non-governmental institutions by undertaking leadership roles to propagate awareness on tobacco hazards and sensitising policy makers that resulted in steps to strengthen legislation based on the Cigarettes and Other Tobacco Products Act (COTPA), 2008. Not to forget the fact that all these efforts led to an increase in taxation of tobacco products resulted in tobacco being placed under the highest GST slab with cess attached.

Data from Population Based Cancer Registry of Thiruvananthapuram district shows that tobacco related cancers (oral cavity, lung, larynx, oropharynx, hypopharynx, oesophagus, urinary bladder, stomach, pancreas, liver, kidney, uterine cervix and myeloid leukemia) constituted for 37% of all cancers in men and 11% of all cancers in women in Kerala[8].

Needless to say, primary prevention offers the best hope to control these cancers and one of the responsibilities that could be taken care of is tobacco cessation programmes in addition to sustainable awareness programmes among school students.

As health care providers, it is our duty and responsibility to undertake tobacco cessation activities in each health centre with the collaboration of support staff to assist tobacco users quit the habit. (Appendix-1)

Diet, Body Weight, Physical Activity and Cancer

A topic gaining momentum and being discussed widely in the social media, often laced with criticism, is of particular dietary components termed as 'protective' or 'causal' misleading the general community who might accept it as a fact.

There is a strong hypothesis evolving in the community that plant foods, particularly fruits and vegetables may be protective against cancer. On one hand, there are studies that had shown the association between diet, bodyweight and cancer occurrence, but on the other side, it is notoriously difficult to quantify how a person's dietary intake influence disease occurrence and progression.

In the case of colon cancer, a biological plausibility could be derived to showcase a protective effect associated with dietary fiber/whole grain consumption. Whole grain foods may decrease the risk by increasing stool bulk, diluting faecal carcinogens, and decreasing transit time, thus reducing the contact between carcinogens and the lining of the colorectum[9]. Colorectal cancers rank fourth and fifth positions among males and females in India according to the GLOBOCAN 2018 report.

The WHO however reports that 14% of gastrointestinal cancer deaths globally were associated with insufficient intake of fruits and vegetables[10].

The mechanisms through which adulthood diet may influence cancer risk are not fully known but the possibility that it is partially mediated through bodyweight cannot be ruled out. It was estimated that 3-6% of all cancers (4,81,000 cases) that occurred in the year 2012 worldwide were attributed to high body mass index (25 kg/m^2 or greater)[11]. Within this category, the risk is more for cancers occurring in the breast 23.6% (among post menopausal women), corpus uteri(22.3%), colon (17.7%), gall bladder (6.7%), pancreas (5.6%) and others (10.7%)[12].

One of the largest cohort studies in the world conducted among half a million people from 10 European countries has shown interesting findings that would add to our knowledge on diet, nutritional status, life style and cancer. The EPIC (European Prospective Investigation into Cancer and Nutrition) study reported of small inverse association (low risk) of upper gastrointestinal tract cancers with fruit intake but not associated with vegetable intake. Similarly, in the case of colorectal cancer, total fruit and vegetables and total fibre had shown inverse association. Inverse association was also observed with liver cancer and intake of total fiber[13]. While discussing diet, the role of alcohol consumption in the occurrence of certain cancers also needs to be looked upon. Contrary to the popular belief that alcohol is more of a social problem than a health issue, clear patterns have emerged between alcohol and certain types of cancers particularly head and neck cancers, esophageal cancer, breast cancer and colo-rectal cancer. A linear dose response relationship has been shown to be a risk factor for liver cirrhosis leading to hepatocellular carcinoma. Multiple habits viz alcohol and tobacco also increases the cancer risk (Eg: head and neck cancers, esophageal cancers etc).

According to the National Family Health Survey (4), the prevalence of alcohol use in Kerala among males in the age group 15-49 years was 37%, while among females it was 1.6%[14].

Considering the increase in alcohol prevalence, stringent alcohol control policies are essential along with awareness programmes targeting adolescents and young adults to counter this problem.

Diet, physical activity and overweight -The Kerala Fact sheet

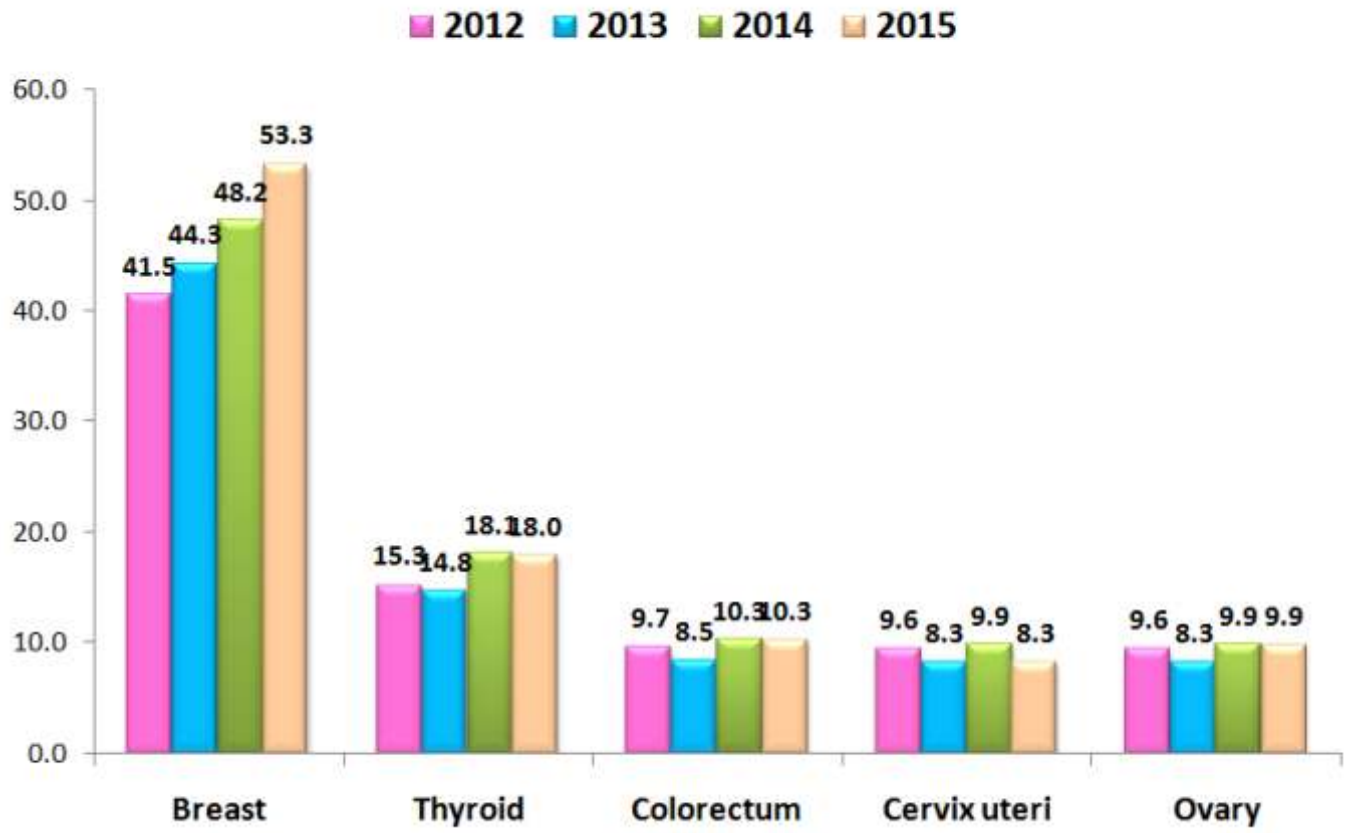
Studies have shown that globally, 35% of the adult population aged 20 years and more are overweight (BMI more than 25 kg/m^2), of which 12% classified as obese (BMI more than 30 kg/m^2)[15].

Hence, consumption of fruits and vegetables and regular physical activity has emerged as key factors for cancer prevention and control. A report on the prevention and control of Non Communicable Disease (NCD) 2016-2017 in Kerala conducted by the Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram (SCTIMST) representing all districts has come up with certain alarming findings. The average intake of vegetables and fruits among Keralites was reported to be 2.34 and 1.8 servings per day respectively which is totally inadequate for a healthy living taking into consideration the global recommendation of 5 servings per day[16]. The WHO /Food and Agricultural Organisation recommends a minimum of 400 grams of fruits and vegetables in a day excluding potatoes and starchy tubers. This could be subdivided into 5 servings of 80 gram each day[17].

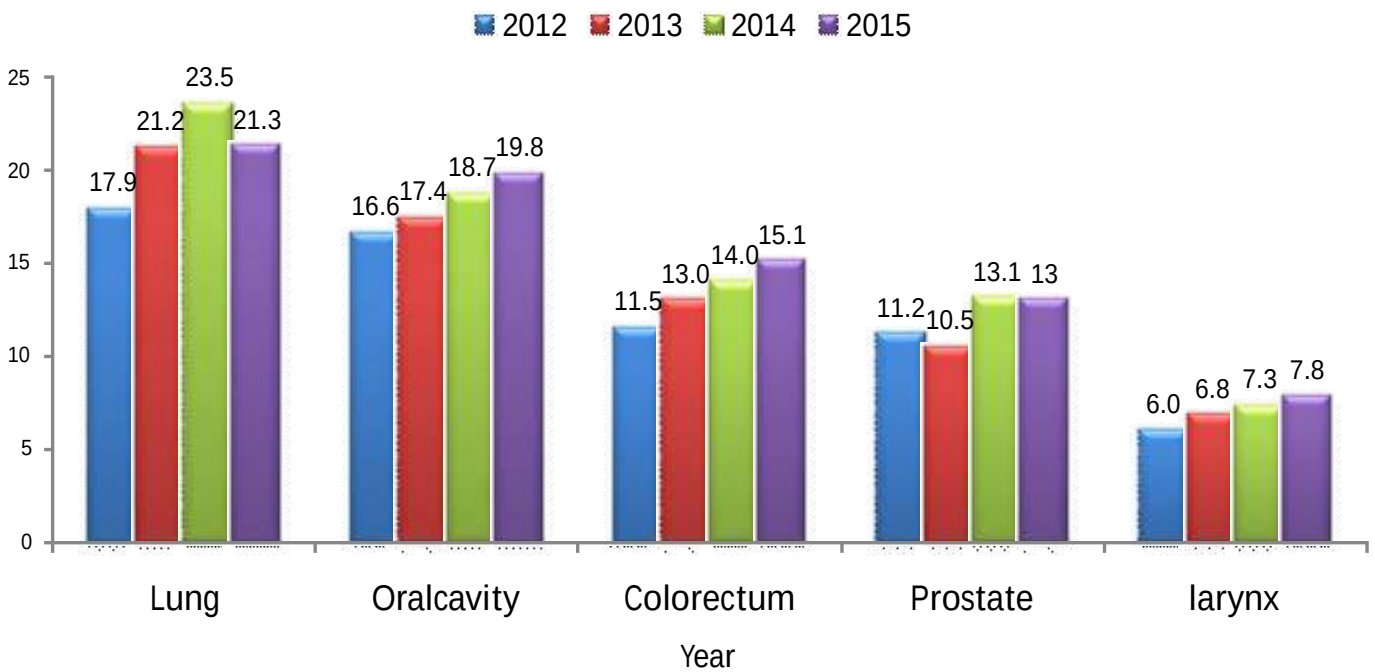
Over weight -Kerala's growing concern

The SCTIMST study also reported on the anthropometric measurements of Keralites and came with the conclusion that over a third of the study population were overweight (BMI =25 kg/m^2) while 70% of the female study participants had abdominal obesity. All the above factors could become a gateway to an increase in NCD's in the state.

Crude Incidence Rate (per 100,000) Females
(District Cancer Registry Trivandrum) (2012-2015)



Crude Incidence Rate (per 100,000) males
(District Cancer Registry Trivandrum) (2012-2015)



Physical activity and cancer risk

The potential benefits of physical activity in reducing cancer risks has been accumulating rapidly, though not for all but for some of the common cancers. Evidence on regular physical activity and reduction in cancer risk has been convincing for breast and colon cancers; probable (inadequate evidence among humans while sufficient evidence among experimental animals) for prostate cancer and possible (limited evidence among humans while less than sufficient evidence among experimental animals) for lung and endometrial cancer[18].Breast cancer risk reduction was more evident among post menopausal women with adequate physical activity[19].

The WHO recommends at least 150 minutes of moderate aerobic exercise in a week for adults aged 18-64 or at least 75 minutes of vigorous physical activity throughout a week[20].

Physical activity in Kerala

The SCTIMST report points to the fact that 22% of the respondents in the NCD study had low physical activity levels, while less than a third (29.4%) of the study population reported moderate to vigorous leisure-time physical activity. Low physical inactivity was more among urban residents and individuals with higher education. In this scenario, health care providers have got a major role to play in enhancing the physical activity of the community. To name a few, this include sensitising school authorities to promote physical education for school children, community level motivation campaigns, worksite wellness programmes, opening school playgrounds of government schools to the public outside the school hours with the support of government departments and Local Self Government etc.

To summarise, care must be taken to substantiate these findings and to say vehemently of the association between diet and cancer due to the possibility of potential confounders (another factor (s) that influence our hypothetical factor that could also influence the outcome).

For example, a person consuming high fiber could be health conscious, wherein other health behaviours like no smoking and alcohol, higher intakes of calcium or folate, higher levels of physical activity and low intake of processed meat might have complimented the outcome.

Infections and Cancers

Other than tobacco and diet, infections are the most important known risk factor for cancer. In the year 2012, more than 15% of cancers (2.2 million) worldwide are attributed to the long term consequences of infections acquired earlier in life. In this category, the common infectious agents recognised are helicobacter pylori (770,000 cases), Human Papilloma virus (640,000), hepatitis B (420,000), hepatitis C (170,000) and Epstein Barr virus (120,000)[21]

Helicobacter Pylori

Epidemiologic studies have shown that persons infected with H.Pylori have an increased risk of non-cardia gastric cancer. The risk is almost eight fold among infected people compared to those who are not infected[22]. Considering poor survival, primary prevention offers the best scope to prevent gastric cancer. Prevention strategies should include infection control, increased intake of fresh fruits and vegetables and greater responsibility for hygienic cooking environment and improved food storage.

Human papilloma virus (HPV)

Genital infection with HPV is not uncommon in women, but in most cases the infection is transient while in few, it may be in a latent state and further the infection may evolve to cancer. There are more than 100 types of HPV, of which at least 14 strains belongs to the high risk type.

More than 70% of cervical cancers and precancers are attributed to two types (16 and 18). In India, cervical cancer is the second leading cancer among women in the year 2018. Among the total cancers among women, cervical cancer accounts for 16.5% of the total cancers. In addition to cervix, HPV infection associated cancer of the vulva, penis and head and neck are also being reported.

Apart from early detection programmes, primary prevention including community education on safe sexual practices and vaccination of girls in the age group 11-12 years should be propagated to reduce cancer incidence due to HPV .

Hepatitis B and C viruses

Hepato Cellular Carcinoma is the fourth leading cause of mortality worldwide and Hepatitis B virus infection accounts for over 75% of all HCC[23]. Other known risk factors of HCC include Hepatitis C, food contaminated by aflatoxin, cirrhosis etc. The risk of developing HCC among HBV/HCV carriers is 11 times higher than for non infectious people[24]. Vaccination against HBV offers the best scope for prevention from infection. School authorities should take up vaccination as mandatory for school admissions. Awareness on HBV should be promoted considering the fact that the virus gets into the body through perinatal transmission, sexual transmission and by using contaminated needles and syringes.

Conclusion

The importance for primary prevention in a country like India is immense considering the fact that a third of the common cancers occurring in the country are preventable. The Kerala Cancer Control Strategy plan, with a vision for the year 2030, envisages the significance of augmenting cancer prevention and control measures to attain the goal of reducing cancer burden and to ensure a good quality of life for cancer patients. The State Health Service Department with its well-knit health system network, could effectively utilise its trained manpower for multimodal approaches and collaborate with various departments to achieve specific targets in primary prevention.

In this era of digitalization, primary prevention programmes could use digital platform to reach the remote areas of the state thereby enhancing people's participation in primary prevention activities.

WHO PEN Protocol 2

Health Education and Counseling on Healthy Behaviours

(to be applied to ALL)

Educate your patient to

- Take regular physical activity
- Eat a “heart healthy” diet
- Stop tobacco and avoid harmful use of alcohol
- Attend regular medical follow-up

Take regular physical activity

- Progressively increase physical activity to moderate levels (such as brisk walking); at least 150 minutes per week
- Control body weight and avoid overweight by reducing high calorie food and taking adequate physical activity

Eat a heart healthy diet

Salt (sodium chloride)

- Restrict to less than 5 grams (1 teaspoon) per day
- Reduce salt when cooking, limit processed and fast foods

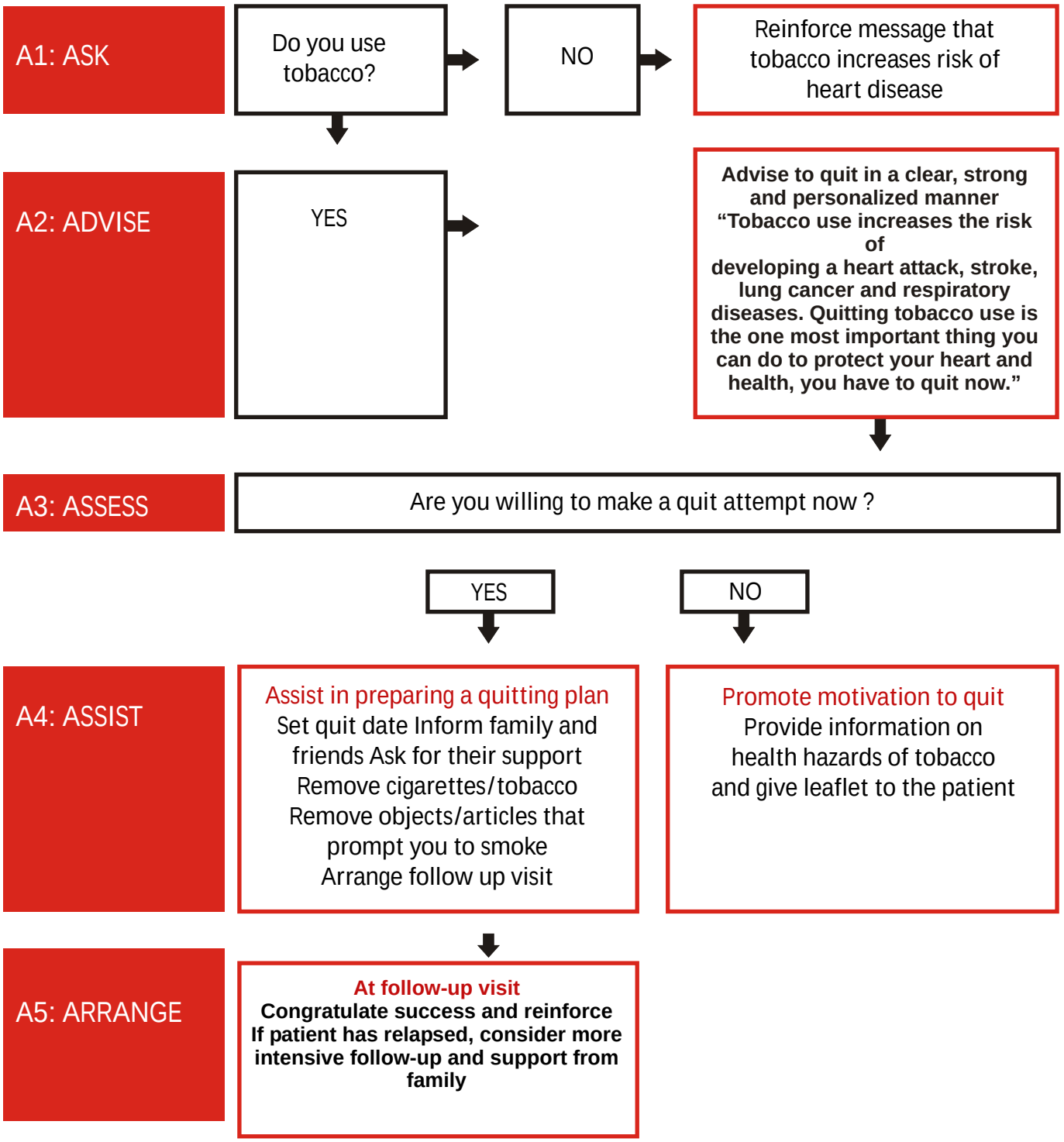
Fruits and vegetables

- 5 servings (400-500 grams) of fruits and vegetable per day
- 1 serving is equivalent to 1 orange, apple, mango, banana or 3 tablespoons of cooked vegetables

Fatty food

- Limit fatty meat, dairy fat and cooking oil (less than two tablespoons per day)
- Replace palm and coconut oil with olive, soya, corn, rapeseed or safflower oil
- Replace other meat with chicken (without skin)

5 A's for Tobacco Cessation



Source:Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings
Available at https://www.who.int/ncds/management/Protocol2_Health_education_and_counseling.pdf?ua=1
Reprinted with permission from the World Health Organisation .

Further Reference, please refer : Manual for tobacco cessation .
Available at : http://www.searo.who.int/india/topics/tobacco/Tobacco_Free_Initiative_Manual_for_Tobacco_ Cessation.pdf

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Oral Precancers - Diagnosis and Management

Dr. Gigi Thomas
Additional Professor and Head, Community Oncology Division
Regional Cancer Centre, Thiruvananthapuram

Oral Cancer is generally preceded by some benign lesions or conditions for a varying length of time. These lesions or conditions share the same etiologic factors with oral cancer, particularly the use of tobacco and exhibit the same site and habit relationship. Some of these lesions show a high potential to become cancers and are called "precancerous". The main purpose of identifying precancers is to prevent the subsequent possibility of a malignant transformation by initiating adequate treatment. Hence early detection and treatment of oral cancers will prevent progression on to oral carcinoma, thus reducing patient mortality.

The World Health Organization has accepted the classification of precancers into precancerous lesions and precancerous conditions.[1]

Precancerous Lesions

A precancerous lesion is defined as a morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart.

The common precancerous lesions are

1. Leukoplakia
2. Erythroplakia
3. Stomatitis Nicotina or Smoker's Palate
4. Chronic Traumatic Ulcer
5. Bowen's disease
6. Actinic Keratosis

Precancerous Conditions

A precancerous condition is defined as a generalized state or condition associated with significantly increased risk for cancer development. This indicates that a neoplasm can arise in any part of the oral cavity.

The common oral precancerous conditions are

1. Oral Sub mucous Fibrosis (OSF)
2. Erosive Lichen Planus
3. Sideropenic dysphagia
4. Xeroderma Pigmentosum
5. Syphilitic Glossitis
6. Discoid Lupus Erythematosus
7. Dyskeratosis Congenita

Precancerous Lesions

1.Leukoplakia

The term leukoplakia was first used in 1877 by Schwimmer and it originates from two Greek words leuko, i.e white and plakia, i.e. patch. The W.H.O definition of leukoplakia is a whitish patch or plaque that cannot be characterized, clinically or pathologically, as any other disease and which is not associated with any other physical or chemical causative agent except the use of tobacco. This is the most common lesion representing about 85% of premalignant lesions[2,3]. Leukoplakia has been subtyped according to clinical description into homogenous (low risk variety) and non-homogenous lesions(high risk variety).

Homogenous leukoplakia

Homogenous leukoplakia right buccal mucosa

Homogenous leukoplakia is a localized lesion or extensive white patch with a consistent texture throughout. It is the commonest type of leukoplakia and is usually seen in healthy and younger individuals. In a community based cluster randomized oral cancer screening study in Trivandrum, Kerala, (TOCS study), they account for 41% of precancerous lesions[4]. The surface of the lesion may be described variously as

1.Flat-having a smooth surface

2.Corrugated- like a beach at ebbing tide.It is usually seen in leukoplakia that occur in the floor of the mouth due to the loose binding and consequent movement of the mucosa in the floor of mouth.

3.Pumice like with a pattern of fine lines or cristae.

4.Wrinkled having a dry, cracked mud surface.

Non Homogenous Leukoplakia

It is a predominantly white or white and red lesion that may be irregularly flat, nodular or exophytic.

It can be classified clinically into :

a.Ulcerated leukoplakia

b.Nodular or Speckled Leukoplakia

c.Verrucous leukoplakia

a.Ulcerated leukoplakia

Ulcerated leukoplakia is characterized by red area at the center with white patches at the periphery. Sometimes the red areas may exhibit yellowish areas of fibrin giving the appearance of ulceration.In chronic bidi and cigarette smokers, ulcerated leukoplakia can be commonly seen occurring bilaterally in the commissures with varying degrees of pigmentation at the periphery of the lesion. These lesions are usually seen to regress following cessation of habits. Ulcerated leukoplakia accounted to 27% in the TOCS study.

Ulcerated leukoplakia right buccal mucosa

b.Nodular or Speckled Leukoplakia

Nodular or Speckled Leukoplakia is characterized by small white specks or nodules on an erythematous base. The nodules may be very fine (speckled), pin head sized or even larger. The margins of the lesion may not be well defined. The speckled appearance may be due to the candidial growth on the epithelial surface.

Nodular leukoplakia are almost always associated with candidial infection. This type of lesion is of special importance because of its extremely high rate of malignant transformation.It accounted to 3% in the TOCS study.

c.Verrucous leukoplakia

Verrucous leukoplakia usually appear as well circumscribed exophytic lesions in which the mucosal surface is broken up by multiple raised finger like or papillary projections that is heavily keratinised. They are usually slow growing and persistent.

Verrucous leukoplakia dorsum tongue in a patient with oral submucous fibrosis

In course of time, an erythematous component may develop in the lesion. Later, it can transform into a lesion that clinically and histopathologically resembles verrucous carcinoma. In the TOCS study, verrucous leukoplakia accounted for 2%.Extensive lesions of verrucous leukoplakia are called 'Oral Florid Papillomatosis'.

Verrucous carcinoma dorsum tongue

Two or more different clinical types of leukoplakia can be present in the oral cavity of the same person. It is desirable to take a baseline biopsy from all the leukoplakia that do not show signs of regression even three weeks after complete elimination of etiological factors. A repeat biopsy is indicated at the earliest clinical indication of malignant transformation or after a period of six months if there is no clinical improvement of leukoplakia.

In mixed red and white patches, the biopsy should be taken from the erythematous areas. Biopsy should always be taken from the areas that exhibit greater surface irregularities such as cracks, granular areas or deep fissures. A leukoplakia is suspected to undergo malignant transformation when an exophytic growth, ulcer, granular area or deep fissure develops in it. In the TOCS study, the rate of malignant transformation was highest for nodular leukoplakia (21.7%), followed by verrucous leukoplakia (20%), ulcerated leukoplakia (5.5%) and it was 2% for homogenous leukoplakia over a follow up period of 10 years.

Leukoplakia with malignant transformation left lateral margin of the tongue

Management of leukoplakia

The management of leukoplakia can be based on the information obtained from microscopic examination of leukoplakia. The epithelial dysplasia is subdivided into mild, moderate and severe which is assumed to correlate with the risk of malignant transformation. Till date, there are no specific molecular markers that predict malignant transformation in oral precancers.

Hence microscopic evaluation of leukoplakia is the most accurate predictor of malignant transformation. The first step in the management of leukoplakia is elimination of local irritants such as betel quid chewing, smoking and alcohol. Nodular leukoplakia is almost always associated with candidial infection. Hence antifungal treatment must be given.

It can be administered as topical application of 1% Clotrimazole mouth paint or Hamycin oral suspension three times daily for a period of 2-3weeks. In severe cases, systemic treatment can be given in the form of 200 mg of Fluconazole stat followed by 100-150 mg of Fluconazole daily for two weeks.

The two main modalities of management of leukoplakia are medical and surgical management. Since usually leukoplakia presents as diffuse lesions with multiple sites of involvement, the usual treatment protocol is medical or conservative management using chemoprevention so as to reduce the size of the lesion. When the lesions become smaller and excisable, they can be subjected to surgical excision. The commonly used chemopreventive agents in leukoplakia are Vitamin A and related compounds which include retinoids and carotenoids, Vitamin E, Selenium, N-Acetyl Cysteine, naturally occurring algae such as Spirulina fusiformis and Dunaliella and combination of micronutrients. The usual dose of Vitamin A is 200,000 IU once weekly for six months and a maintenance dose of 50,000 IU should be given once weekly for one year. Even though systemic administration of Vitamin A causes regression of leukoplakia, recurrence after discontinuation of treatment is the most important disadvantage.

Topical chemotherapy using topical application of anticancer chemotherapeutic agents such as Bleomycin and human fibroblast interferon has been used with success in limited cases. A combined parenteral and locally applied treatment modality in the form of Photo Dynamic Therapy (PDT) using haematoporphyrins is also found to be effective in the treatment of leukoplakia.

The standard surgical treatment for leukoplakia includes surgical excision, laser ablation or cryosurgery. Surgical excision is indicated in lesions which are localized and accessible.

Laser excision is commonly used in the treatment of leukoplakia in the Western countries. Laser surgery allows precision of tissue removal and mucosa can be removed easily and thoroughly to a constant depth. Since there is minimal instrumentation, very little damage is caused to the adjacent tissues. Thereby, it reduces tissue scarring, wound contracture and concomitant interference with function of intra oral structures. Laser surgery offers the advantage of better visibility and an essentially bloodless operative field due to its immediate hemostatic effect by sealing small blood vessels. But due to the high cost of the equipment, the facilities of laser surgery are not freely available in India. Currently, cryosurgery is not used in the management of leukoplakia due to several disadvantages such as inaccurate margins of destruction, absence of a histological specimen, high recurrence rate and marked pain and post-operative oedema due to damage to adjacent tissue.

Till date, there is no consensus on the most appropriate management of leukoplakia. Irrespective of the management procedure, recurrence or malignant transformation of leukoplakia is observed. Hence it is mandatory that all leukoplakia should be kept on follow-up. Usually, leukoplakia with mild or no dysplasia should be followed up once in six months. Surgical excision is desirable in leukoplakia with moderate and severe dysplasia but if it is not feasible due to the diffuse nature, they should be kept on close follow up ranging from one to three months based on the individual case.

2. Erythroplakia

Erythroplakia is used to denote lesions which appear as bright red velvety patches or plaques which cannot be characterized clinically or pathologically as any other condition. Reddish colour results from the absence of surface keratin layer.

It is also due to the presence of connective tissue papilla containing enlarged capillaries extending very high in to the epithelium and epithelium over the connective tissue papilla is very thin.

Various studies have demonstrated that 80-90% of erythroplakia on histopathological examination are either severe epithelial dysplasia, carcinoma in situ or invasive carcinoma and hence it is rated as a very high risk lesion. In the TOCS study about 4.3% of the lesions were erythroplakia and the risk of malignant transformation was 8.6%.

Management:

Treatment of erythroplakia is similar to leukoplakia but it should be treated promptly as they have much higher degree of malignant potential than leukoplakia.Early detection of occult malignancy is important. In view of the high malignant potential of these lesions, the recommended treatment is surgical excision. Even after surgical excision, long term follow-up is essential as there are chances for recurrence.

3. Smoker's Palate or Stomatitis Nicotina

Palatal changes are seen in people who smoke with the lighted end of tobacco product inside the mouth known as reverse smoking and also in heavy cigarette and bidi smokers. It is most common in males and there is redness and inflammation of the palate. The changes usually seen are palatal keratosis, excrescences, white patches, red areas, ulcerations and hyperpigmentation. Over 90% of oral cancers are seen in the palate in reverse smokers.

Management:-

Palatal changes can remain stationary, regress, recur or progress to carcinoma of the palate. Hence, all palatal patches, red areas and ulcerations should be promptly biopsied. If they show moderate or severe dysplasia, they must be managed accordingly. All patients must be educated to discontinue their tobacco use as discontinuation will lead to higher regression of palatal changes.

4. Chronic Traumatic Ulcer

Traumatic ulcer refers to an ulcerated area in the oral cavity that is clearly related to an identifiable local irritant and that resolves following elimination of the irritant.

They are usually found in association with sharp broken teeth, rough edges on dentures and clasps of removable partial dentures. Traumatic ulcers that are of long duration can predispose to oral cancer. Next to tobacco, chronic trauma is the most important cause of oral cancer.

Management:-

Traumatic ulcers are usually found in association with identifiable, locally acting irritants. The irritating factor should be removed immediately and the lesion should be re-evaluated after two weeks. The majority of traumatic ulcer will either be reduced in size or completely disappear. During the review, any lesion that persists should be biopsied immediately. If there is a strong clinical suspicion of malignant transformation at the first visit such as induration on palpation, biopsy of the lesion should be done immediately along with removal of the local irritant to avoid delay in treatment.

5.Bowen's disease

It is a localized 'intraepidermoid carcinoma' that may progress to invasive carcinoma over many years. It is characterized by progressive scaly or crusted plaque like lesion and is seen in individuals with chronic exposure to the sun or by Arsenic ingestion either by accident or as part of treatment in alternative medicine.

Management:-

Surgical excision of the entire lesion is the treatment modality of choice. Treatment has been tried with diathermy, cauterization, radiotherapy and application of cytotoxic drugs.

6.Actinic Keratosis

Actinic keratosis is clinically characterized by ulcerative, crust forming lesions on the labial mucosa along the vermillion border of the lip. Histological examination usually exhibits hyperkeratosis with or without epithelial dysplasia.

Keratin may be accumulated and forms surface plaque.The underlying connective tissue usually shows basophilic degeneration of collagen and elastosis . Squamous cell carcinoma may occur in untreated cases. The diagnosis is confirmed by biopsy.

Management:

Localised lesions are easily treated with electrosurgery. Extensive lesions require vermilionectomy. Avoiding further exposure to the sun and close follow-up is recommended.

Precancerous conditions

1.Oral Submucous Fibrosis

Oral Submucous Fibrosis(OSF) is a generalized pathological state of the oral mucosa. It takes the form of an insidious, chronic disease in which the oral mucosa becomes stiff due to fibroelastic transformation of the juxtaepithelial layer. This leads to progressive inability to open the mouth, difficulty in protruding the tongue, as well as difficulty in eating, swallowing and phonation. The condition can be diagnosed by palpating the fibrous bands in the buccal mucosa. There is atrophy of the papillae of the tongue and the patient has severe burning sensation especially while eating spicy food. Malignant transformation is characterized by development of exophytic growth, ulceration or granular areas from the atrophic epithelium. Due to the field cancerisation effect, multiple independent cancers can develop simultaneously over a period of time. Arecanut chewing either alone or as an ingredient in the betel quid and the use of pan masala are risk factors for OSF. Oral Submucous Fibrosis accounted for 18.6% of the premalignancies in the TOCS study and 13% of the patients developed malignant transformation over a follow up period of 10 years.

Management:

All patients with Oral Submucous Fibrosis must be biopsied especially if there are granular, ulcerative areas or leukoplakic patches. The biopsy must include those areas, which are clinically suspicious for malignancy.

Oral sub mucous fibrosis with malignancy on dorsum tongue

The cases which histologically reveal a carcinoma or severe dysplasia should be treated along the lines of management of carcinoma and dysplasia. The treatment of patients with Oral Submucous Fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is effective. However, it is often irreversible in Oral Submucous Fibrosis patients who present with severe disease. Several therapeutic and surgical methods have been tried in the management of Oral Submucous Fibrosis. Ideally, following treatment, the oral mucosa should reverse to normal and there should be a reduction in the risk for oral cancer. However, no such definitive and widely accepted treatment is currently available for this condition. Some temporary relief from the symptoms and improvement in mouth opening has been observed with certain modalities of treatment. In view of the lack of availability of curative treatment and the precancerous nature of the disease, it is essential to follow up the patients regularly. Furthermore, they must be educated to discontinue the use of arecanut and tobacco in any form with the aim of preventing further progress of the disease and reducing the risk of oral cancer.

The various treatment regimens employed in the management of Oral Submucous Fibrosis are:

Local drug delivery:

Local injections of a variety of drugs such as Triamcinolone acetonide, Hydrocortisone, enzymes such as hyaluronidase and collagenase were tried in the past and have shown improvement in symptoms.

Placental extracts (aqueous solution of human placenta) in the form of local injections have been tried with good results[5]. The usual dosage is 2 ml of Placentrex given as submucous infiltration at multiple sites around the fibrotic bands on both buccal mucosa, bi-weekly for 10 weeks. It was found that Placentrex, in addition to being cheap, did not have any side effects and the effect was found to be long lasting.

Combined therapy:

Significant results were achieved when Nylidrin Hydrochloride, a peripheral vasodilator was supplemented with vitamins A,E,B-complex, Iodine, Placentral extract, local and systemic corticosteroids and physiotherapy[6]. Topical application of 5-Flurouracil, local injections of Placentrex and intra-muscular injections of Ranidone (Iodine-B-complex preparation) was found to produce favourable results[7]. Singh etal[8] obtained remarkable results with a combination of local injections of Placentrex, vitamin C and deep intramuscular injection of whole liver extract. There was marked symptomatic improvement and no signs of relapse were reported two and a half years following treatment.

Surgical management:

Very early workers had reported that surgical measures in Oral Submucous Fibrosis such as forcing the mouth open and cutting the fibrotic bands under anaesthesia resulted in more fibrosis and disability[9]. The only effective surgical procedure is that of split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy.

Relapse is a common complication that occurs after surgical release of the oral trismus caused by Submucous Fibrosis.

Hence a treatment approach that combined surgery with an oral stent to improve the jaw opening was found necessary to prevent relapse. The principle of the oral stent is to prevent scar tissue contracture. The oral stent has to be worn for a prolonged period post-surgically, once the jaws have been stretched, to allow the tissue to heal at the new increased opening position and to prevent relapse.

Nutritional support:

A combination of micronutrients namely Vitamins A, B-complex, C, D and E and minerals such as Calcium, Copper, Zinc and Magnesium were found to produce a beneficial clinical response.

Physiotherapy:

Various methods of physiotherapy have been used in the treatment of Oral Submucous Fibrosis. The use of microwave diathermy was found to be of much value for early and moderately advanced stages of Oral Submucous Fibrosis but poor in advanced cases[10]. Heat therapy in the form of hot rinses and lukewarm water or selective heating therapies like short wave diathermy was found to have a satisfactory effect. It was found that daily mouthy opening exercises along with lukewarm water gargle was useful in managing Oral Submucous Fibrosis in early and advanced stages of progression[11].

2.Lichen Planus

Lichen Planus is a chronic auto immune mucocutaneous disease, which can affect the oral mucosa, skin, genital mucosa, scalp and nails. Oral lesions often occur in the absence of skin lesions. The disease is more often seen among middle aged people, especially females. Clinically, the lesions appear as pearly, polygonal papules with peripheral fine, milky white ,lace-like reticular pattern which are termed as Wickham's striae. They usually appear bilaterally unlike leukoplakia and are often superimposed with candidial infection. Clinical variants of Lichen Planus are :

a)Reticular Lichen Planus
b)Erosive Lichen Planus
c)Papular or Bullous Lichen Planus
d)Plaque-like Lichen Planus

Lichen planus - right buccal mucosa

Management:

Partial resolution of the lesion can be obtained with topical application of an antifungal agent for three weeks as Candida can be present as an opportunistic agent. Generally, lichen planus is asymptomatic However, the erosive forms can cause symptoms ranging from a burning sensation to severe pain, and require treatment. Maintenance of good oral hygiene, and removal of factors which exacerbate these lesions can enhance healing and lessen symptoms. Topical Isotretinoin gel and Tretinoin ointment are useful in the resolution of the lesion, but withdrawal of the medication leads to recurrence of the lesion. Topical Tacrolimus and Cyclosporin have also been tried in the treatment of lichen planus with variable success. Symptomatic treatment of oral lesions can be achieved by topical analgesics and topical corticosteroids to encourage healing of ulcerated areas.Two or three weekly intralesional injections of Triamcinolone acetonide are useful in healing non responsive and extensively eroded areas of mucosa. Even though several interventions have been tried, with varying success rates , a permanent cure is not yet possible for Lichen Planus.[12]

There is considerable controversy regarding the malignant potential of Lichen Planus. Several studies have shown the malignant potential of Lichen Planus, ranging from 0.4 to 3.7%,however, the highest rate is seen in erosive and bullous variants.

3.Sideropenic Dysphagia

Sideropenic Dysphagia (Paterson- Kelly or Plummer- Vinson's Syndrome) affects middle- aged women with iron deficiency being the underlying cause.The oral and oropharyngeal mucosa appear shiny ,red and atrophic. Leukoplakia and multiple cancer may develop in the oral and oropharyngeal mucosa due to the epithelial atrophy seen among such patients.

4.Xeroderma Pigmentosum

Xeroderma Pigmentosum is a genetically inherited skin condition in which there is a defect at the subcellular level in the DNA repair mechanisms. The entire skin shows an abundance of pigmentation and the skin gets easily affected with melanoma and squamous cell carcinoma. The skin including the lips is affected, showing epithelial atrophy and hyperpigmentation. These patients are extremely sensitive to light and show an increased predisposition to UV- associated malignancies of the skin. Carcinoma of the tongue has also been reported. The diagnosis of Xeroderma Pigmentosum is established by biopsy. Use of sunscreen and avoidance of sun exposure are recommended. Oral retinoids have shown some benefit in the prevention of neoplasm in patients with Xeroderma Pigmentosum.

Discoid Lupus Erythematosus and Dyskeratois Congenita are both rare conditions which once diagnosed requires close follow up for early detection of malignant transformation.

The management of Sideropenic dysphagia, Discoid Lupus Erythematosus and Dyskeratosis Congenita are not discussed due to the rarity of the condition.

There is no definitive and widely accepted treatment for oral precancers. Whatever be the method of management employed, the oral precancer should be kept under close follow up and if it has shown any evidence of malignant transformation, it must be managed promptly along the lines of management of carcinoma.

More than 90% of oral cancer occurs in people with specific life style risks namely smokers, alcohol abusers and betel nut chewers. People belonging to this high risk group can be identified and programmes for screening, preventive treatment and selective education are being conducted with the aim of downstaging this disease.

Therefore, public education and training of general practitioners and dentists for early detection, management and close follow up of oral precancer is very important.

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Radiotherapy in Head and Neck Cancers

Dr. Ramadas K
Professor and head , Division of Radiation Oncology
Regional Cancer Centre, Thiruvananthapuram

DEFINITION

Radiotherapy or Radiation Therapy is the treatment of diseases using ionizing radiation. Ionizing radiation is used for both therapeutic and diagnostic purposes. For therapy, high-energy radiation in mega-voltage range is preferred whereas for diagnosis, Kilo voltage energy is used.

Methods of delivery of radiotherapy

Based on the method of delivery radiotherapy treatment is classified into teletherapy, brachytherapy and internal therapy.

BRACHYTHERAPY

The term brachytherapy was first proposed by Dr .G. Forsell in 1931.It is derived from the Greek word brachio, meaning short and refers to treatment with a radioisotope at a short distance less than 5cm from a tumour. Interest in brachytherapy remained low due to the radiation exposure to operating staff. The development of safe after loading technique especially the high dose rate remote after loading methods has given renewed interest in this field. The advantage of brachytherapy is that it is a highly localized form of treatment causing minimal and excellent tumour control. Short treatment time is another advantage of this technique. The disadvantage is that it can be used only in selected cases especially in early stage disease at accessible site.

It requires anesthesia and excellent expertise. This is an invasive procedure.

Brachytherapy may be used either alone or in combination with external beam radiation and /or surgery. The radioactive sources used for bachytherapy come in the form of small seeds, needles or wires. The dose of radiation and length of time prescribed will depend on the tumour size, location, and sensitivity to radiation. Generally a dose of 65 Gy over 6-7 days is given when it is used as the sole treatment..

Depending upon the loading , brachytherapy is classified into preload and afterload techniques. In preload technique , radioactive isotope is directly handled by the staff and all staff members involved in the procedure get radiation whereas in afterload technique first metal or plastic tubes are inserted into the tumour and these tubes are later loaded with radioactive source.This can be done manually or with the help of machine (remote after loading techniques). In remote after loading technique the radiation hazard to the personnel involved is almost nil.

EXTERNAL BEAM THERAPY (TELETHERAPY)

Radiation given using machines kept at a distance away from the patient. Based on the energy this is subdivided into:

Superficial Therapy

Superficial voltage machine generate X-rays 30-125 KV. This is used to treat superficial tumors like skin cancer.

Orthovoltage Therapy (Kilovoltage)

Orthovoltage machines produce medium energy X-rays in the range of 200-300 KV. Primarily used to treat superficially situated tumors. In this situation skin dose is high and cannot be used to treat deep seated tumors.

Megavoltage Therapy

Megavoltage machines such as telecobalt and linear acceleraters generate radiations having energy above one megavoltage. These machines are used to treat deeply situated tumors delivering lesser dose to the overlying skin.

TelecobaltTeletherapy (Co^{60})

In telecobalt machine radioactive isotope *(Co^{60})* which emit gamma rays having an average energy of 1.25 MeV is used.

Linear Accelerator

These are the most commonly used radiotherapy machines. This does not contain a continuously emitting radioactive isotope. In this machine, electrons are generated, accelerated and made to strike a target to produce high voltage X rays. The advantage of this machine is that both X rays and electrons can be utilised for treatment. Electrons are commonly used to treat superficial tumors without damaging underlying critical structures.

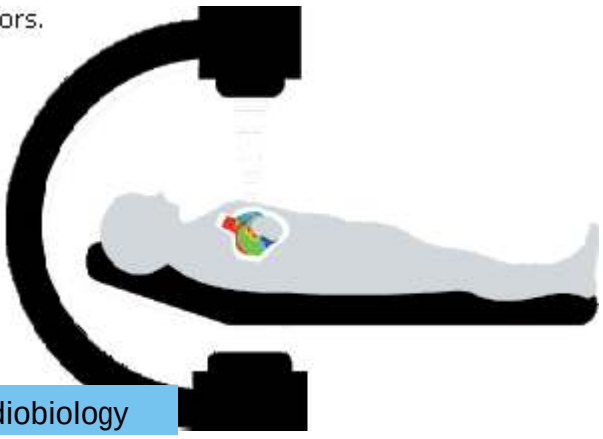
INTERNAL THERAPY

Radioisotope is either injected or taken as a drink to treat tumors. For example: Radioactive iodine (I^{131}) in the treatment of thyroid cancer.

Phosphorus -32 in the treatment of polycythemia vera.

PRINCIPLES OF RADIOTHERAPY (RT)

Radiotherapy is based on the basic principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cell. This differential cell kill is used for the treatment of tumors.



Radiobiology

Ionizing radiation when passes through the tissue of a patient affects the biology of both normal and tumor tissues. This radiation causes both direct and indirect effects on biologic targets. The DNA of a cell may be directly affected by the secondary electrons generated as ionizing radiation interacts with tissue. The radiation may also have an indirect effect due to the formation of free radicals; these free radicals in turn cause most of the chemical damage to the DNA. In addition, there are number of other cellular functions that are disrupted by radiation induced damage. This damage is modified by oxygen concentration, temperature and other intracellular components.

Goal of radiotherapy is to sterilize tumor and to preserve adjacent normal tissue. Ionizing radiation deposits energy that injures or destroys cells by damaging their genetic material, making it impossible for these cells to continue to grow[1]

Response of cells to radiation depends upon several factors such as radiation quality, dose rate, dose fractionation, oxygen concentration, phase in the cell cycle, presence of chemical protectors and sensitizers, recovery and repair process. Presence of oxygen is among the best known sensitizer of radiation damage. Cells in S-phase generally are more radio resistant as compared to cells in G2 and M phases.

PHYSICAL CONCEPTS IN RADIATION ONCOLOGY

Ionizing radiation used to treat cancers is divided into electromagnetic radiation and particle radiation. Electromagnetic radiation is the predominant therapeutic modality for radiation therapy. The electromagnetic spectrum ranges from low energy to higher energy. This includes megavoltage radiations such as gamma rays and megavoltage X-rays. Particle radiations include electrons, neutrons and protons.

X-rays (Linear accelerator) and gamma rays (Telecobalt machine) are essentially the same type of electromagnetic radiation (photon). They differ in the ways they are produced. X-ray are produced by manmade devices by introducing a target material along the pathway of fast moving electrons. Gamma rays are emitted from a radioactive isotope as part of the process of naturally occurring radioactive decay. RT with particle radiation differs from photon radiotherapy in that it involves the use of fast-moving subatomic particles to treat localized cancers. Most particles (neutrons, protons etc) deposit more energy while passing through tissues, thus causing more damage to the cells they hit. Recent advance in radiotherapy research is the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Tumor-specific antibodies against tumour antigens labeled with radioactive isotopes (radiolabeling) are injected into the body, which actively seek out the cancer cells and destroy them by the cytotoxic action of the radiation. This approach can minimize the risk of radiation damage to healthy cells.

Dose of Radiotherapy.

The radiation dosage is determined by:
i.Tumour site
ii.Size of the lesion
iii.Volume to be irradiated (Target volume)
iv.No of fractions of treatment
v.Various techniques of delivery of Radiotherapy
vi.Tolerance of various structures
Vii.Associated medical conditions like diabetes, collagen disorders etc

A dose of 66-70 Gy over 7 weeks is required for control of gross tumour. The initial dose is usually 50Gy to the primary lesion and the regional nodes using a wide field technique followed by boost dose upto 66-70 Gy using smaller volume covering gross disease. Spinal cord is shielded after 45 Gy.

FRACTIONATION IN RADIOTHERAPY[2]

Fractionation is a term used to describe the manner in which daily dose of radiation is given. Fractionation of the total dose of radiation helps in minimizing normal tissue reaction. The clinical effects of fractionated radiotherapy are influenced by the ability to repair sublethal damage, reoxygenation of tumour during the course of radiation, repopulation of tumour and normal tissues between fractions and redistribution of cells into a more sensitive phase in cell cycle treatment. (The 4 R's of radiobiology).

CONVENTIONAL FRACTIONATION

Conventional fractionation is the application of daily doses of 180-200 cGy and 5 fractions per week to a total dose of 40-70 Gy depending upon the type of tumor.

HYPERFRACTIONATION

Two or more fractions per day of reduced dose (115-120 cGy) with overall treatment time similar to that of conventional fractionation. Hyperfractionation helps in increasing the total dose without increasing the late reactions.

ACCELERATED FRACTIONATION

Accelerated fractionation is a means of decreasing the overall duration of treatment in an effort to reduce the repopulation of tumour cells in rapidly proliferating cancers. Repopulation (tumour cell regeneration)occur during treatment when the overall duration of treatment is inceased. Shortening of overall treatment time can increase the tumour control in selected situation.

ACCELERATED HYPERFRACTIONATION

Delivering two or more fractions per day of normal dose per fraction helps in reducing overall treatment time without increasing the risk of late complication.

CONCOMITANT-BOOST TECHNIQUE

A variant of accelerated fractionation is the concomitant boost technique. With this technique, treatment is delivered once daily for the first 3.5 weeks and then twice daily during the final 2 to 2.5 weeks, when tumour cells can begin to repopulate more rapidly.

HYPOFRACTIONATION

Here less than four fractions per week with higher dose per fraction than conventional is planned. In selected situations this is found to be useful especially in the treatment of melanomas.

SPLIT COURSE THERAPY

Radiation is given in small courses with a rest period in between.

SIDE EFFECTS OF RADIATION IN HEAD AND NECK CANCER PATIENTS

Radiotherapy side effects are classified into acute and late.

ACUTE REACTION

Acute reaction occurs during and immediately after treatment upto 6 weeks. Acute effects are related to dose per treatment, total dose, volume of tissue irradiated and the site. These reactions are limited to the area irradiated and not seen outside the treatment volume. This is mainly due to the inflammation of the tissues during treatment. Symptoms include xerostomia, pain in the mouth and throat, skin reactions and falling of hair within the treatment volume may occur. The mucous membrane with in the irradiated area gets inflamed leading to patchy ulceration. During therapy salivary secretion decreases and it become thicker and forms a coating over the tongue. This cause change in the pH of the saliva, which can lead to changes in the bacteria flora.

During radiotherapy there will be alteration of taste.

These acute reactions are self limiting and usually subsides in 2-3 weeks following completion of radiotherapy. There can be superadded bacterial and fungal infections. This is managed by antibiotic, antifungal and analgesics. During therapy , patients are advised to take high calorie non-spicy bland food. Frequent use of soda bicarbonate and saline mouthwash is advisable. They should not use very hot and very cold food during treatment. During treatment,patient should avoid application of creams and oils and rubbing of the skin with rough clothes should be avoided.

LATE REACTION

This is the dose limiting toxicity and usually occurs months or years after treatment. This depends upon the dose per fraction, total dose and volume of tissue irradiated. This includes dryness of mouth, intolerance to spicy food, hair loss and oedema of the skin with in the irradiated area. Necrosis, fistula formation, non-healing ulceration and osteonecrosis are rare. However modern radiotherapy delivery is very precise and accurate and damage to critical structures are extremely rare.

ADVANTAGES OF RADIOTHERAPY

· No tissue or functional loss

· Good cosmetic outcome compared to surgery Control of subclinical disease in the regional nodes is possible without added morbidity

· Can simultaneously treat multiple primaries.

· Better surgical salvage of radiotherapy failures than radiotherapy salvage of surgical failures.

· Rare treatment related mortality

DISADVANTAGES OF RADIOTHERAPY

· Undesirable acute side effects such as painful mucositis, loss of taste, dryness of mouth etc.

· Potential late complications of soft tissues and bone

· Protracted treatment course

· Requires good infrastructure

· Rare possibility of development of second malignancy

MANAGEMENT OF ORAL CANCER

Oral cancer is a malignant disease that spreads to the locoregional areas via infiltration and lymphatic spread. Most patients with oral cancer die due to uncontrolled disease.Hence locoregional control of disease is very important. Local forms of treatment like surgery and radiotherapy play an important role in the management of these tumours

Early stages (I and II) are managed by surgery or radiotherapy, which give almost equal results. The management of the neck depends on the chance of having occult disease in the regional nodes. Advanced stages are managed by combined modality of treatment involving surgery and radiotherapy. Chemotherapy is increasingly being used along with radiotherapy for organ preservation and avoiding surgery, but without compromising on survival. Chemotherapy alone is sub-optimal and should never be resorted to for curative treatment of head and neck cancers. It is considered mainly for palliation of symptoms in advanced incurable tumours.

Radiation therapy for oral cancers can be external beam therapy or interstitial therapy. Small superficial tumours can be treated with local interstitial brachytherapy alone.

Larger tumours are generally managed with external beam radiotherapy to cover primary tumours along with regional nodes, even if they are not clinically involved. Interstitial treatment can be used as a boost to a large primary lesion or bulky node for better loco regional control.

Early superficial lesions of the oral cavity can be managed by wide excision. If regional nodes are involved, or if the chance of having occult nodal disease is high (thick infiltrating lesions of tongue or floor of mouth), cervical node dissection is carried out in continuity with primary resection. The need for post-operative radiotherapy is based on the histopathological evaluation of the resected specimen.

Large tumours require proper reconstructive methods and prosthodontic rehabilitation to ensure the best possible quality of life. Both modalities, surgery or radiotherapy, produce 70-90% cure rates in early lesions with no regional lymphnode involvement.

FACTORS INFLUENCING TREATMENT SELECTION

The choice of treatment depends on factors such as cell type or degree of differentiation, site and extent of the primary lesions, gross characteristics of the tumour (exophytic, superficial vs endophytic, infiltrative), involvement of bone and muscle, metastatic nodal status, likelihood of complete surgical resection, possibility of preservation of speech or swallowing mechanisms, age of the patient, social status and occupation of the patient, associated comorbidities, experience and skill of both the surgeon and the radiation oncologist and infrastructure. The most important factor in treatment selection is patient preference.

PRINCIPLES OF RADIOTHERAPY IN ORAL CANCER

The use of radiation therapy in the management of squamous cell carcinoma of the oral cancer is based on the following principles[3].

1.Squamous cell carcinoma is generally radioresponsive and in early stage highly radiocurable.

2.The more differentiated the tumor, the less rapid the radiation response and resolution and the higher the radiation dose required.

3.Exophytic and well oxygenated tumors are more radioresponsive than deeply ulcerative and infiltrative hypoxic tumors.

4.Squamous cell carcinoma, when limited to the mucosa are highly radio-curable.

5.Bone and muscle involvement by carcinoma adversely alters radioresponsiveness and subsequently decrease radiocurability.

The early small metastases can be controlled with radiation therapy alone. Advanced cervical metastatic lymph nodes are better treated with combined therapy.

INDICATIONS OF RT

1.T1-T2 lesions as single modality
(Surgery or radiation)
2.T3 - T_4 locally-advanced lesions.
3.Combined surgery and radiotherapy or combination of chemoradiotherapy.

COMBINED SURGERY AND RADIOTHERAPY

Radiotherapy can be given before or after surgery. Each sequence has theoretical advantages and disadvantages.

However, the results from randomized studies favor postoperative radiotherapy.[45] In practice, most surgeons also prefer to operate in an unirradiated field where frozen section control of resection margin can be obtained. In certain clinical settings, however, planned preoperative radiotherapy may be favoured. These include situations where cancer is not respectable at presentation or when a free osteomyocutaneous graft is to be used for mandibular soft tissue reconstruction.

In the latter situation ,avoidance of irradiating the graft and delivery of a lower dose to the mandibular stump than would be necessary in postoperative setting both facilitate integration of the vascular graft.

INDICATIONS FOR POSTOPERATIVE RADIOTHERAPY

· Positive resected margins
· Locally-advanced primary regardless of margin
· Multiple involved nodes
· Extracapsular extension
· Perineural spread
· Vascular and lymphatic emboli

TIMING OF RADIATION

The general guideline is to commence radiotherapy when tissues are well healed. Radiotherapy should be started as early as possible after proper wound healing preferably within 6 weeks. The longer the interval before the commencement of radiation, the greater the opportunity for presumed clonogens to proliferate. A delay of more than 6 weeks can adversely affect the outcome.[6]

COMBINED CHEMOTHERAPY AND RADIOTHERAPY TREATMENT

Chemotherapy is generally used along with radiation in organ conservation settings, especially in locally advanced tumours to avoid surgery.

Neoadjuvant /Anterior / InductionChemotherapy

Chemotherapy is given before local treatment like radiotherapy and surgery. This has 2% survival benefit[8].

Concurrent Or Concomitant Chemotherapy

Chemotherapy is given along with RT. This has 6.5 % survival benefit[9].

Adjuvant Chemotherapy

Chemotherapy is given after local form of treatment like radiotherapy or surgery.

This has 1 % survival benefit.

Relative survival rates in 11375 cases			
Site	Stage	No of cases	5-year survival rate
Lip	I-II	7125	95
	III-IV	288	78
Oral tongue	I-II	787	67
	III-IV	866	20
Floor of mouth	I-II	324	68
	III-IV	1669	41
Gingiva	I-II	70	55
	III-IV	822	4 4
Buccal mucosa	I-II	58	78
	III-IV	256	40

Table.1: Survival rates in oral cancer

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Screeening For Breast and Cervical Cancer

Dr. Kalavathy M. C
Associate Professor, Cancer Epidemiology & Biostatistics
Regional Cancer Centre, Thiruvananthapuram

Breast cancer

Breast cancer is the leading cancer in women worldwide (annual age-standardised incidence rate in 2012 of 43·1 per 100 000 women) and 24.7 per 100 000 in India(1). Breast cancer is the most frequently diagnosed malignancy in Kerala with around 10,500 cases annually(2). Despite a lower incidence compared with the annual incidence worldwide, mortality for breast cancer in India (12·7 per 100 000) is similar to worldwide mortality (12·9 per 100 000). The 5-year relative survival for breast cancer varies from 76·3% for localised cancers to 14·9% for advanced stage disease (3).Early detection of breast cancer improves survival and reduces associated medical costs (10,11) Factors strongly associated with increased risk of female breast cancer are older age, menopausal status ,early menarche , late menopause, nulliparity ,older age at first full term birth, family history of breast cancer, especially in first and second degree relatives. Other important risk factors are absence or shorter duration of breastfeeding, genetic factors (BRCA1/2 mutations), and hormonal factors, such as prolonged use of combination hormone replacement therapy after menopause. A high fat diet, obesity, increased alcohol intake, and reduced physical activity have also been associated with risk of breast cancer (11,12).With the exception of the increased breast cancer risk associated with deleterious mutations of BRCA1 and BRCA2, most of these risk factors convey a low-level increased breast cancer risk (RR =2·0), suggesting that the cause of breast cancer is probably multifactorial. Although risk factor modification through exercise and diet might favourably affect breast cancer risk, the magnitude of that risk benefit is likely to be low.

Breast cancer is less amenable to primary prevention through risk factor modification than are other cancers with strong and modifiable risk factors. For example, the incidence and mortality of tobacco-associated cancers are greatly reduced through effective tobacco-control programmes. Modification of breast cancer risk factors (eg, changing reproductive health patterns) is more difficult, and has a much smaller potential quantifiable benefit as measured by shifting incidence or mortality.

Thus, the establishment of programmes that promote early detection, accurate diagnosis, and prompt treatment is a top priority for breast cancer reduction in the Indian health system. Also the control of this disease can be achieved through widespread physicians, paramedical professional'sand other health activists. The message about the methods of early detection, warning signals and probable risk factors for breast cancer should reach the common women folk of our country.

Primary early detection methods for breast cancer include patient awareness and patient education with regards to screening methods such as breast self-examination, clinical breast examination, breast ultra sound and screening mammography. Low awareness of breast cancer and its presentation as painless lumps or thickenings is a common obstacle to early detection in women from low income and middle-income countries.

Breast self-examination

Breast self-examination is the systematic assessment of both breasts by women themselves; any abnormality such as lumps or any change in colour or discharge should be noted and followed up. Formal breast self-examination training is not better than basic breast cancer awareness education in improving breast cancer outcomes, and can increase the biopsy frequency of benign lesions. As such, formal breast self-examination training is not recommended as a public health screening approach(14,15.) Nonetheless, women should be encouraged to seek evaluation of breast abnormalities that they find and diagnostic systems need to be in place to ensure that women with breast abnormalities can undergo prompt and accurate evaluation, since some of these women will be presenting with early stage cancers(16). Women need to be made aware that self-detected breast lumps should be assessed and possibly sampled to detect breast cancer at early stages (12).

Clinical breast examination

Clinical breast examination of both breasts is a thorough, systematic visual and tactile palpation conducted in both sitting and supine positions by a doctor or trained primary health caregivers. Although reported sensitivity is low (28.54%), the specificity of clinical breast examination is high (94.99%), and it has been shown to be cost effective. 80 The success of clinical breast examinations is still under trial in India, although preliminary evidence suggests downstaging of the disease.(18) Nonetheless, clinical breast examination is a fundamental instrument for breast assessment and should be used as a routine method for breast cancer diagnosis(17)

Screening mammography

Screening mammography is the most thoroughly studied screening approach and is the only method that has been shown through randomised trials to reduce breast cancer mortality. Although there is some decrease in mortality, the number of women who have to undergo further investigations and invasive procedures is high. Reported sensitivity varies from 64% to 90% and specificity from 82% to 93%. For women younger than 40 years, who have fewer breast cancers and also have denser breasts on average compared with women older than 40 years, the yield of cancers diagnosed is very low, which increases the number of false positives reported. Feasibility and affordability of mammography, along with the risk of increased false positives and over diagnosis are major concerns with mass routine mammography screening in low-income and middle income countries such as India. In India, where the peak incidence of breast cancer is in younger women, breast cancer detection by mammography will probably be lower than in other countries.

Breast ultrasonography

Breast ultrasonography is a key diagnostic adjunct to any early detection programme based on mammography or clinical breast examination (18).Reports from low-income and middle-income countries suggest that the use of screening ultrasonography (USS) might be an effective alternative screening facility that can be adopted in low-resource settings, with an overall sensitivity of 53.67% and specificity of 89.99%. Ultrasound might be particularly helpful in younger women (aged 40-49 years) with dense breasts, where sensitivity using ultrasound can exceed 75%. However, the requirement of trained professionals to perform and interpret ultrasound is a major hurdle. Although ultrasound is not recommended as a clinical screening test, its usefulness in population-based mass screening programmes is significant, but false positives and subsequent numbers of unnecessary biopsies and surgeries are also important.

Tissue sampling

Tissue sampling also has an important role.It can give a result within hours. The most common method in breast screening is Fine Needle Aspiration Cytology (FNAC)

Other technologies

Other technologies for breast cancer screening that need further investigation include MRI .

Screening strategies are moving towards a risk-based approach. To use this risk-based approach, one has to assess risk factors and incorporate this information into breast cancer screening in the near future (19).

Recommendations

First, early detection of breast cancer is crucial in our society. These programmes should not land up in unwanted biopies etc. also. So clinical breast examination combined with diagnostic ultrasound should be considered for breast cancer screening in this setting, especially in women younger than 50 years. It is useful for diagnostic work-up in a resource-limited setting and can improve the specificity of clinical breast examination findings.

In a low-resource setting like India, Mammography is not a cost effective population-based screening approach. Wherever available, it can be primarily used for diagnostic assessment of breast lumps, thickenings, or localised symptoms and it is useful in women with signs or symptoms of breast cancer. Women in the 50-65 age group should be subjected for mammogram since the breast density is low and probability of having malignancy is high in this age.

FNAC tests are low-cost tissue sampling and should be considered for community early detection and screening programmes, particularly in young women but it requires highly trained cytologists to provide accurate diagnosis.

Ultrasound-guided core biopsy can be used in settings where lesions are not amenable for simple FNAC.

Second, for effective breast cancer prevention, awareness and education (starting at age 30 years) supplemented with clinical breast examination screening and early detection programmes (at age 40-60 years) should be promoted in women at least once in every 3 years. Education and screening can be included in antenatal and postnatal check-ups to encourage a lifelong habit and create awareness about breast cancer.

Third, to provide patient access to prompt diagnosis and treatment, proper follow up should be there for FNAC services,USS and Mammogram results etc. Systems can and should be set up in different ways depending on the unique environment and organisation of the health system in different regions.

Fourth, on the basis of the epidemiological profile of breast and cervical cancers in India, education and clinical breast examination could be integrated in one screening visit along with cervical cancer screening that begins at the age of 30 years.

Fifth, women should be provided with awareness, education about breast cancer, partnered with access to diagnostic services and prompt and adequate stage-based treatment.

Next, the most practical and sustainable strategy is the one which can be integrated into the existing government health system, and a rough sketch for this is given below. This is a basic structure, which may be shaped according to the available resources, administrative and other issues.

Management of women coming for breast cancer screening should be dependant on the individual risk factors , whether it is in the Cancer Detection Centre in RCC, District Hospital or Taluk Hospital. Women can be categorised into Average risk for breast bancer, High risk for breast cancer and Very high risk for breast bancer.

Breast Cancer Screening strategy according to risk category
(Recommendations vary between different organisations and regions)

Women with Average population Risk

This include women with no family history of breast, ovary, colon cancers, parous with first delivery below 30 years, healthy body mass index, no oral contraceptive pills or hormone replacement therapy.

Below 40 years

Clinical Breast Examination with awareness creation regarding understanding of cancer related changes in breast, may be complemented with USS. The same may be continued annually optionally depending on the clinical findings and other findings.

40- 45 years

USS followed by Mammogram. USS may be continued annually depending on the clinical situation.

45-54 years

Mammogram can be done, which may be continued biannually. May be subjected for USS initially depending on the density of breast tissue.

Above 54years

Mammogram, may be repeated annually or biannually.

Women with High Risk

Women with high risk for developing breast cancer (Family history of breast or ovarian cancer for first degree relative (age at the time of disease is important),single or multiple, history of breast and or ovarian cancer for second degree relative especially if more than 1 person affected, high BMI, nulliparous, late age of first delivery, history of OCP/HRT)

Below 30 years

Annual clinical breast examination should start early, USS breast also to be done as and when directed by the doctor.

30-40 years

Clinical examination and a baseline Mammogram can be done. Annual USS can be repeated and Mammogram may be repeated as and when directed by the concerned Physician

40-59 years

Clinical examination and Mammogram should be done. These procedures may be repeated annually.

40-59 years

Same as above

In addition ,in women with strong family history of multiple breast,ovary,colorectal cancers etc, more specific investigations like MRI etc may be considered if indicated.

1.Hospital Based Screening

A.A District Cancer Control (DCC) unit should be set up in every District Hospital, under a Medical Officer (MO), preferably a lady who is interested in Cancer Control activities (which is very important for the sustainable regular and punctual operation of the clinic) . This MO may be given training in RCC. This unit should have 2 full time Doctors (1 may be the charge MO and the other may be a Dentist) 1 or 2 Cytotechnologist (Science Post graduates who undergo one year training in Papsmear reporting), Cytotechnician (Lab Technician trained in Cytotechnics), a Junior Public Health Nurse and a Helper. This unit should have Colposcopy and Papsmear Clinic . This unit also should have breast examination facilities, Fine Needle Aspiration facilities, with preferably at least Ultra Sound facilities (Radiologist may be hired on a regular basis).This unit should be functional everyday. Recurring expenses for the unit may be met from the charges collected for the services.

FNACs collected from each Taluk Head Quarters Hospital (THQH) have to be reported by the Cytotechnologist in DCC.FNAC reports can be handled in the following manner.

1.Inadequate, blood only --- To be repeated depending on the clinical presentation.

2.Normal adipocytes ---- No need of any intervention

3.Fibroadenoma/Benign proliferative breast diseases--- May be referred to General Surgeon.

4.Atypical fibroadenoma--- Has to be investigated further with Bilateral Mammogram and to be referred to Surgeon.

5.Proliferative breast diseases---Has to be investigated further and to be referred to surgeon also.

6.Moderate atypia/Ductal Carcinoma in situ/carcinoma etc----To be referred to higher centre like nearest Medical College, RCC etc

7.But in all these cases, a good clinical and risk factor assessment is crucial before deciding next level of management.

Guidelines to be followed depending on the USS/Mammogram findings:

1.BIRADS 1 Normal

2.BIRADS 11- Benign

3.BIRADS 3- Probably benign, to be followed up with Breast USS

4.BIRADS 4-Suspicious finding Requires FNAC/Mammogram/Excision

4a- Low suspicion of malignancy (2-10%)

4b- Moderate suspicion of malignancy (10-50%)

4c- Strong suspicion of malignancy (>50%)

5.BIRADS 5- Highly suggestive of malignancy-Referral to higher centre.

B.Setting up of regular weekly FNAC clinics in Taluk Head Quarters Hospitals (THQH).The collected samples can be processed in THQH itself and reported by trained Cytotechnologists who are posted in each District Hospital. A Medical Officer, preferably a lady,may be given the additional charge of Breast Clinic unit in THQH. She can be given training in RCC for 1 month. One Lab Technician in THQH may be given the charge of FNAC/Pap smear clinic and the related administrative assistance. She will be responsible for the collection (procedure to be done by doctor but assistance to be given), processing and transportation of samples to District Cancer Control Unit (DCC) in District Hospital . She will also be responsible for the timely collection of FNAC/Pap smear reports from DCC and distributing it to the patient not later than 1 week. The cost for Papsmear/FNAC can be fixed and may be collected from the patients or may be met from the included Grama Panchayath projects.

C.Regular primary screening at Primary Health Centre (PHC) level to identify women to be send for weekly FNAC/Pap smear clinic at THQH. Women with definite lump in the breast can be referred for FNAC to THQH. But those who have Family history or any other risk factors, but no definite lump can be referred to DCC (provided USS facility is available there).

2.Population Level Screening

Breast and cervical cancer detection campaigns have to be arranged by Grama Panchayath and PHC at regular intervals. Accredited Social Health Activists (ASHA) have to be trained to motivate women by doing house to house survey under the supervision of Junior Public Health Nurse (JPHN). Women in the age group 35-64 have to be interviewed and data regarding family history of breast cancer, nulliparity, previous breast surgeries, presence of any lump in the breasts etc are collected. Women with any of these risk factors are requested to attend the detection campaigns arranged in the PHC.

Cervical cancer

Cervical cancer is one of the most common cancers in women worldwide, with an estimated prevalence of 96,922 cases in 2018 (1). In India, cervical cancer is the second most common cancer in women, higher than the worldwide rates (14·7 vs 13·0/100,000). Kerala has attained a lower incidence of around 8 / 100,000(2). Overall 5-year relative survival of 46% for all cervical cancers in India is highly dependant on the stage at diagnosis, The survival is 7·4% for advanced stage disease , the same being 73·2% for localised cancer(3) Persistent infection with high-risk oncogenic HPV 16&18 (Human Papilloma Virus), followed by types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73, which are less oncogenic is proved to be the primary risk factor for cervical cancer. Other confirmed and suspected risk factors include: lifestyle factors (early sexual activity, many sexual partners, many pregnancies, abortions and smoking); and family history in first degree relatives co infections with many HPV types and Chlamydia trachomatis; (4) Cervical cancer is clearly amenable to screening because its natural history is well understood and it has a reasonably long precancerous state (10.2 years).

Cervical cancer screening methods

Visual inspection with Acetic acid and Lugols Iodine

Widely used methods for screening of precancerous cervical lesions include naked eye visual inspection with acetic acid or Lugol's iodine; visual inspection under a magnifying device with acetic acid; conventional (Papanicolaou [Pap]smear) or liquid-based cytological tests; and HPV DNA testing. These methods have been discussed recently in the context of resource-constrained countries such as India (5).Visualisation of the cervix after acetic acid application with the naked eye or under low-level magnification aims to examine the transformation zone for cervical cancer or its precursors as well defined, dense, opaque white areas or growths 1 min after the application of 35% acetic acid under a good light source. The transformation zone appears mustard yellow with Lugol's iodine in the presence of cervical pre cancers or cancers. Studies reported sensitivity of these screening tests varies widely with naked eye visual inspection and acetic acid (41.79%), with Lugol's iodine (56.98%), and under low-level magnification (60.82%). Reported specificity ranges from 14% to 98% with naked eye visual inspection with acetic acid, 75.85% with Lugol's iodine, and 85.88% under low level magnification. Studies show that magnification does not improve the performance of visual inspection with acetic acid significantly (6-9).

Conventional Pap smear

Conventional Pap smear testing or liquid-based cytological tests are widely accepted and routinely used screening methods in high-income countries in which a trained health worker obtains cervical samples that are stained in a laboratory and then analysed by a trained cytotechnician or cyto pathologist. The sensitivity of cytological tests are low (26.7%), but the specificity can be as high as 96.99% (6,7,8). Because cytological interpretation is highly subjective, good quality samples and an experienced cytologist are essential, which can be challenging in a resource-limited setting.

Liquid-based Cytology

Liquid-based cytological tests have similar sensitivity and specificity to Pap smears.(19) The liquid-based methods benefit from standardised preparations with minimum artifacts and the ability to use the same samples for further molecular assays of HPV(20,21) however, they are more expensive than other screening methods such as visual inspection with acetic acid or Lugol's iodine.

HPV DNA testing

For HPV DNA testing, a health-care provider or the woman herself uses a brush to obtain a cervical sample (9). Several technologies are available to detect either DNA of the most common high-risk HPV types. Some HPV detection tests provide HPV genotype information in addition to detecting viral DNA. The sensitivity of HPV testing is higher than for other methods at 66.95%, with specificity between 76% and 95% (7). HPV DNA testing is objective, has good reproducibility, and needs little training and experience. However, HPV DNA testing is not recommended in women younger than 30 years because of spontaneous regression of HPV infections in this age group (17).The costs involved for this procedure is the potential disadvantage of HPV DNA testing as a primary community screening test in a country such as India. If available at a reasonable cost, development of a simple, rapid, and accurate test for HPV DNA detection, could make HPV DNA testing a viable screening option in women who are older than 30 years.

Recommendations

First, primary screening with HPV DNA testing is the most reproducible and sensitive approach, even in a resource-limited setting such as in India, since a highly sensitive test such as HPV detection needs less frequent screening and could save programme costs. However, issues such as cost per test, protocols for transportation of cervical cell specimens, testing, reporting, treatment, and follow-up care of HPV-positive women still need to be addressed.

Second, self-collection of vaginal samples for HPV DNA testing for detection of cervical cancer would reduce the need for human resources and has the advantage of self-empowerment and privacy for these women. This could be achieved, in part, by community health workers. The National Health Mission is a large community-oriented, multifaceted basic health-care delivery programme in India that employs many female community health workers (known as Accredited Social Health Activists) and these women can be trained to perform door-to-door counselling and motivate women to undergo cervical cancer screening.

Third, the number of screening programmes based on visual inspection with acetic acid has been increasing in India. A pilot programme in Tamil Nadu, India, showed the feasibility of an approach to integrate this type of screening into the existing health system. Visual inspection with acetic acid (VIA) screening is likely to be used in national programmes following WHO guidelines until resources allow the introduction of HPV tests. The development of strategies for enhancing the implementation of visual inspection with acetic acid screening in India would help to introduce HPV testing as and when a more affordable and point-of-care test is available in the future.

Fourth, if HPV testing is introduced and resources for high-quality cytological tests are available, women who are HPV positive can be triaged on the basis of this tests before referral to colposcopy.

Fifth, the task group consensus recommendation for the appropriate age and way to screen HPV, is to include visual inspection with acetic acid screening for women aged between 30 and 49 years and HPV testing as it becomes affordable for women aged 30 years and older. On the basis of present WHO guidelines,a woman should be screened for cervical cancer at least once in her lifetime in a poor resource setting. Once this is achieved, screening women for cervical cancer at more regular intervals (5 years or 10 years) can be considered.

Sixth, screening of eligible women who visit healthcare systems for other reasons (opportunistic screening) will increase the level of awareness of cervical cancer in women, and help to integrate cervical cancer screening with other non-communicable disease services.

Seventh, the most practical and sustainable strategy is the one which can be integrated into the existing Govt health system and a sketch for this is given below. This is a basic structure, which may be shaped according to the available resources, administrative and other issues.

A District Cancer Control (DCC) unit should be set up in every District Hospital, under a Medical Officer (MO), preferably a lady who is interested in cancer control activities (which is very important for the sustainable regular and punctual operation of the clinic). This MO may be given training in RCC. This unit should have 2 full time doctors (1 may be the MO in charge and the other may be a dental surgeon) 1 or 2 Cytotechnologist (science post graduates who undergo one year training in Pap smear reporting), Cytotechnician(Lab Technician trained in Cytotechnics), a Junior Public Health Nurse and a helper. This unit should have Colposcopy and Pap smear Clinic etc. This unit also should have breast examination facilities, Fine Needle Aspiration facilities, and at least Ultra Sound facilities Radiologists may be hired on a regular basis). This unit should be functional everyday. Recurring expenses for the unit may be met from the charges collected for the services.

Pap smears/FNACs collected from each THQH have to be reported by the Cytotechnologist in DCC. Those with Pap smear report of Atypical Squamous Cells of Undetermined Significance (ASCUS), Low Grade Squamous Intraepithelial Lesion (LSIL) or High Grade Squamous Intraepithelial Lesion (HSIL) can be subjected for VIA, VILI and Colposcopy and if indicated for biopsy in the clinic.

Setting up of regular weekly Pap smear/FNAC clinics in Taluk Head Quarters Hospitals (THQH).

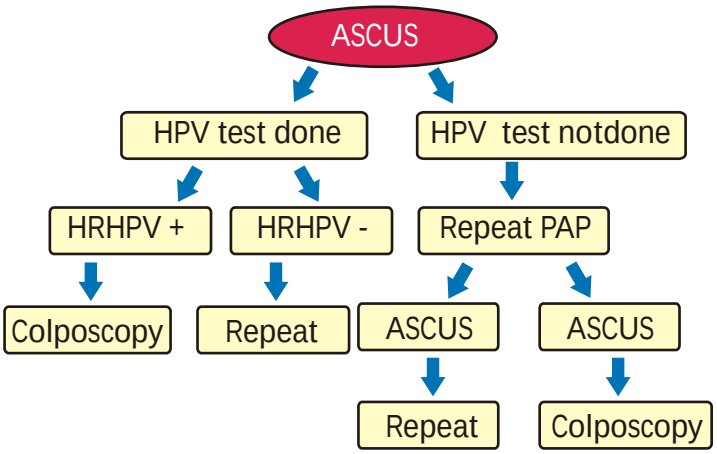
The collected samples can be processed in THQH itself and reported by trained Cytotechnologists who are posted in each District Hospital. Those with ASCUS and higher lesions can be referred for Colposcopy etc to DCC. A Medical Officer, preferably a lady , may be given the additional charge of Pap smear unit in THQH. She can be given training in RCC for 1 month. 1 Lab Technician in THQH may be given the charge of Pap smear clinic and she will be responsible for the collection and processing of Pap smear and transportation of samples to District Cancer Control Unit (DCC) in District Hospital . She will also be responsible for the timely collection of papsmear reports from DCC and distributing it to the patient not later than 1 week. The cost for Papsmear/FNAC can be fixed and may be collected from the patients or may be met from the concerned Grama Panchayath projects.

Regular primary screening at Primary Health Centre (PHC) level to identify women to be sent for weekly Pap smear clinic at THQH. This may include women in 30-64 age group, women with some gynaecologic symptoms, women with history of abortions, multi parous women etc.

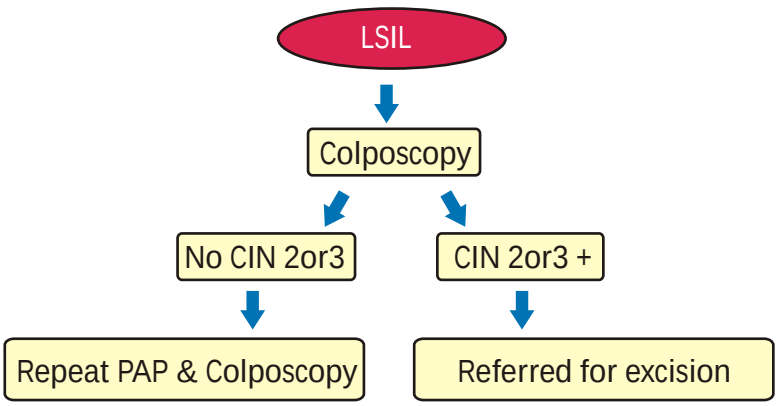
Cervical cancer detection campaigns have to be arranged by Grama Panchayath and PHC at regular intervals. Accredited Social Health Activists (ASHA) have to be trained to motivate women by doing house to house survey under the supervision of Junior Public Health Nurse (JPHN). Married women aged above 30, women with more number of childbirths, women with history of abortions,women with any gynaecological problems like discharge per vagina etc are invited to attend the campaign. Women can be subjected for Pap smear and there after for VIA, VILI by Medical Officer in THQH . The Pap smear have to be processed at DCC and the results should be collected by the Medical Officer in the PHC. Those with abnormal Pap smears have to be managed as given in the flow chart.

Management guidelines for women with Positive Cytology

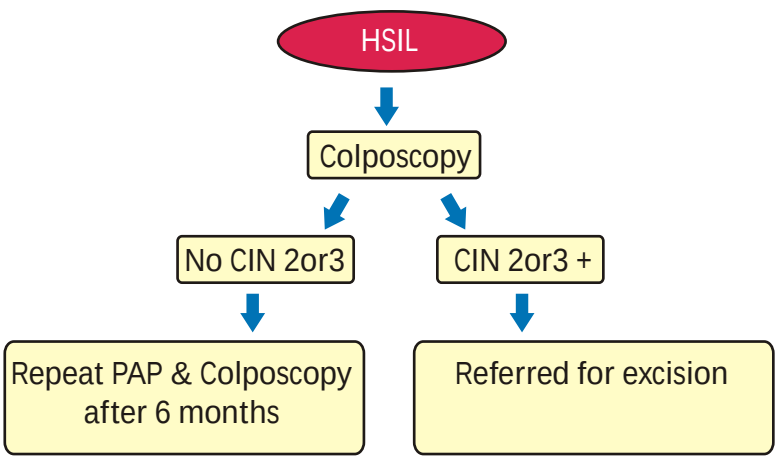
Management guidelines for ASCUS



Management guidelines for LSIL

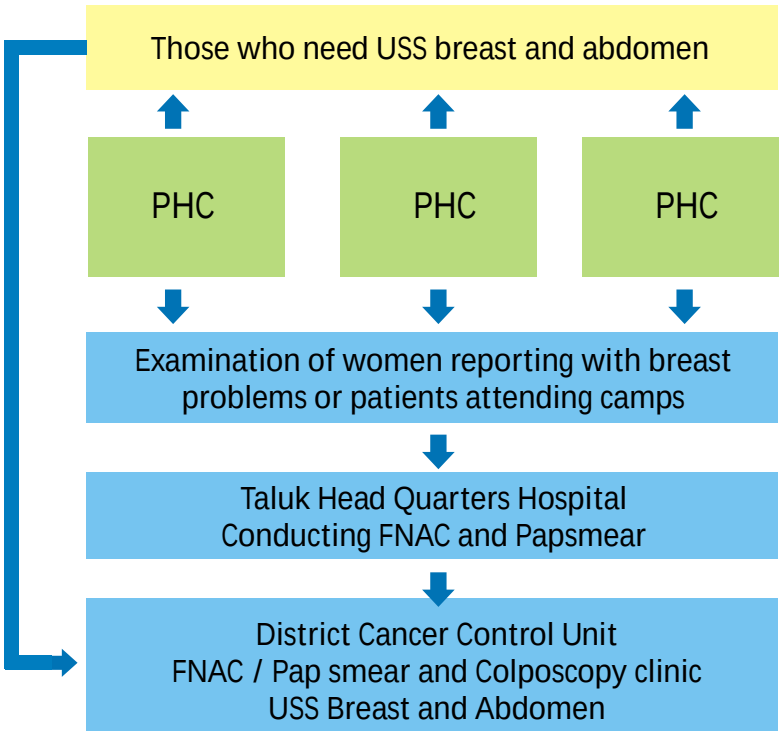


Management guidelines for HSIL



Flow Chart of District Cancer Control Programme

(Draft to be modified according to administrative, financial and other technical feasibilities)



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Detection and Management of Benign Breast Diseases

Dr.Rexeena Bharghavan
Associate Professor, Surgical Oncology Division
Regional Cancer Centre, Thiruvananthapuram

Introduction

Benign breast disease in women is a very common finding and is a cause of constant anxiety to her. 90 % of the palpable breast masses in women from their 20s to early 50s are benign.[1] However excluding breast cancer is a crucial step in all ages. An understanding of the hormonal and growth factor control of breast development and function is the key to the rational and systematic evaluation and treatment of these patients.

Purpose of evaluation of benign breast disease

1.To alleviate, when possible, symptoms attributable to benign breast disease,

2.To distinguish benign from malignant breast disease and

3.To identify patients with an increased risk of breast cancer so that increased surveillance or preventive therapy can be initiated.

Specific benign breast lesions

A wide variety of benign breast lesions have been described and the histologic appearance fully characterized. On a practical basis, these can be subdivided into those associated with no substantial increased risk of breast cancer (i.e. < 1.49%), those with an increase of 1.5-2% and those with a >2% increased risk. [2]

No Increased risk:

Fibrocystic changes, Periductal fibrosis, Hamartomas, Lipomas, Phylloides tumours, neurofibromas and Duct ectasia

1.5 to 2.0 fold Increase in Relative Risk:

Fibroadenomas when complex and containing cysts >3mm in diameter or sclerosing adenosis or epithelial calcification or papillary change, Hyperplasia without atypia, Papillomas, Papillomatosis, Radial scar, Blunt duct adenosis and sclerosing adenosis.

Greater than Two-Fold Increase in Relative Risk:

1.Atypical hyperplasia

Recent data from the Mayo Clinic report the *absolute rates* of breast cancer during prolonged 20+ year follow-up and the important role of multifocality. [3,4] The risk approximates 24% with one lesion, 36% with two and 47% with 3 or more lesions.

The presence of atypical hyperplasia imparts a risk over time of both ipsilateral and contralateral breast cancer.

2. Mammographic Density

The percentage of breast tissue which is dense on a mammogram is determined by computer assisted analysis and classified as none, <10%, 10-25%, 25-50%, 50-75%, >75%.The relative risk of breast cancer increases with each step of increased breast density. Women with a high breast density compared to women with a low breast density have a four- to sixfold increased risk of developing breast cancer.[5]

Clinical Manifestations

Clinical presentations of benign breast disease are divided into those with

1.Pain (cyclic or non-cyclic)
2.Lumps (consistency, fixity) and /or
3.Nipple discharge(sanguineous/non sanguineous)

A detailed history and physical examination with systematic evaluation of the entire breast and chest wall with focus on areas involving the patient's symptoms should be done. High suspicion of malignancy should be there in a recently detected lesion in a post-menopausal woman. Triple Assessment is recommended which includes clinical examination, imaging and percutaneous biopsy (Figure 1)

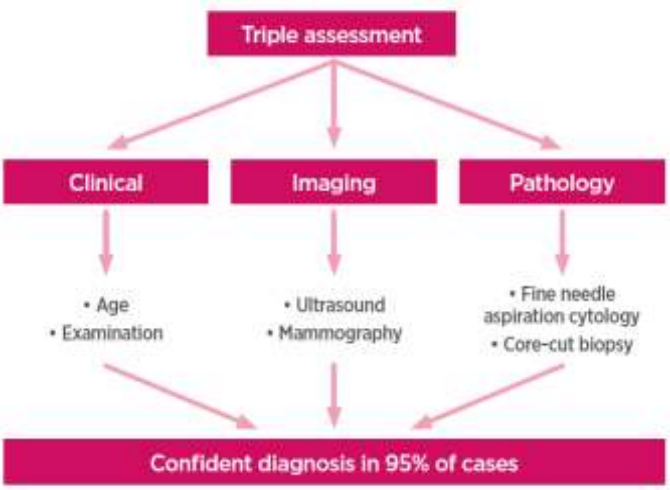

Figure 1 Triple assessment

The most important component is clinical examination. Adequate assessment of all the quadrants of both breasts and axilla should be done at least in sitting and lying down positions. Mammography, often in conjunction with ultrasound examination is required for evaluation of discrete palpable lesions in women over 35 years whereas ultrasound provides an optional substitute in younger women. Round dense lesions on mammography often represent cysts which require only ultrasonography to distinguish them from solid lesions. Complex cysts containing both fluid and solid matter require biopsy. For solid lesions, radiographically or ultrasonically directed core biopsy provides highly discriminative information regarding the presence or absence of malignancy. Pathological evaluation with FNAC and core biopsy(preferred) should be done. Incision or excision biopsy must be avoided as it hinders with further surgery if the final pathology is malignancy. If excision biopsy is required then excision with adequate margins should be done. Piecemeal excision must be avoided. In case of nipple discharge nipple cytology can be done if the discharge is sanguineous or any clinical suspicion of malignancy.

Management

If triple assessment is negative,reassurance and follow up is needed.Excision is advisable only if severe symptoms are present.There are many pharmaceutical agents advised for management of benign breast disease but their benefit is debatable. In case of atypical ductal hyperplasia excision with negative margins is advised and the patient should be referred to an oncologist for further management. If any suspicion of malignancy on any of the factors in triple assessment,patient is to be referred to an oncologist for further evaluation. It is very important to take this opportunity to explain breast awareness to the patient. Patient should be kept on regular follow-up and should be advised to report if any new lesions are detected.

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Principles of management of Breast cancers.

Dr Beela Sarah Mathew
Professor of Radiation Oncology,
Regional Cancer Centre, Thiruvananthapuram

Breast cancer is the most frequent cancer occurring in women accounting for 11.6% of all cancers diagnosed worldwide and 14% of newly diagnosed cancers in India. (GLOBOCAN 2018).[1] It is also the leading cause of cancer mortality among women (11.1% of deaths/year in India). At the Regional Cancer Centre, Thiruvananthapuram breast cancer accounts for 29% of all cancers in women.[2] The treatment for a breast cancer patient requires an estimation of the individual risk of recurrence and cancer related mortality, followed by a tailored multi-disciplinary approach from an armamentarium of therapeutic options comprising of surgery, radiation therapy, chemotherapy, endocrine (hormonal) therapy and targeted (biological) therapy. Individualization also takes into account risks of treatment related short term toxicities and chronic morbidity.

Diagnosis and Staging

The diagnosis of breast cancer requires the Triple test- clinical examination followed by radiological and pathological investigations. Classically a firm or hard lump that is not freely movable within the breast tissue +/- palpable axillary nodes is suggestive of breast cancer. However, some cancers may present as ill-defined masses perceived as textural changes in comparison to the contralateral breast. Mammographic abnormalities indicative of a malignant pathology includes a mass, micro calcifications, asymmetric densities or architectural distortions.

Confirmatory test of choice is a core (tru-cut biopsy) which is a simple, out-patient procedure that provides details of histological type and tumor biology (Estrogen receptors (ER) and Progesterone receptors (PR) and HER 2 receptor expression). Fine needle aspiration cytology (FNAC) may provide a diagnosis of malignant cells and may be employed when patients are being planned for a primary surgical approach. However a negative cytology report should not be interpreted as conclusive evidence of non-cancerous nature.

Staging of breast cancer includes assigning a clinical stage and pathological stage (post-surgery). Clinical stage incorporates the clinical and radiological findings. Bone, lungs and liver are the commonest sites of metastasis. Imaging of these sites is recommended for patients who have locally advanced disease or symptoms/ blood chemistry suggestive of dissemination.

The most recent staging system (AJCC 8th Edition) of breast cancer includes anatomical information regarding local tumor characteristics (T), regional nodal involvement (N) and dissemination to other organs (M) and categorizes patients into prognostic groups incorporating the TNM stage, grade and biomarker (ER,PR, HER 2) expression.[3]

Treatment

Principles

The treatment of breast cancer involves integrating loco-regionally directed therapies (surgery and radiotherapy) and systemic therapies depending on the stage and prognostic grouping.

Early stage disease includes in-situ carcinomas, stage I and stage IIA disease. These patients undergo primary surgical treatment with an aim to excise all gross disease followed by adjuvant therapy. Adjuvant therapy is the term used to denote treatment directed at controlling microscopic disease (not demonstrable clinically and radiologically). This uses appropriate combinations of chemotherapy, hormone therapy, biological therapy and radiation therapy depending on the pathological stage of the disease and biological sub-type.

Stage IIB (T2 N1, T3 N0) and Stage IIIA (T3 N1 M0) cancers are operable but may sometimes receive primary (neo-adjuvant / pre-operative) systemic therapy in situations such as those requiring down-staging to facilitate breast conservative surgeries or for aggressive sub-types such as Triple Negative (TNBC) or HER 2 enriched cancers where early institution of systemic therapy may confer long term benefit.

Locally advanced cancers - stage III (any T4, any N2, any N3) - are generally not amenable to a primary surgical approach owing to disease characteristics such as skin or chest wall involvement, large volume axillary disease, internal mammary or supraclavicular nodal disease. Such patients benefit from neo-adjuvant therapy with appropriate systemic agents which would shrink the tumor and downstage disease facilitating optimal surgery as well as help in controlling probable dissemination. Once adequate tumor shrinkage is achieved patients undergo surgery followed by adjuvant therapy.

Metastatic (stage IV) cancer remains essentially incurable despite advances in breast cancer treatment. The goals of therapy include palliation of symptoms, delay of disease progression and prolongation of survival without impacting the quality of life. There is no single standard of care for such patients, as treatment plans require an individualized approach based on factors such as tumor biology, growth rate of cancer sub-type, presence of visceral metastases, history of prior therapy and response, risk of toxicity and patient preference.

The mainstay of therapy is systemic treatment with chemotherapy and/or hormone therapy with /without biological therapy. Typically the role of surgery or radiation in stage IV cancers is confined to palliation of situations such as a bleeding/ ulcerated breast mass, bone and brain metastases etc. Nevertheless, for certain patients with limited (<5) number of metastases, predicted indolent behavior, access to effective systemic therapy and estimated better prognosis a more radical approach incorporating surgery and radiotherapy to the loco-regional and metastatic site may provide better disease control. Decisions for such aggressive approaches should be individualized and made through multi-disciplinary agreement regarding clinically meaningful benefit for the patient.

Types of treatment

Loco-regional treatment

Surgery and radiation are the modalities of therapy used to achieve tumor control in the primary and regional nodal drainage area. Since local failures are often forerunners for systemic dissemination optimal surgery and radiotherapy are important components for breast cancer treatment.

Surgery

Modified radical mastectomy (MRM) has traditionally been the most widely accepted surgical approach for patients with breast cancer. This involves removal of the entire breast and axillary nodes. The pectoralis muscles are usually preserved. Removal of the primary tumor helps in local tumor control and reduces the potential for metastases in patients with disease confined to the loco-regional site. Axillary lymph node dissection provides good control of tumor in the axilla in addition to information for accurate staging and prognostication. Patients undergoing mastectomy should be offered primary (at the time of MRM) or delayed reconstruction with either implants or myocutaneous flaps.

Long term results of randomized trials have proven equivalent success rates for breast conserving therapy (BCT) and modified radical mastectomy in stage I or II disease. [4] BCT involves removal of the primary tumor with a margin of normal breast tissue and axillary dissection followed by radiation therapy. Patients for BCT have to be carefully chosen based on tumor and patient characteristics.

The four critical elements for patient selection are:

1.History and physical examination
2.Mammography
3.Assessment of patient's desire and expectations
4.Histological assessment of the resected specimen

Due diligence is required while selecting patients for breast conservation. There are certain situations which preclude the performance of breast conservative surgery with good cosmesis or prevent instituting appropriate dose of radiotherapy during the optimal time period to prevent recurrence.

Absolute contra-indications for Breast Conservation are:

· Diffuse microcalcifications
· Multi-centric disease
(involvement of 2 or more quadrants)
· Positive pathologic margins
· First trimester pregnancy

Relative contraindications

· Focally positive margins
· Connective tissue disorders affecting skin
· Multi-focal disease requiring 2 or more separate surgical excisions
· Previous history of radiation to the breast/chest wall

Mammography is used to define the extent of disease, detect multi-focality and multi-centricity and assess status of the contra-lateral breast. Once it is determined that patient is suitable for BCT it is important to ascertain that the patient is desirous of undergoing this procedure and is not wary of preserving the breast.

Postoperatively careful histological examination should be done to ensure that the entire tumor has been removed and that the margins do not contain tumor. Patients with pathologically positive margins may undergo re-excision (if sufficient breast tissue is present to achieve good cosmesis) or would need mastectomy for optimal control of disease.

Lymphatic mapping and sentinel lymph node biopsy

This is a technique that identifies patients with lymph node involvement with minimal morbidity. For patients with no clinical evidence of nodal metastases this technique helps to avoid unnecessary axillary surgery and thus reducing the morbidity considerably. Blue dye or a radio-colloid or both are injected around the areola. This drains to the lymph nodes that are identified as sentinel nodes. These are excised and examined for presence of metastatic disease. If these nodes are negative, no further axillary surgery is required whereas if they are positive an axillary dissection is done.

Radiotherapy

Radiation is used as adjuvant treatment to kill microscopic disease that may be present in the breast/ chest wall or regional lymph nodes after surgery. Meta-analysis of randomized trials has demonstrated the efficacy of radiation in reducing recurrence and death rates for breast cancer patients.[5,6] All patients who undergo breast-conserving surgery mandatorily receive radiation to the breast. Rare exceptions are elderly patients with early stage, low risk cancers who are on endocrine therapy and have competing co-morbidities compromising life expectancy. Nodal irradiation in the patients with conserved breast is indicated for those at high risk for failure (node positive or large (>5cm) tumors +/- skin or muscle involvement). Post mastectomy radiation (PMRT) reduces the risk of local recurrence and improves survival for patients with poor prognostic features. The indications for PMRT are tumor size>5cms, infiltration of skin or chest wall, positive resection margins, extensive node positive disease (4 or more).

Radiotherapy is generally administered after completion of chemotherapy in order to decrease toxicity.

Systemic Therapy

Contrary to the practice of reserving systemic therapy for patients with regional or metastatic disease earlier, it is now proven that systemic interventions such as chemotherapy, hormonal therapy and biological therapy improve survival even in patients with early stage disease. Currently systemic treatment forms part of the treatment programme for almost all stages of breast cancer. Selection of the type of systemic treatment is based on prognostic and predictive factors such as tumor pathology, size and grade, lymph node involvement, hormone receptor status, Her 2 amplification, age and general physical health of the patient.

Chemotherapy

Chemotherapy may be employed as adjuvant therapy, neoadjuvant or preoperative therapy or as the sole modality of treatment depending on the stage and sub-type. Most chemotherapeutic agents exert their action by direct cell kill.

Meta-analysis of adjuvant chemotherapy trials has shown that chemotherapy produces significant reductions in the risk of recurrence and death for all patients aged < 70 years irrespective of nodal status.[7] Adjuvant chemotherapy is generally recommended for all patients except those with good prognostic features such as small (<2 cm), grade I, node negative cancers with strong expression of hormone receptors and HER 2 negativity. Multi-gene panel tests have been shown to provide valuable information in selected patients with clinic-pathologically intermediate risk cancer who may be considered for avoiding chemotherapy. However these tests are prohibitively expensive precluding their use in routine practice.

Patients with large operable tumors or locally advanced disease receive preoperative chemotherapy to downstage the disease prior to surgery. Apart from achieving tumor shrinkage this also helps to destroy probable circulating metastatic cells.

Preoperative chemotherapy also helps to assess the response of the tumor to a particular chemotherapeutic agent that would help in further prognostication and tailoring of therapy. Chemotherapy is the mainstay of treatment for most patients with metastatic disease. It provides substantial clinical benefit in terms of palliation of symptoms and quality of life although this does not often translate into an improved overall survival.

The drugs commonly used are taxanes (docetaxel, paclitaxel), anthracyclines (doxorubicin, epirubicin), cyclophosphamide, 5flourouracil, capecitabine, methotrexate, gemcitabine, vinorelbine and platinum compounds (cisplatin / carboplatin). Combination chemotherapy is recommended in the adjuvant and neoadjuvant setting and the duration of chemotherapy ranges from 4-6 months. Sequential use of single agents are preferred in metastatic cancer as combinations cause toxicities and compromised quality of life without any additional benefit on survival. Chemotherapy causes side-effects such as hair loss, nausea, vomiting, mucositis, myelo-suppression, peripheral neuropathy etc most of which can be ameliorated easily with adequate supportive care.

Endocrine (Hormone) therapy

It is estimated that overall approximately 60-70% patients have hormone receptor positive disease. Long term follow up data show that endocrine milieu manipulation results in 12% absolute reduction in the odds of recurrence and 9% absolute reduction in the risk of death at 15 years for patients with hormone receptor positive disease.[8] Currently, all patients whose tumors express ER and /or PR are advised endocrine therapy irrespective of age, menstrual status or stage of the disease.

Tamoxifen is the most frequently used form of endocrine therapy in breast cancer. This drug is a selective estrogen receptor modulator (SERM) exerting both agonistic and antagnostic effects on different tissues expressing ER receptors. Tamoxifen combines with the ER receptors on breast cancer cells, thus blocking estrogen stimulation of the cancer growth. Tamoxifen can be used in both pre and postmenopausal women.

Inducing ovarian suppression by surgical or radioablative oopherectomy or LHRH analogues is also a method of endocrine therapy employed in premenopausal women. Aromatase inhibitors (anastrozole, letrozole and exemestane) that inhibit extra-ovarian estrogen synthesis have demonstrated superior activity over tamoxifen in postmenopausal women.

Endocrine therapy is used as adjuvant therapy in early stage breast cancer and as neoadjuvant treatment in selected patients with locally advanced disease. It is also used in metastatic cancer either following chemotherapy or as the primary modality of therapy in patients who are likely to achieve good responses with endocrine therapy alone indolent disease either confined to bone or soft tissue or with visceral involvement but no functional derangement warranting use of therapies producing faster responses and disease control.

Targeted (Biological) therapy

This form of treatment utilizes monoclonal antibodies developed against specific molecular targets identified on the tumor tissue. One such target is the HER 2 receptor. Approximately 25% breast cancers have amplification of Human Epidermal Growth Factor receptor-2 (Her2 neu or c-erbB-2) that is implicated as having a pivotal role in the development of breast cancer. Trastuzumab, Pertuzumab, Emtansine and Lapatinib are agents which have shown ability to inhibit HER 2 induced cancer growth. Randomized clinical trials have reported incremental benefits from using these agents in both curative (stage I-III) and metastatic cancer.[9]

Other targeted agents which have demonstrated benefit in the metastatic setting include mTOR inhibitors (Everolimus), CD K 4/6 inhibitors (Palbociclib, Ribociclib) and PARP inhibitor Olaparib.

Post-therapy surveillance

Post therapy follow-up includes regular history and physical examination and periodic mammography for early detection of a recurrence in either a conserved breast or contralateral breast.

Routine performance of investigations such as tumor markers or imaging studies such as CT/PET-CT etc in an asymptomatic patient do not provide any benefit in terms of survival or ability to palliate recurrent disease and hence are not recommended.

Pregnancy Associated Breast Cancer

The most common cancer occurring in pregnant women is breast cancer. The prognosis of pregnancy associated breast cancer is similar to other breast cancers if diagnosed early and treated appropriately. For patients detected to have a lump, ultrasound evaluation followed by core biopsy is recommended for diagnosis. X-ray / radio-nuclide investigations are avoided. Careful discussion and collaboration of the surgeon, oncologist and obstetrician is required for providing optimal treatment. If diagnosed during first trimester, termination of the pregnancy may be required to institute prompt therapy to save the patient. Surgery can be performed during any trimester but is preferred in the second trimester. Mastectomy and Breast Conservation are both reasonable approaches particularly if optimally timed radiotherapy can be delivered post-partum. Chemotherapy can be safely administered during the second and third trimesters. Chemotherapeutic agents proven to be safe during pregnancy (anthracyclines, cyclophosphamide, 5FU) are used. Chemotherapy should be stopped at least 3-4 weeks prior to the expected date of confinement to facilitate safe delivery without complications such as bleeding and infections. Further chemotherapy may be continued post-partum. Radiotherapy, Endocrine therapy and Targeted therapy is administered only post-delivery due to concerns of fetal safety.

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Management of Breast Cancer: A Surgeon's Perspective

Dr.Paul Augustine
Head , Division of Surgical Oncology
Regional Cancer Centre, Thiruvananthapuram

The most common cancer seen in women around the world is breast cancer. It is also the most common cause of death among women in India. In Kerala, a third of all cancers in women are breast cancer, and it is becoming more common in younger women.

Early detection is vital in preventing the morbidity and mortality associated with breast cancer. Mammogram is not cost effective for early detection of breast cancer in our country. This is especially true as the number of young patients is ever increasing. Almost 20% of those diagnosed with breast cancer are under 40 years, and in these cases breast is dense and the mammogram is likely to miss the lump. However, in general, mammogram is useful to pick up very early lesions which may not cause any problem.

Clinical breast examinations by trained doctors or volunteers could be equally helpful in detecting early tumours. In order to detect breast cancer at an early stage, all women above 30 years of age should be encouraged to have regular clinical breast examination by a trained person. In the event of detecting breast cancer it is possible to conserve the breast and treat the patient with least morbidity.

The mainstay of treatment for breast cancer is surgery.In some cases can be cured with surgery alone. In early stages of breast cancer with good biology (ER+ PR+ Her2neunegative, Ki67 low),surgery alone, or with additional hormonal therapy, could achieve cure rates ofabove 90-95%.

An excision biopsy to diagnose breast cancer is to be avoided .Surgery for breast cancer should be done as a curative procedure after proper planning. A preoperative diagnosis of cancer is possible in more than 95% of cases by means of an FNAC or Core biopsy. If it is not possible to achieve a diagnosis with these investigations,then proper surgical excision has to be planned with frozen section and, if malignant, a curative surgery which addresses the breast and axilla can be done at the same sitting.

Adequate surgery for invasive breast cancer has to address the breast and axilla. It can be either Breast Conserving Surgery (BCS) or Modified Radical Mastectomy (MRM). In BCS the disease in breast has to be removed with a clear margin (no ink on tumour). In Ductal Carcinoma In Situ a margin of 2mm is recommended. If an MRM is done, it has to remove at least 90% of the breast tissue. Keeping more residual breast tissue may lead to unnecessary radiotherapy being given to the remnant breast.

If there is no axillary lymph nodal involvement, a sentinel lymph node biopsy(SLNB) can be done to identify if any node is actually involved. A full axillary clearance needs to be done only if sentinel nodes are involved. This reduces the chance of swelling of the upper limb (Lymphedema). SLNB may not be possible in a patient after an excision biopsy, as the blue dye injected to locate the sentinel node could be blocked by the scar of the excision from reaching the node. This explains the importance of avoiding an unplanned excision for diagnosing breast cancer.

An unplanned excision also jeopardizes the chance of cure (if a margin positive excision or a piece meal excision is done). An improper incision during the initial unplanned excision can also ruin the chance of conserving the breast. If proper axillary lymph node dissection (removal of at least 10 lymph nodes) is not done in cases where axillary nodes were already involved, another surgery to achieve that or additional radiotherapy to axilla will have to be given. This would have the side effects associated with radiation, including lymphedema, which could have been avoided had a proper surgery been done in the first place.

The surgeon can conserve the breast in appropriate cases . In situations where total removal of breast is warranted, reconstruction of the breast can be done using tissue taken from the abdomen.

After surgery,chemotherapy, radiation, endocrine therapy(Tamoxifen/Letrozole) or biological therapy (Traztuzumab) may be required to improve the outcome. In certain situations, chemotherapy may be advised before surgery, especially if the cancer is in an advanced stage. In such situations also, cure is possible only if surgery (BCS or MRM) is done to remove the disease after chemotherapy.

Performing a good surgery, which is paramount in achieving both cure and good quality of life for the patient, is not the end of a surgeon's role. Follow-up of the patient is equally important. An experienced surgeon will be able to pick up an early local recurrence, and do a curative resection of the lesion. He/she would also be the best person to pick up any new breast cancers which are more common in the contralateral breast, and offer proper surgical treatment to cure that cancer as well.

Sometimes, the disease would have spread to distant sites of the body and cure may not be possible. In such situations, surgery may not be offered and patient would have only medical treatment. Surgery may be done in such situations only to palliate a bleeding or fungating breast cancer.

Curative surgery may be attempted; if the spread is limited to a few areas of the bone only, or if it is possible to resect all the disease in the body, especially if the cancer is of good biology.

Treatment of breast cancer requires a good team, starting with the imageologist and pathologist. Many a time, improper mammogram reports and pathology reports made by inadequately trained professionals lead to an excision biopsy by an untrained surgeon. Sometimes, surgeons do an unplanned excision without a mammogram or a needle biopsy. These should be avoided at all costs.

The surgeon should be able to offer BCS wherever feasible and achieve the same results as an MRM. All axillary lymphnodes should not be removed when a SLNB would have sufficed. The treating medical team should also be mature enough to avoid over treatment with agents which offer very minimal benefit or may be harmful in the long run.

If the patient and society is to benefit, accreditation of all the specialists involved in the management of breast diseases is necessary after ensuring that they have had proper training.

Management of Cervical Pre Cancers and cancers.

Dr. P. Rema
Additional Professor, Surgical Oncology
Regional Cancer Centre, Thiruvananthapuram

Cervical cancer is the leading cancer in Indian women and the second most common cancer in women worldwide. In the developed world, endometrial and ovarian cancers are the most gynaecological cancers while cervical cancer is more common in the developing countries including India. About 5 lakh women develop cervical cancer every year of which 75% come from developing countries. In India one woman dies every 7 minute due to cervical cancer. Cervical cancers are the most formidable health care challenge to our society. It burdens the patient, her family, the community and the state. Hence the prevention and treatment of cervical cancer needs the utmost priority.

Etiopathogenesis

Cervical cancer is caused by Human papilloma virus infection. HPV infection is very common in reproductive age group. The reported prevalence in India is 6%. 80% of women in reproductive age group get HPV infection in their life time. But majority of HPV infections are transient and gets spontaneously cleared in 12 - 24 months. In a minority , the infection persists and leads on to development of cervical precancers which if untreated can progress to invasive cervical cancer.

HPV virus enters the cervical epithelium through minor aberrations. The virus infects the basal layer of cervical squamous epithelium and produces dysplastic cells. Invasive cervical cancers are preceded by a long phase of preinvasive disease called Cervical Intraepithelial Neoplasia (CIN).

The term dysplasia was first introduced in 1953 by Regan et al to describe cellular changes intermediate between normal cervical epithelium and invasive cervical cancer, which he further classified depending on the cellular abnormalities into mild, moderate and severe. The term CIN was coined by Richardt in 1968, CIN 1 corresponds to mild dysplasia, CIN2 to moderate, and CIN3 to severe. When the dysplastic cells are confined to the lower one-third of cervical squamous epithelium, it is called CIN1. When the dysplastic cells reach upto middle third it is CIN2 and when upto upper third it is CIN3. When the basement membrane is breached and the cells invade the underlying cervical stroma it becomes invasive cervical cancer. In 1990 revision of CIN terminology was revised as Low grade CIN for CIN 1 and High grade CIN for CIN 2&3. CIN can progress to invasive cancer in 10 -20 years . If detected early CIN can be effectively treated by various outpatient procedures with good patient compliance and excellent cure rates Early detection and treatment of CIN hence is needed for preventing cervical cancer.

Primary prevention - HPV Vaccination

Considering the fact that HPV infections cause almost all of the cervical cancers, primary prevention of cervical cancer by HPV vaccination is the logical solution to this dreaded disease. When HPV vaccines were licensed in 2006 after extensive trials it was speculated that this could lead to eradication of cervical cancer the major cancer killer among females. Although this has not happened due to the so called barriers in immunization, the vaccine has probably stood the test of time.

We have now long term results of safety and efficacy of the vaccine and the vaccine has been introduced in the immunization programme of over 60 countries.

One major issue with implementation of vaccination programme in our country is the cost of the vaccine. There has been considerable reduction in the vaccine costs recently and an Indian vaccine at much lower cost is under clinical trials. Another strategy for cost reduction is reducing the number of dosages. There are studies looking into the immunogenicity of HPV infection after 1, 2 or 3 doses of vaccine including a large randomized study from India concluding that in girls less than 15 years two doses of vaccine at 6-12 month interval have equally good immunological response.

HPV vaccine is recommended by the Indian academy of Pediatrics (IAP). The minimum age of vaccine is 9 years. For girls aged 9-14 years 2 dosage schedule and for more than 15 years 3 dosage schedule with second dose 1-2 months after first and third 6-12 months after first dose is followed. For immuno-compromised individuals, including HIV-infected, the three-dose schedule is recommended irrespective of age. Both bivalent and quadrivalent vaccines are licensed in India and either of the two brands can be used but the same brand should be used for the entire series.

Trials on vaccination of women over 25 years has showed that the vaccine is effective even in older women as there is a continued risk of acquiring HPV infection throughout the reproductive age. So catch up vaccination is permitted up to 45 years. This expands the indications of HPV vaccination but the cost effectiveness of the vaccine in this age group especially in our country is yet to be evaluated.

In addition to the quadrivalent and bivalent vaccine, now a nano valent vaccine also has been licensed. It is effective against HPV 6,11,16,18,31,33,45,52 and 58. It has similar immunological response as the quadrivalent vaccine and greater efficacy compared to older vaccines.

Screening for cancer cervix

In developed countries cervical cancer incidence has reduced dramatically when effective screening programmes were implemented. The goal of a screening programme for cervical cancer is to reduce cervical cancer and related mortality with relatively few adverse events. The programme must include a screening test and should be linked to appropriate treatments for CIN, and also provide referral for treatment of women with invasive cervical cancer. Common screening tests that are widely used include cervical cytology, tests for human papillomavirus (HPV) and unaided visual inspection with acetic acid (VIA).

Cervical cytology

This is the most commonly used screening technique. Cervical cytology was introduced by George Papanicolaou in 1943. Cervical cytology is done by the traditional Pap smear or by liquid based cytology. In Pap test, Ayers spatula is used to scrape cells from the cervix which is spread on a glass slide and before it dries it is immersed in fixative made of equal parts of 95% ethyl alcohol and ether. This is stained with Papanicolaou stain and examined under the microscope. In liquid based cytology a liquid based medium is used to collect the sample and cells are trapped onto a filter and then made into a monolayer on a glass slide. This helps to avoid errors and increase the sensitivity. The reported sensitivity and specificity of cytology are 62.11% and 93.51% respectively. The low sensitivity, lack of adequate trained cytopathologists and lack of necessary infrastructure and quality control limits cervical cytology as a screening technique in low resource countries.

HPV DNA Testing:

HPV DNA testing for high risk HPVs has higher sensitivity and specificity compared to cervical cytology. Detection of oncogenic HPV is also a specific test in women more than 30 years with a specificity of 92-95%.

HPV testing is more helpful in women older than 30 in whom transient HPV infection is less likely. Hybrid capture test (HC2) and PCR for high risk HPV are the available HPV tests now. Unlike cervical cytology, HPV testing is reproducible and is devoid of inter observer variation but is costly. A low cost, rapid HPV test would be more suitable for mass screening programme in our population in the age group 30-49years. Literature shows HPV screening with its better sensitivity allows extension of screening intervals to 5- 10 years.

Visual inspection after acetic acid (VIA)

Successful screening in low resource settings needs low-cost, low-technology screening methods which can give wide coverage of at-risk women. WHO has recommended VIA as an alternative to cytology for screening in low resource settings. VIA includes examination of cervix by naked eye after application of 3-5% acetic acid with good light source. VIA is considered to be positive when distinct opaque acetowhite area is present. VIA is a simple visual test, does not require laboratory and results available immediately. Paramedical workers can also be trained in performing VIA. Indian studies by Sankaranarayanan et al also showed that VIA compares favorably with pap screening in terms of sensitivity and specificity. A task force constituted by the Government of India has recommended the introduction of VIA-based screening for cancer cervix.

Screening should be combined with appropriate educational programmes and there should be a built-in mechanism for evaluation of the screening programme. It is important to develop culturally appropriate education materials and to involve women's groups utilizing existing community health promotion programmes.

Recommendations for screening

Most screening recommendations advise that it should commence either at 21 years or within 3 years of onset of sexual activity. WHO guide lines for developing countries recommend screening once in three years starting from 30 years till the age of 50 years.

After 50 years in a person who had regular screening till then the screening interval can be increased to once in 5 years till 65 years and at 65 if previous three smears were normal screening can be stopped. Annual screening is never recommended at any age and it is not cost effective to begin screening before the age of 25.

Treatment of CIN

Cervical Intraepithelial Neoplasia (CIN) are detected by screening. When the screening tests are abnormal the patient undergoes colposcopic biopsy. Colpscope is a high power microscope used to visualize the cervix and biopsies are taken from abnormal areas seen in colposcopy.

CIN1 otherwise called low grade CIN are usually transient lesion and are considered as histopathologic evidence of HPV infection. 60-80% of CIN1 lesions regress to normal, only 10% progress to CIN3. On the other hand CIN2 and3 are considered as high grade lesions and 50% progress to invasive cancer if untreated. The progression to carcinoma occurs over a period of 5- 20 years. Hence all high grade CINs mandate treatment while low-grade CINs can be followed up by pap smear and colposcopy 6 monthly. During follow up if the lesion is progressing or if it is persisting after 24 months they are treated. Treatment is also offered for patients not compliant on follow up even when the lesion is low grade.

Treatment modalities

Treatment of CIN depends on the age of the patient, her desire for child bearing, the grade of CIN and also the availability of treatment modalities.The treatment modalities for CIN include ablative techniques and excisional techniques. In ablative techniques the lesion is abladed or destroyed, while in excisional technique the lesion is excised. These simple, safe effective techniques have replaced hysterectomy as the treatment of CIN.

Ablative techniques

In ablative techniques the CIN lesion along with the adjacent transformation zone is destroyed. Ablative techniques include cryotherapy, laser ablation, cold coagulation and radical diathermy.

The most commonly used ablative technique is cryotherapy. Radical diathermy because of its high morbidity is no longer done for CIN. Ablative techniques are simple safe methods done as outpatient procedures and can be done by trained health workers also.

Indications for Ablative techniques

1.Low grade CIN

2.Lesion involves <75% of ectocervix

3.No endocervical canal involvement

4.No evidence of invasive cancer

Ablative techniques are performed after colposcopic biopsy to rule out invasive cancer.

Cryotherapy

During cryotherapy tissues are frozen which results in crystallization of intracellular water which leads on to cell death. The refrigerant gases used include carbon dioxide and nitrous oxide. The cryoprobe is applied on the ectocervix and the gases are released under high pressure which results in cooling. The technique used in double freeze technique, which includes freezing for 3 minutes, thawing for 5 minutes and repeat freezing for 5 minutes. An ideal candidate for cryotherapy should have CIN1 confined to ectocervix. The cure rate for properly selected patents is around 90-95%. Cryotherapy is a safe procedure with very less complications.The most common problem after cryotherapy is copious vaginal discharge.

Cold coagulation

The term cold coagulation is a misnomer because here heat is used instead of cold to achieve tissue destruction. This technique was introduced by Semm and popularized by Duncon. Heat is applied using a probe with a temperature of 100-120 degree Celsius. Duration of each application is 40 seconds and multiple overlapping applications are done to cover the entire ectocervix. The procedure is painless as ectocervix has very few nerve endings.

The cold coagulator is a small compact easily transportable machine which works with electric current.

The treatment time is also short and many patients can be treated in the same sitting. In view of better patient comfort and less consumables used this technique is now upcoming for treatment of CIN in low resource settings.

Laser ablation

Ablative techniques using CO2 laser was popularized by Anderson, Jordan, Baggish in the 1980s. The advantage is the procedure can be done with exact precision. The laser machines being costly and unavailable makes the procedure less popular in developing countries including India.

Excisional techniques

Excisional methods are the mainstay of treatment for CIN as they are suitable to almost all CIN lesions. Excision techniques are superior to ablation not in their cure rates because both carry almost the same cure rates(90-95%). But after excision we get the specimen for histopathological study whereby we can confirm the diagnosis, assess the margins and there is no danger of missing invasive cancer.

Indications for excision techniques

1.High grade CIN -CIN 2&3

2.Large lesions involving more than 75% of ectocervix

3.Lesion extending to endocervical canal

4.Glandular lesions suspected

5.Invasive cancer suspected

6.Several previous treatments for CIN (treatment failures)

Excisional techniques include Loop Electrosurgical Excision Procedure (LEEP), Cervical conisation and laser excision.

LEEP(Loop Electrosurgical Excision Procedure)

Loop Electrosurgical Excision Procedure involves excision of CIN using loop electrodes made of stainless steel or tungsten wires activated by electric current from an electrosurgical generator.

This is an outpatient procedure done under local anaesthesia and can be used to treat endo & ecto cervical disease upto 1.5 cm into endocervical canal.

Equipments needed for LEEP include an electro surgical unit, colposcope and a smoke evacuator. This is an outpatient procedure done under colposcopic guidance. Patient is placed in modified lithotomy position, cervix is exposed with insulated speculum. Colposcopy is done to delineate the lesion. Local anaesthesia is given intracervically with xylocaine. Loop electrode is selected based on the extent of lesion. Using the activated loop the lesion with the involved transformation zone is excised. If the lesion is extensive multiple passes with the loop will be needed to excise it entirely. Hemostasis is attained using ball electrodes by fulgeration, which sprays current to the crater.

LEEP is a simple and safe procedure with excellent social acceptance. It is done as an out patient procedure and patients are sent home 2-3 hours after the procedure. The cure rate is also very good ranging from 90-95%. The most important advantage is being an excisional technique there is no danger of missing an invasive cancer.

Complications of LEEP include bleeding, vaginal burns and infection. Bleeding is usually controlled by dessication and fulgeration and for uncontrolled bleeding figure of eight sutures are put on the cervix. Bleeding can also occur 4-6 days after treatment which is usually due to infective etiology and are treated by antibiotics. Long term complications include infertility due to cervical stenosis and deficient cervical mucous. Due to shortened cervix cervical incompetence can also occur leading on to preterm labour and premature rupture of membranes. Cervical mucous acts as a potential barrier for ascending infection and hence infections can occur during pregnancy leading on to chorio amnionitis and preterm labour.

Hysterectomy

Hysterectomy is not considered as a first-line treatment for CIN because the risk of significant morbidity with hysterectomy is higher than with less invasive treatment modalities like LEEP and Cryotherapy.

Cervical cancer

Signs and symptoms

1.Inter-menstrual bleeding

2.Post-coital bleeding

3.Post-menopausal bleeding

4.Vaginal discharge -blood stained or foul smelling

5.Pelvic pain, bladder symptoms in advanced cases

Routes of spread

Cervical cancer can spread by direct extension or by lymphatic dissemination. Direct extension involves the endometrium, vagina, parametria, bladder, or rectum. Ovarian involvement by direct extension of cervical cancer is rare; ovarian metastases occur in approximately 0.5 percent of squamous cell carcinomas and 1.7 percent of adenocarcinomas. Hematogenous spread is rare and occurs to the lungs and liver .

Diagnosis and Staging

The diagnosis of cervical cancer is made by histopathological examination of cervical biopsies. Cervical cancer is clinically staged using the FIGO criteria. FIGO staging does not take into account imaging findings including CT or MRI.

FIGO staging classification for cancer cervix

FIGO stage		Description
0		Carcinoma in situ (pre- invasive carcinoma)
I		Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
I A		Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions - even with superficial invasion - are stage IB
	I A 1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread.
	I A 2	Stromal invasion more than 3.0 mm in depth and not more than 5.0 mm with a horizontal spread 7.0 mm or less.
I B		Clinically visible lesion confined to the cervix or microscopic lesion greater than I A 2
	I B 1	Clinically visible lesion 4.0 cm or less in greatest dimesion.
	I B 2	Clinically visible lesion more than 4.0 cm in greatest dimesion.
II		Tumour invades beyond the uterus but not to the pelvic wall or to lower third of vagina.
	II A	Without parametrial invasion
	II B	With parametrial invasion
III		Tumour extends to pelvic wall and / or involves lower third of vagina and / or causes hydronephrosis or non- functioning kidney.
	III A	Tumour involves lower thrid of vagina , no extension to pelvic wall
	III B	Tumour extends to pelvic wall and / or causes hydronephrosis or non- functioning kidney.
	IV A	Tumour invades mucosa of bladder or rectum and / or extends beyond true pelvis.
	IV B	Distant metastasis

a: 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.

b: The presence of bullous oedema is not sufficient to classify a tumour as stage IV .

Treatment of cancer cervix

Early cancer cervix is treated by surgery and advanced cases by chemo radiation.

Surgery

Surgical treatment is by radical hysterectomy which involves the en-bloc removal of uterus, cervix, parametrial tissues and upper vagina. It is usually combined with pelvic lymphadenectomy. The extent of parametrial tissue removed determines whether a class II or class III RH. Surgery conserves ovarian function and avoids the effects of early menopause and hence is ideal for a young patient. There is less shortening and fibrosis of the vagina occurs as compared to radical radiotherapy and thus better sexual function after surgical treatment. Patient selection is important before planning surgical treatment because the combined treatment of radical surgery and postoperative radiotherapy increases overall morbidity compared to either alone. Patients with stage IA, IB1, IIA1 are considered for surgical treatment. Preoperative MRI helps in identifying an ideal patient for radical hysterectomy which can be performed by laparotomy, laparoscopy or by robotic surgery. Removal of pelvic lymph nodes is not recommended during treatment for FIGO 1A1 disease but pelvic lymph nodes should be removed from 1A2 disease onwards.

Concurrent Chemoradiation

Advanced cervical cancer including FIGO stages IB2, IIA2, IIB, IIIA, IIIB and IVA are treated by chemoradiation. Surgery is not offered to this group of women because of the significant risk of positive margins and positive nodes which would mandate adjuvant radiation. Concurrent chemoradiation with platinum based chemotherapy is better than radiation alone for the treatment of advanced cervical cancer. Single agent Cisplatin weekly at 40mg/m2 is administered during radiotherapy. Radiotherapy includes External beam radiation to the pelvis with intracavitory brachytherapy to maximize local control.

Colorectal Cancers
-A Rising Concern?

Dr. J. Siva Ranjith,
Assistant Professor, Surgical Oncology
Regional Cancer Centre, Thiruvananthapuram

Introduction

Globally, 1.8 million new cases of colorectal cancers (CRC) are diagnosed and 900,000 deaths occur annually (Globocan 2018). In the developed countries, screening and improved treatment is reducing incidence and mortality considerably, although the rates remain relatively high, with age-standardized rates per 100,000 persons per year estimated to be 30.8 for incidence and 10.6 for mortality(worldwide rates are 19.7 and 8.9, respectively)(Globocan 2018).

Generally, industrialization and economic growth lead to a western dietary pattern, sedentary lifestyle and increasing obesity, all of which are major risk factors for CRC. Thus, the westernization of countries tends to be followed by a rise in CRC incidence rates. This pattern is supported by higher CRC incidence rates observed in economically developed countries as indicated by a higher human development index, a composite score of life expectancy, education and income .

Age-standardized incidence rates vary more than 45-fold between the highest (51.2 cases per100,000 persons per year in Hungary) to lowest (1.1 cases per 100,000 persons per year in the Gambia)(Globocan) . The large international variation represents a combined effect of multiple factors, including lifestyle, genetics,life expectancy (for example, underdeveloped countries might have lower incidence rates even after age standardization because fewer people reach the age of 65-79 years, when most CRC is diagnosed) and data quality of cancer registries.

The Changing Trend

According to 2012 International Agency for Research on Cancer Globocan data, 1.4 million new cases and almost 700 000 deaths were reported whereas according to Globocan 2018, globally, CRC constituted approximately1.8 million new cases and 900,000 deaths annually, making it the third most commonly diagnosed malignancy and the second leading cause of cancer deaths. (Fig 1)

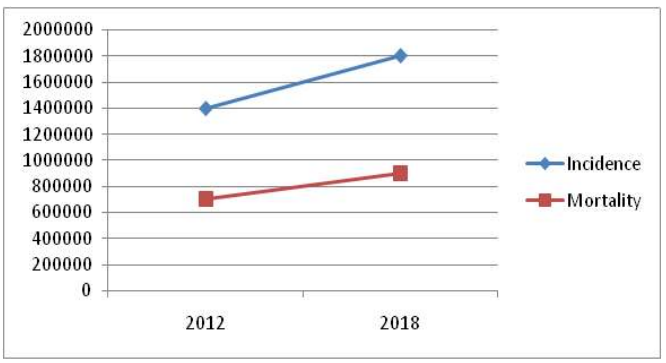


Figure 1 : Incidence and Mortality due to CRC from Globocan 2012 to 2018

Given the temporal profiles and demographic projections, the global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030

The regional trends across the Globe

In South America, Eastern Europe and Asia, economically transitioning countries are experiencing increasing incidence rates (e.g. Brazil,Slovakia and China). In high-income countries of North America, Europe and Oceania (e.g. the USA, France and New Zealand), incidence rates are either relatively stable or increasing (e.g., Italy, Norway and Spain) (Fig. 2).

Figure 2: World wide age standardized incidence rates of CRC

The Indian Scenario

Compared to the western world, the incidence of colorectal cancers in India is low. According to the Globocan 2018 data, the ASR per 10000 is 5.8 for men and 4.4 for women, which is far lower than most of the higher income countries in the world. (Fig.3)

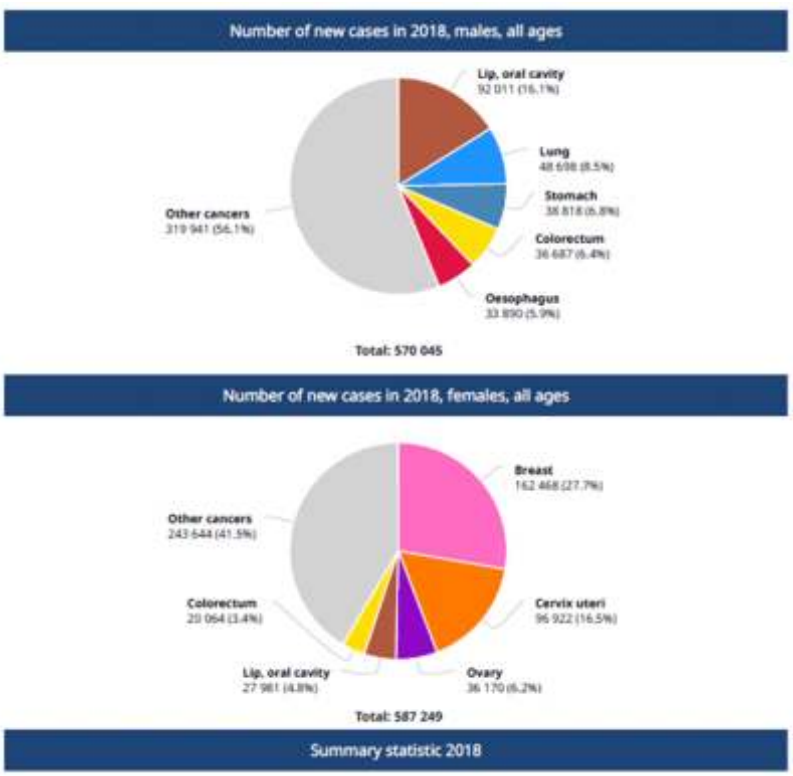
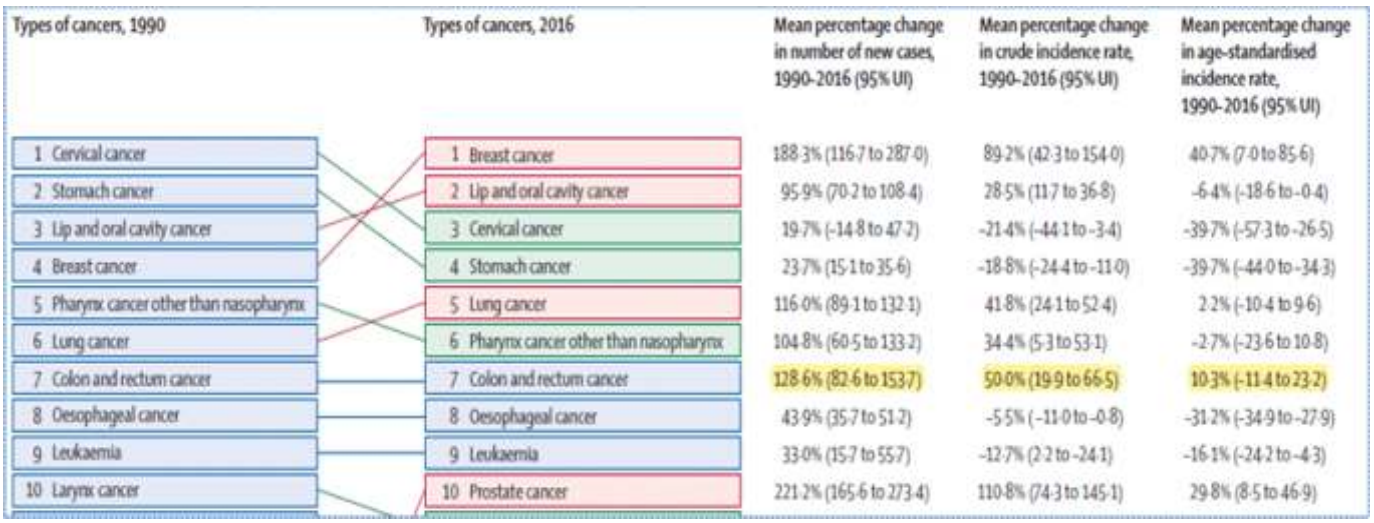


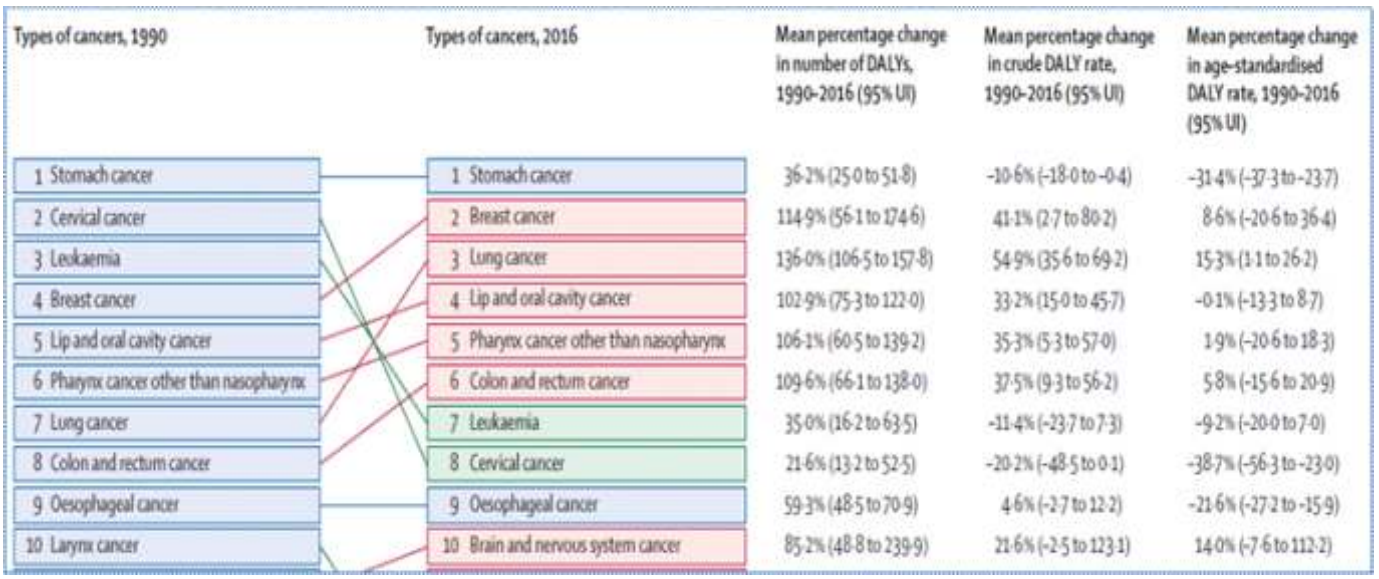
Figure 3 : Summary Statistic 2018 Globocan for India

However, over the years, India has seen a slow but steady rise in the incidence, disability-adjusted life-years (DALYs) and mortality due to colorectal cancers.Mean percentage change in crude incidence rate, from 1990 to 2016 (95% UI) was 50·0% (19·9 to 66·5) and Mean percentage change in age standardised incidence rate, from 1990 to 2016 was 10·3% (11·4 to 23·2)(Fig 4, 5 ref 3). So, the numbers confirm a rising trend in colorectal malignancies in our country.



Types of cancers, 1990	Types of cancers, 2016	Mean percentage change in number of new cases, 1990-2016 (95% UI)	Mean percentage change in crude incidence rate, 1990-2016 (95% UI)	Mean percentage change in age-standardised incidence rate, 1990-2016 (95% UI)
1 Cervical cancer	1 Breast cancer	188·3% (116·7 to 287·0)	89·2% (42·3 to 154·0)	40·7% (7·0 to 85·6)
2 Stomach cancer	2 Lip and oral cavity cancer	95·9% (70·2 to 108·4)	28·5% (11·7 to 36·8)	-6·4% (-18·6 to -0·4)
3 Lip and oral cavity cancer	3 Cervical cancer	19·7% (-14·8 to 47·2)	-21·4% (-44·1 to -3·4)	-39·7% (-57·3 to -26·5)
4 Breast cancer	4 Stomach cancer	23·7% (15·1 to 35·6)	-18·8% (-24·4 to -11·0)	-39·7% (-44·0 to -34·3)
5 Pharynx cancer other than nasopharynx	5 Lung cancer	116·0% (89·1 to 132·1)	41·8% (24·1 to 52·4)	2·2% (-10·4 to 9·6)
6 Lung cancer	6 Pharynx cancer other than nasopharynx	104·8% (60·5 to 133·2)	34·4% (5·3 to 53·1)	-2·7% (-23·6 to 10·8)
7 Colon and rectum cancer	7 Colon and rectum cancer	128·6% (82·6 to 153·7)	50·0% (19·9 to 66·5)	10·3% (-11·4 to 23·2)
8 Oesophageal cancer	8 Oesophageal cancer	43·9% (35·7 to 51·2)	-5·5% (-11·0 to -0·8)	-31·2% (-34·9 to -27·9)
9 Leukaemia	9 Leukaemia	33·0% (15·7 to 55·7)	-12·7% (2·2 to -24·1)	-16·1% (-24·2 to -4·3)
10 Larynx cancer	10 Prostate cancer	221·2% (165·6 to 273·4)	110·8% (74·3 to 145·1)	29·8% (8·5 to 46·9)

Figure 4 : Rising Incidence of CRC in India from year 1990 to 2016



Types of cancers, 1990	Types of cancers, 2016	Mean percentage change in number of DALYs, 1990-2016 (95% UI)	Mean percentage change in crude DALY rate, 1990-2016 (95% UI)	Mean percentage change in age-standardised DALY rate, 1990-2016 (95% UI)
1 Stomach cancer	1 Stomach cancer	36·2% (25·0 to 51·8)	-10·6% (-18·0 to -0·4)	-31·4% (-37·3 to -23·7)
2 Cervical cancer	2 Breast cancer	114·9% (56·1 to 174·6)	41·1% (2·7 to 80·2)	8·6% (-20·6 to 36·4)
3 Leukaemia	3 Lung cancer	136·0% (106·5 to 157·8)	54·9% (35·6 to 69·2)	15·3% (1·1 to 26·2)
4 Breast cancer	4 Lip and oral cavity cancer	102·9% (75·3 to 122·0)	33·2% (15·0 to 45·7)	-0·1% (-13·3 to 8·7)
5 Lip and oral cavity cancer	5 Pharynx cancer other than nasopharynx	106·1% (60·5 to 139·2)	35·3% (5·3 to 57·0)	1·9% (-20·6 to 18·3)
6 Pharynx cancer other than nasopharynx	6 Colon and rectum cancer	109·6% (66·1 to 138·0)	37·5% (9·3 to 56·2)	5·8% (-15·6 to 20·9)
7 Lung cancer	7 Leukaemia	35·0% (16·2 to 63·5)	-11·4% (-23·7 to 7·3)	-9·2% (-20·0 to 7·0)
8 Colon and rectum cancer	8 Cervical cancer	21·6% (13·2 to 52·5)	-20·2% (-48·5 to 0·1)	-38·7% (-56·3 to -23·0)
9 Oesophageal cancer	9 Oesophageal cancer	59·3% (48·5 to 70·9)	4·6% (-2·7 to 12·2)	-21·6% (-27·2 to -15·9)
10 Larynx cancer	10 Brain and nervous system cancer	85·2% (48·8 to 239·9)	21·6% (-2·5 to 123·1)	14·0% (-7·6 to 112·2)

Figure 5 : Increasing DALY rates for CRC in India from 1990 to 2016

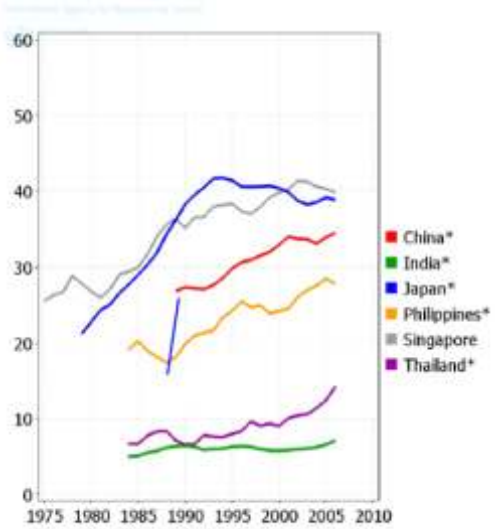
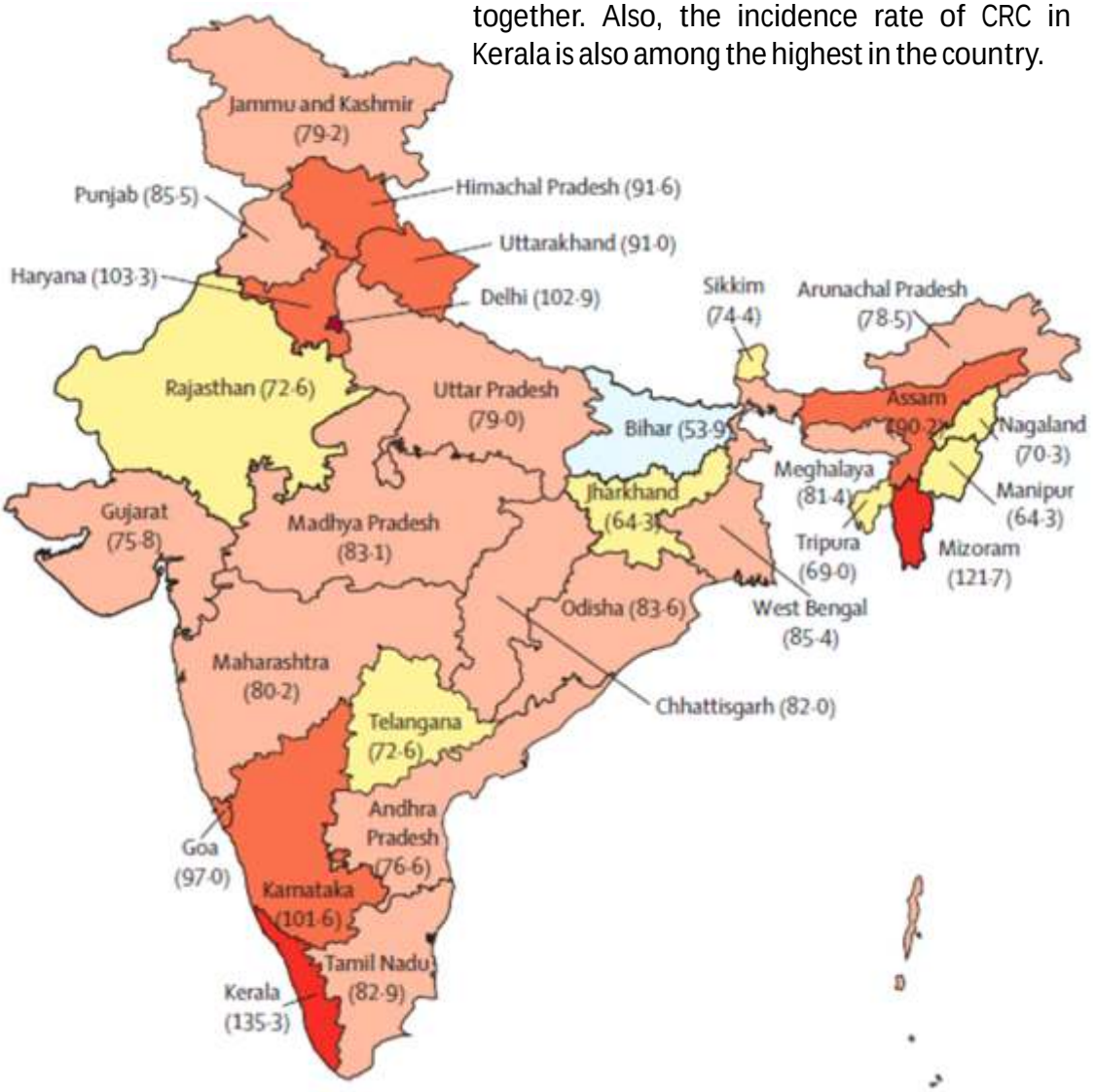


Figure 6 : Slow but stea rise in incidence, over t years

Kerala Our State

Among the Indian States, Kerala has the highest crude cancer incidence rate for all cancers taken together. Also, the incidence rate of CRC in Kerala is also among the highest in the country.



As per the Indian National Cancer Registry Programme Report 2016, the incidence rates by gender (ASR) of colonic cancers were highest in Thiruvananthapuram. However the age adjusted incidence rates (AAR) of colonic cancers in males was highest in Aizawl District (6.8), followed by Mizoram (5.4), Kamrup Urban District (5.2) and Thiruvananthapuram (4.5). In Females, Aizawl District had the highest AAR (5.4), followed by Kamrup Urban District (4.3) and Mizoram state (3.9), with Thiruvananthapuram in fifth position with an AAR of 3.0.

The data from Population Based Cancer Registry (PBCR) and Regional Cancer Centre Hospital Based Cancer Registry (HBCR) point towards a slowly increasing trend. However the rise and the rate of rise is not at all alarming, and with the available data, it cannot be scientifically attributed to any particular cause or aetiology.

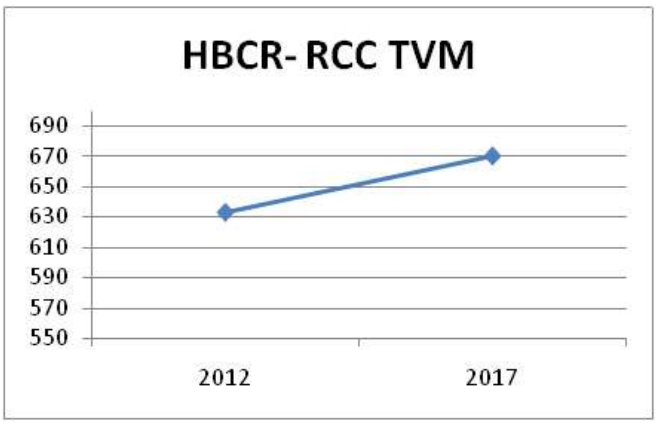


Figure 7: The total number of CRC in 2012 HBCR was 633, whereas it was 670 in 2017, which, though a slow rise, should raise concern but not panic

How does colorectal cancer start?

CRC usually begins as a noncancerous growth called a polyp that develops on the inner lining of the colon or rectum and grows slowly, over a period of 10 to 20 years. Fewer than 10% are estimated to progress to invasive cancer

What are the symptoms of colorectal cancer?

Early CRC often has no symptoms, which is why screening is so important. As a tumour grows, it may bleed or obstruct the intestine. In some cases, blood loss from the cancer leads to anaemia. Additional warning signs include:

-Bleeding from the rectum

-Blood in the stool or in the toilet after having a bowel movement

-Dark or black stools

-A change in bowel habits or the shape of the stool (e.g., more narrow than usual)

-An urge to have a bowel movement when the bowel is empty

-Constipation or diarrhea that lasts for more than a few days

-Decreased appetite

-Unintentional weight loss

Colorectal Cancer Risk Factors

Factors that increase risk		Relative Risk
Family History	1st Degree Relative	2.2
	More than 1 relative	4
	Relative with diagnosis before age of 45yrs	3.9
Inflammatory Bowel Disease		1.7
Diabetes		1.3
Behavioural Factors	Alcohol > 3 drink per day	1.4
	Smoking	1.2
Obesity	BMI > 30 kg/m2	1.3
Diet	Processed meat (50g/day)	1.2
	Red Meat (100g/day)	1.2

Factors that decrease risk	Relative Risk
Physical activity	0.7
Milk / Diary consumption	0.8

Colorectal Cancer Prevention - Screening

The slow course of growth from precancerous polyp to invasive cancer provides a unique opportunity for the prevention and early detection of CRC. The evidence is convincing that in adults 50-75 years of age, screening for colorectal cancer detects early-stage cancer or premalignant polyps thereby decreasing the CRC mortality.

The screening tests validated are :

(1) Faecal occult blood tests

(2) Flexible Sigmoidoscopy

(3) Flexible Colonoscopy.

Sensitivity and specificity is highest for colonoscopy and hence colonoscopy is considered as the gold standard for colo-rectal screening. Positive results from any test other than colonoscopy should be followed with a colonoscopy for complete diagnostic evaluation.

The United States Preventive Task Force recommends screening for all adults between 50 - 75 years of age with either of the above modalities. Those population with an increased risk on account of family history or any of the hereditary colonic cancer syndromes, an earlier age of onset of screening is recommended as per the genetic abnormality or the family history.

Summary of Treatment Options in CRC

For Colon cancer, primary surgery remains the standard of care. The need for adjuvant chemotherapy should be determined on an individual basis, depending on the stage of the disease. For Rectal cancer, Neoadjuvant chemo-radiotherapy (NACTRT) should be strongly considered for all locally advanced cancers, even if it is resectable, for downstaging and anal sphincter preservation. Patients with limited liver or lung colorectal metastases should be referred early to an onco-surgeon to assess resectability. For unresectable metastatic disease, chemotherapy is the usual modality, with 5-Fluourouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX) or Capecitabine and oxaliplatin (CAPEOX) as first-line. Regular surveillance after completion of curative resection or treatment of advanced disease is mandatory.

Conclusion

Global Patterns and trends in CRC incidence and mortality correlate with present human development levels and their incremental changes might reflect the adoption of more western lifestyles. In India and Kerala, the statistics over the last decade, shows that the CRC incidence is on slow and minimal rise, but not at all an alarming rate. Westernised life style, physical inactivity, obesity may be the contributing factors.

Targeted resource dependent interventions, including primary prevention in low-income, supplemented with early detection in high income settings, are needed to reduce the number of patients with CRC in future decades.

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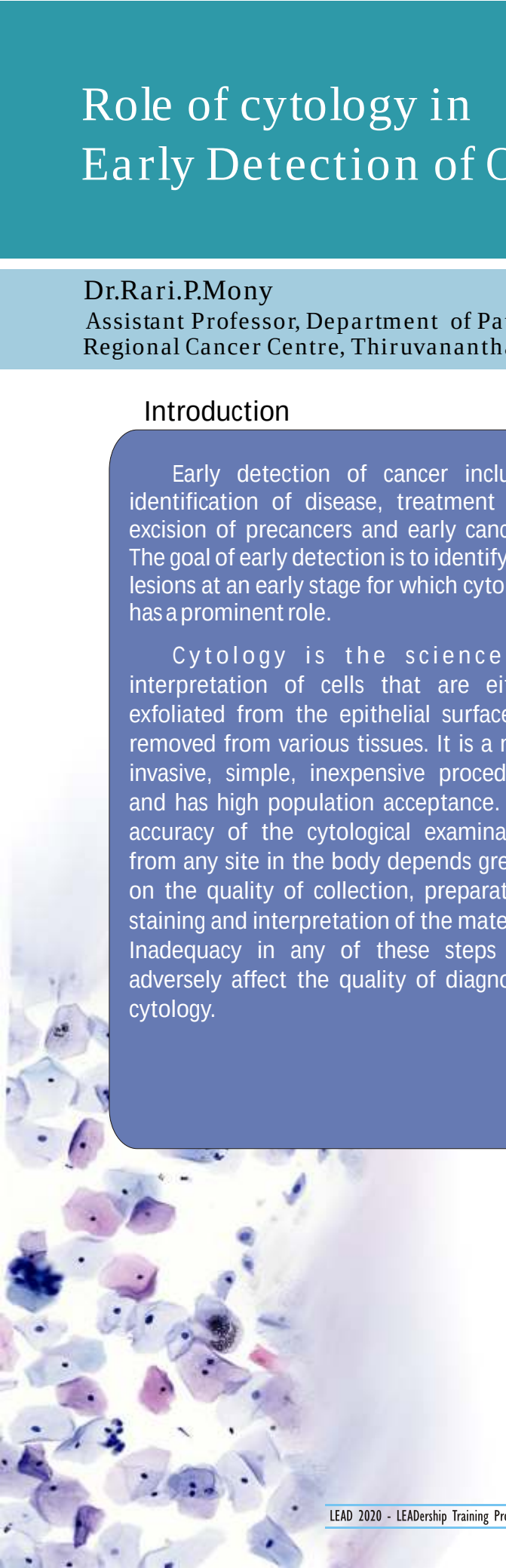
Role of cytology in Early Detection of Cancer

Dr.Rari.P.Mony
Assistant Professor, Department of Pathology
Regional Cancer Centre, Thiruvananthapuram

Introduction

Early detection of cancer includes identification of disease, treatment and excision of precancers and early cancers. The goal of early detection is to identify the lesions at an early stage for which cytology has a prominent role.

Cytology is the science of interpretation of cells that are either exfoliated from the epithelial surface or removed from various tissues. It is a non-invasive, simple, inexpensive procedure, and has high population acceptance. The accuracy of the cytological examination from any site in the body depends greatly on the quality of collection, preparation, staining and interpretation of the material. Inadequacy in any of these steps will adversely affect the quality of diagnostic cytology.



Collection & preparation of materials for cytology

Accurate interpretation of cellular material is dependent on factors such as:-

1. Methods of specimen collection.

2.Fixation and fixatives

3.Preservation of fluid specimen prior to processing.

4.Preparation of material for microscopic examination.

5.Staining and mounting of cell samples.

Methods of specimen collection

1.Exfoliative cytology
2.Fine Needle Aspiration Cytology (FNAC)
3.Body fluids
4.Abrasive cytology

1.Exfoliative cytology:

It is the study of cells that have been shed or removed from the epithelial surface of various organs. It includes secretions such as urine, sputum and vaginal or prostatic fluids or by artificial means such as paracentesis or lavage.

a.Female genital system:

The cytological specimen collected includes cervical smear(pap smear), vaginal smear, vaginal pool smear and endometrial smear. Almost all invasive cancers of the cervix are preceded by a phase of pre-invasive disease which can(10-20years) lead to an invasive cancer after 10-20 years.Pap test has got many advantages like no anesthesia is required and it is a simple, painless procedure which can be done in outpatient clinics. It is also useful for identification of inflammatory conditions such as Trichomonas Vaginalis, bacterial vaginosis and candidiasis.

Patient preparation for pap smear : Smear should be taken after two weeks from first day of menstruation without any vaginal medication on previous day.

Sampling: No lubricants are used for specimen collection. Excess mucus has to be removed . Sample is to be taken before application of acetic acid/ Lugol's Iodine .Optimal sample should include cells from cervix and endocervix/ transformation zone.

Preparation of smear: Smear is evenly smeared on the centre of the non-frosted area of the glass slide by rotating both the sides of the scrape end of the spatula in multiple clockwise swirls and it has to be fixed immediately. Two slides can be prepared if more thick material is obtained. This reduces the incidence of unsatisfactory smears and helps to detect more abnormalities.

Vaginal smear: It is taken from the lateral vaginal wall using broad and flat end of Ayre's spatula.If no spatula is available a cotton swab dipped in normal saline can be used.

Endometrial aspiration smear: A sterile cannula is introduced into the uterine cavity and aspirated with a syringe. It is spread on a glass slide and rapidly fixed.

b.Respiratory tract:

Sputum cytology- Morning specimen ensuing from overnight accumulation of secretion yields best results. Three to five consecutive days sputum samples should be examined to ensure maximum diagnostic accuracy.

Fresh unfixed specimen are better than pre fixed specimen (in 70% ethyl alcohol). Pre-fixed specimen should be smeared on albumin or polylysine coated slides.

C.Nipple discharge:

Spontaneous nipple discharge and discharge obtained by pressure are taken directly to the slide and immediately put in fixative.

2.Fine needle aspiration cytology (FNAC)

Indications

Useful in lesions such as growth of skin, subcutaneous soft tissue tumors, thyroid, lymph node, salivary gland and breast lump.

Guided aspirations- Useful in inaccessible sites such as mediastinum, abdominal and retroperitoneal organs and prostate .

Pre- requisites for a meaningful diagnosis on FNAC are-

Proper technique which includes correct procedure of taking FNAC (preparation of smears, fixation, staining, microscopic evaluation of smears and correlation of morphology with clinical picture).

Materials needed for FNAC

Needles-Disposable needle ranging from 22-24 gauge 1-11/2 inch needles are used.

For small subcutaneous lesions 23 gauge needle is ideal . Disposable plastic syringes of 10ml are used and it should produce good negative pressure. 5cc syringes are used for vascular organs such as thyroid.

Slides: Plain glass slides(clean, dry, transparent and grease free) is used.

Fixative: 95% Ethyl alcohol (fixative) is kept ready in coplin jars.

Other materials needed- Test tubes, pencil for marking, alcohol, swabs. All the materials needed for FNAC should be ready before starting the procedure. Any delay in fixation can make interpretation of smear difficult.

Aspiration procedure:

Steps:

- Relevant history and clinical details, radiological findings, provisional diagnosis and site of FNAC should be clearly mentioned by the requesting physician in the request form.

- Lesion to be aspirated is palpated and its suitability For aspiration has to be assessed by the doctor.

- Procedure has to be clearly explained to the patient and consent form should be duly signed and cooperation of the patient should be ensured before undertaking the procedure.

- Comfort position : The patient is made comfortable and can be made to lie supine on the couch.

- Immobilization of the lesion is the next step. The site is cleaned with alcohol swab and the lesion is fixed between thumb and index finger. After that , penetrate the lesion grasping the syringe with the needle attached and obtain the material following creation of vacuum. If pus or necrotic material is aspirated. FNAC should be repeated from the periphery of the lesion. If cystic fluid is aspirated fluid should be send for centrifugation followed by preparation of the smears. If the aspirate is cystic fluid consistency, colour and amount of fluid obtained should be mentioned. If lesion is sclerotic, finer needle should be used for aspiration. After the aspirate is obtained vacuum is released and needle is withdrawn. Aspirate is pushed in to the glass slide and the smear is prepared. Rapid fixation is done in alcohol for pap staining and H&E staining which gives better nuclear details.

Causes for unsatisfactory smears:

Non representative/ inadequate samples are taken due to poor quality of preparation like (thick smear, admixture of blood, delayed fixation, overstaining).

3.Body fluids

Effusion and Washings:

Freshly collected fluid is ideal, 10-15ml fluid is required. Do not take fluid from the draining bottle.Instead, it should be collected directly from the involved site or cavity.

CSF:

The site of puncture should be mentioned correctly such as Cisternal puncture / ventricular puncture to help in correct diagnosis. The sample should be processed within one hour of the procedure.

Urine:

Freshly voided urine sample on three consecutive days is to be tested.

Urine from collection bag should not be used.

Preservation of fluid before processing:

High protein containing effusion fluid should be preserved in room temperature for 24hours.High mucus containing specimen can be preserved for 12-24 hours ,if refrigerated. If preservation of fluid before processing cannot be done, pre-fixation is done using equal volume of 50% ethyl alcohol.

4.Abrasive cytology

In large ulcerative lesions and exophytic growth smear is taken directly from the lesion and slides are prepared and interpreted to get the diagnosis without any invasive procedure.

Clinical correlation and final interpretation by the pathologist

Communication between clinician and pathologist helps to maintain high quality of diagnosis and safe guard against error. Clinical information is critical and is a part of FNAC diagnosis as the morphological features may vary with the site of FNAC.

Systematic inclusion of clinical and lab data should be considered as a part of procedure.

The technique(aspirator), morphological interpretation(pathologist) and the clinical information (clinician) constitute a diagnostic triad on which the FNA diagnosis rests.

It is preferable not to report on technically poor slides or give a definite diagnosis without adequate clinical information and correlation. Clinical data serves as a safeguard in avoiding errors.

Clinical Problems in Head and Neck Oncology

Dr. Aparna. S
Assistant Professor ,Radiation Oncology
Regional Cancer Centre, Thiruvananthapuram

&

Dr. Kainickal Cessal Thommachan
Additional Professor, Radiation Oncology
Regional Cancer Centre, Thiruvananthapuram

Head and neck cancer encompasses a variety of cancers, mostly squamous cell carcinoma, arising from upper aero digestive tract. Early stage diseases are lesions less than 4 cm without infiltration of nearby structures and cervical nodal involvement. Locally advanced head and neck squamous cell carcinoma involves Stage III -T3 or N1 and Stage IVa - T4a or N2 disease which is managed with radical intent treatment. Whereas very advanced stage disease like Stage IVb -T4b or N3 disease or Stage IVc - merits palliative intent treatment to control the symptoms due to disease. The five-year overall survival rate is around 80% for early stage disease which dramatically drops to less than 30% for stage IV disease. Unfortunately, majority of the patients present with stage III& IV disease.

Head and neck squamous cell carcinoma is a loco regional disease and the primary aim of treatment is loco-regional control. Metastasis at presentation is rare in head and neck cancers. Early stage disease (Stage I&II) is treated with single modality treatment either radiotherapy or surgery. Stage III & IVa disease is managed by combined modality treatment either with radical chemo radiation or surgery followed by adjuvant treatment. Patients with advanced disease and poor performance status may not tolerate the radical approach treatment and in those patients palliative intent treatment with metronomic chemotherapy or short course radiotherapy is an option.

There are tremendous amount of research undergoing in the field of Oncology. Better surgical techniques has evolved from radical mutilating surgery to conservative surgeries, better reconstruction opportunities etc.

The recent evolution of technology in the field of imaging has led to accurate tumor delineation and sophisticated equipments helps precise delivery of radiotherapy beams which leads to better tumor control with minimal normal tissue toxicity. Targeted therapy and immunotherapy is getting momentum nowadays.

Now we will move to some case scenarios.

Case no-1

A 63 year old gentleman underwent chemo radiotherapy for locally advanced carcinoma oropharynx, presents to the OPD, 3 weeks after radiotherapy with poor oral intake, weakness, cough and fever. On examination, patient had grade 3 oral mucositis.Chest was clear.

Management

- Check for vitals and respiratory system
- Do culture and sensitivity
- Blood counts and electrolytes to rule out neutropenia and electrolyte abnormalities
- Start antibiotics
- Proper nutrition, hydration and pain management

Case no-2

A 50 year old gentleman underwent surgery and adjuvant radiotherapy for carcinoma tongue pT3N2bM0 and presents to OPD with oral mucositis.

Check

· Vitals
· Hydration
· Electrolyte + blood count
· Consolidation

Management
· Culture and sensitivity
· Antibiotics
· Ryles tube feeding
· Electrolyte correction
· Pain management

Case no-3

69 year old gentleman received chemo radiation, two weeks ago for carcinoma larynx. He presented to the Emergency Department with history of seizures. On examination,vitals were stable and there were no focal neurological deficits.

Approach

First differential diagnosis in this case scenario is to rule out ,

▪Electrolyte imbalance

▪Second primary Carcinoma Lung with brain metastasis (rare)

▪Other medical problems like cerebrovascular accident.

Always rule out common things like electrolyte abnormalities first and imaging of the brain is indicated if there are any focal neurological deficits.

In patients with electrolyte abnormalities try to identify and correct the factors like poor oral intake, dehydration, excessive vomiting or diarrhoea, hepatorenal dysfunction, use of diuretics, excessive intake of water, medical conditions associated with fluid shift from intracellular compartment to extracellular compartment etc.

Work flow of a patient with hyponatremia and management is given in the flowchart given below.

Sodium and water deficit (Hypovolemia)	
Renal losses	Extrarenal losses
Diuretic excess	Vomiting
Renal tubular acidosis	Diarrhoea
Osmotic diuresis	Pancreatitis
Urinary sodium concentration >20 mmol/litre	Urinary sodium concentration <10mmol/litre
Management -Isotonic saline	Management -Isotonic saline

Water excess(Euvolemia)
Glucocorticoid deficiency
Hypothyroidism

Syndrome of inappropriate ADH Secretion(SIADH)	
Urinary sodium concentration>20 mmol/litre	
Management- water restriction	

Sodium and water excess	
Nephrotic syndrome	Acute and chronic renal failure
Cardiac failure	
Cirrhosis	
Urinary sodium concentration <10mmol/litre	Urinary sodium concentration >20 mmol/litre
Management- sodium and water restriction	Management- sodium and water restriction

Case no- 4

60 year old gentleman underwent radiotherapy for carcinoma left buccal mucosa, presented to OPD with grade III dermatitis (Confluent, moist desquamation).

Always reassure the patient that skin reactions following radiotherapy are reversible. Care must be taken to avoid further skin peeling and avoid rough garments. Nails have to be cut to prevent scratching during sleep. Prophylactic antibiotics and steroid cream (eg-Betnoate N cream) can be prescribed.

Case no-5

56 year old lady underwent second cycle of Neo adjuvant chemotherapy with Carboplatin plus Paclitaxel for Stage IIIC carcinoma ovary - Post chemotherapy day 10, patient presents with102 F fever.

Acute complications of chemotherapy include nausea, vomiting,myelosupression, mucositis and alopecia. Febrile neutropenia is the most morbid complications after chemotherapy, usually occurs in the second week post chemotherapy. Even in those patients who report to casualty with trivial complaints, post chemotherapy, always try to rule out neutropenia.

- Neutropenia: Absolute Neutrophil Count (ANC)< 2,000 cells/mm3
- Mild neutropenia: ANC 1,000 to 1,500 cells/mm3
- Moderate neutropenia: ANC 500 to 1,000 cells/mm3
- Severe neutropenia: ANC < 500 cells/mm3

Usually IDSA (infectious disease society of America guidelines) are followed.

Triage the patients and start broad spectrum IV antibiotics with in one hour of reporting to casualty.Risk stratification based on MASCC(Multinational Association for Supportive Care in Cancer) is done and any patients with score more than 21 belong to low risk and can be managed on OPD basis with Oral Antibiotics using Quinolone plus Semi synthetic penicillin.

High Risk patients are treated with growth factor support, broad spectrum IV antibiotics either use Carbapenems (Imipenem plus cilastatin / meropenem) or piperacillin-tazobactam. Amigo glycosides have to be added if antimicrobial resistance is suspected or proven. In patients who present with hypotension, Pneumonia or Catheter related infection, Vancomycinis to be added. IV fluids, antifungals and other supportive medications have to be continued.

Case no-6

35 year old male diagnosed with Stage III Seminoma, presents 3 days after first Cycle of chemotherapy with BEP (Bleomycin, Etoposide, and Cisplatin regimen).How will you approach the chemotherapy induced nausea and vomiting (CINV) problem?

CINV can be classified into 5 types. Acute CINV occurs within 24 hours of the initial administration of an antineoplastic agent, while delayed CINV occurs after 24 hours and may peak 2 to 3 days post administration.Once a patient experiences CINV, he or she may then experience anticipatory CINV, which occurs when a sensory experience (eg, smell, sound, taste) triggers an episode of nausea and/or vomiting prior to subsequent administration of a chemotherapy regimen. Breakthrough CINV can be defined as nausea and/or vomiting that occurs within 5 days of chemotherapy treatment despite the use of a guideline-recommended antiemetic protocol, which requires the addition of more agents referred to as "rescue medications." Refractory CINV can be described as nausea and/or vomiting that consistently occurs in subsequent chemotherapy cycles despite the use of a guideline-recommended antiemetic regimen.

Pathophysiology

The pathophysiology of CINV includes both peripheral and central nervous system (CNS) pathways with different mechanisms involved in acute CINV and delayed CINV. In acute CINV, free radicals generated by toxic chemotherapeutic agents stimulate enterochromaffin cells in the gastrointestinal tract, causing the release of serotonin. Subsequently, serotonin binds to intestinal vagal afferent nerves via 5-HT3 receptors, which trigger the vomiting reflex via the nucleus of the solitary tract (NTS) and chemoreceptor trigger zone (CTZ) in the CNS. Substance P is considered to be the principal neurotransmitter involved in delayed CINV. Chemotherapy drugs trigger the release of substance P from neurons in the central and peripheral nervous systems, which then binds to neurokinin-1 (NK1) receptors mainly in the NTS to induce vomiting.

In both acute and delayed CINV, coordination of nausea and vomiting occurs in the vomiting center in the medulla oblongata via signals from the NTS, CTZ, or afferent vagal nerves.

Anticipatory CINV is generally regarded as a conditioned response to a prior episode of CINV.A sensory stimulus (eg, sight, sound, smell) present at the time of an episode of CINV conditions the patient to associate the stimulus with nausea and vomiting. Subsequent exposure to the stimulus then triggers the conditioned response of nausea and vomiting.The classic example is the patient who becomes nauseated simply upon arriving in the chemotherapy infusion suite. Prevention of acute and delayed CINV is the best approach to anticipatory CINV so that a sensory stimulus is not established.

Recommendation for highly emetic risk

Three drug combination of 5-HT_3 receptor antagonist, NK_1 antagonist and dexamethasone

Dosing:

•Day 1:NK_1 antagonist (aprepitant 125 mg or fosaprepitant 150 mg)
+ 5-HT_3 receptor antagonist
+ Dexamethasone 12 mg
•Day 2:
Dexamethasone 8 mg + NK1 antagonist,aprepitant 80 mg
•Day 3:Dexamethasone 8 mg *(dexamethasone may be given for 3 or 4 days)* + aprepitant 80 mg

Recommendation for moderate Emetic Risk

–Two drug combination of palonosetron and dexamethasone

Dosing:

▪Palonosetron 0.25 g IV OR 0.50 mg oral, day 1 only
▪Dexamethasone 8 mg (IV or oral), days 1-3

Better understanding of the pathways associated with vomiting and prophylactic use of antiemetics has dramatically reduced the incidence of chemotherapy induced nausea and vomiting.

Case no-7

70 year old gentleman diagnosed with metastatic adenocarcinoma lung (bone and adrenal metastases) had undergone 4 cycles of palliative chemotherapy. Meanwhile he was found to have multiple brain metastases for which he had palliative whole brain radiotherapy. Patient presented to casualty with severe headache. How will you manage the situation?

Patient should be started on anti-edema measures like IV Dexamethasone and Mannitol. No need for prophylactic Antiepileptics.

Case no-8

68 year old gentle man diagnosed with Stage IV Non-small cell lung carcinoma on Anti EGFR therapy with Afatinib presents with severe skin reactions, pustules and generalised itching.

Mechanism of action of anti-Epidermal Growth Factor Receptor (EGFR) therapy.

The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor involved in the proliferation and survival of cancer cells.EGFR is over-expressed in a variety of human tumours, including head and neck, breast, lung, colorectal, prostate, kidney, pancreas, ovary, brain and bladder cancer. Anti-EGFR monoclonal antibodies bind to the extracellular domain of EGFR and small-molecule inhibitors (Tyrosine kinase inhibitors) block the intracellular pathways.

The earliest and most common cutaneous adverse event is rash occurring from 50 to 100% of patients treated with anti EGFR therapy. Because EGFRs are highly expressed in sebaceous epithelium, eruptions are generally presented in seborrheic areas involving the scalp, face, neck, chest, and upper back. Xerosis is the second most common cutaneous adverse event followed by paronychia,trichomegalyetc. Follicular pustules may infrequently occur.

Management of rash

To promote maximal skin hydration, general measures should include washing with tepid water and application of non-greasy, alcohol-free emollients.Sun exposure should be minimized. Antibiotics should be prescribed if superadded infection.Patients with severe skin reactions may require a dose reduction or temporary interruption of therapy.

Case no-9

A 65 year old lady underwent Modified Radical Mastectomy (MRM) for carcinoma left breast pT2N1M0. Patient was Hormone receptor positive and Her-2 Negative. Patient received chemotherapy with three cycles of FEC Regimen followed by three cycles of Docetaxel and adjuvant radiotherapy. Treatment completed 3 years back and is on Tamoxifen 20 mg and complaints of bleeding per vaginum.

Tamoxifen has a stimulant effect on the endometrium, possibly by acting as a partial estrogenic agonist.Tamoxifen use has been associated with an increased incidence of endometrial changes, including hyperplasia, polyps, uterine fibroids and rarely adenocarcinomas of the endometrium and uterine sarcomas. Imaging including trans-vaginal ultrasound and/or endometrial biopsy may be necessary to rule out malignancy.

Case no-10

23 year old girl received chemo radiotherapy for Carcinoma Nasopharynx T2N1M0 and completed treatment 3 years back. She is on follow up. Now, presents with back ache and difficulty in walking. How to proceed?

Most important differential diagnosis is spinal cord compression.

Sensitivity of plain X ray DL spine to detect spinal cord impression is low. We can appreciate loss of pedicle, height reduction or collapse of the vertebra and can be considered as an initial investigation. The gold standard is MRI spine which helps to rule out malignant as well as other causes of neurological deficits. Patient needs neurosurgical decompression in case of oligometastatic disease or palliative radiotherapy on an emergency basis. Steroids should be started at the diagnosis of malignant cord compression. Hypercalcemia is common with skeletal metastasis and management includes correction of the underlying cause with adequate hydration, bisphosphonates, Calcitonin etc.

Massive tumor bleeding is one of the common terminal events in patients with incurable disease, often preceded by warning bleeds.Surgical management by means of External Carotid artery Ligation and embolization is feasible in very few patients. Hence mostly are managed conservatively with local application of adrenaline,antifibrinolytics like tranexamic acid and antihemorrhagic agent like ethamsylate. Stop the anticoagulant medications if patient is taking any. Always counsel the family regarding poor prognosis, chance of uncontrollable bleeding, aspiration and death.

Fungating wounds should be cleaned and dressed on a regular basis with Tab.Metrogyl and care should be given to avoid growth of maggots.

In situations where patient presents with breathlessness not responding to antibiotic and bronchodilator treatment, possibilities of aspiration pneumonia and pleural effusion should be ruled out and managed accordingly. Swallowing and laryngeal dysfunction can lead to aspiration which may be either due to progressive disease or post treatment sequelae (Surgery /radiation therapy).

Pain management is an integral part of treatment of cancer and is prescribed according to WHO step ladder. If not able to manage with conventional analgesics, patient may be referred to nearby palliative care center.

Head and neck cancer is diverse in its presentation and clinical outcome.It often necessitates multimodality treatment, rehabilitation post treatment and best supportive treatment in patients who are not candidates for radical intent treatment.

APPENDIX -1

Oral, Breast and Cervical Cancer Screening-

Points to Remember

Oral Cavity-Clinical Examination, Precancer Management & Referral

-Take a brief medical history including personal history with specific details about tobacco/alcohol habits.

-Systematic examination of oral cavity with aid of good torch light.
-Start inspection from the commissure (angle of mouth) on one side and reach the opposite side in a clock wise /anti clockwise direction taking care to examine the upper and lower gingivobuccal sulcus, hard palate, soft palate, right and left lateral margin of tongue, dorsum tongue, floor of the mouth, lingual sulcus and upper and lower labial mucosa.

Inspection
Watch out for white patch/leukoplakia that cannot be scraped off.

Palpation
·No induration
·Induration
If no induration, differential diagnosis may be traumatic keratosis, fungal infection, lichen planus.

Treatment
-Tobacco and alcohol cessation
-Correction of anemia-Multivitamin and iron tablets.-
Monitoring the lesion and report back if there is a change in the characteristics of lesion such as thickening of white patch, exophytic growth, granular area, appearance of fissures in the white patch. If there are features like induration/presenceof granular areas/ulceration/proliferative growth /infiltration etc, refer the patient to Dental Surgeon/Dental

Follow up
Educate the patient on mouth self-examination and sensitise them about malignant changes such as appearance of granular areas, thickening,fissures/growth/ulceration. Follow up every three to six months or earlier depending on the clinical severity of the lesion.

Erythroplakia:

Clinical examination:Red velvety patch that cannot be scrapped off. Inspection and palpation should be done. More than 50% of these lesions will be harbouring carcinoma in situ and hence excision biopsy is preferred wherever it is feasible.
Differential diagnosis: Erosions due to chemicals and drugs, pan chewer's encrustation.

Treatment: Tobacco and alcohol cessation. Patients should be taught on mouth self-examination. All cases to be referred for biopsy to higher centres.

Submucous fibrosis:

Patient may present with symptoms of intolerance to spicy foods, burning sensation, difficulty in opening mouth or protruding tongue. Leukoplakia may co-exist with oral submucous fibrosis.

Clinical examination may reveal pale atrophic mucosa, depapillation of tongue, fibrotic bands at circumoral/posterior part of buccal mucosa.

Treatment: Correction of anemia using multivitamin and iron tablets. Patients should be taught on mouth self-examination and has to be made aware of the malignant transformation potential of the lesion. If any change in the characteristic of lesion, such as granular areas, exophytic growth and ulceration, patients have to be advised to come for follow up at the earliest. Cessation of habits and oral physiotherapy also has to be advised. Selective grinding of sharp teeth and extraction of root stumps must be advised to eliminate chronic irritation.

Referral criteria: Presence of growth, granular areas, thick white patches and induration has to be referred for biopsy to higher centers.

Follow up: Mandatory three to six month follow up, or earlier, depending on severity.

Lichen planus

Burning sensation (may or may not be present), Erosion (may or may not be present)

Clinical diagnosis: White/red patches with white striations (Wickham striae)

Treatment:Monitor the lesion, advise to relieve tension/anxiety. If drug induced, consider change of medication, educate patient on mouth self-examination and features of malignant transformation

Referral criteria: Presence of growth, granular areas or induration

Follow up: Every three to six months or earlier depending on severity.

Traumatic ulcer

In addition to the above potentially malignant disorders, persistent trauma from sharp teeth/root stump or ill-fitting dentures can often lead to the development of oral cancer.

Clinical diagnosis: Non healing ulcer of more than 2 weeks duration with or without hyperkeratosis.

Treatment:Removal of irritating focus(sharp tooth, root stump, ill-fitting denture) and antibiotics.

Referral criteria: If lesion persists after 2 weeks, refer for biopsy.

Follow up: Ensure the lesion has completely regressed following conservative measures.

Breast Cancer

Breast cancer is the leading cancer among females based on the Population based Cancer Registry report of Thiruvananthapuram district. Over the last two decades, an upward trend was observed in breast cancer incidence in Thiruvananthapuram district. The current incidence rate is 53.3/100,000 population (2014 PBCR report)

Diagnostic criterion -When to suspect/diagnose
A woman with
·Lump(breast/axilla),
·Skin changes in breasts,
·Nipple discharge, retraction, excoriation or inversion
·Previous history of breast cancer
·Family history of breast cancer (especially in first degree relatives)
Inspection and palpation are recommended for women with any of the above features and also for high risk groups.

Differential diagnosis:
Mastitis,breast abscess, fibroadenoma, fibroadenosis, fibrocystic disease and traumatic fat necrosis.

Investigation:
Clinical breast examination should be done in a well lit room with respect to patient's privacy and comfort. If found suspicious, refer to higher centers.

Treatment:
Women should be taught on breast self examination.
A short course of antibiotics can be given if there is mastitis/breast abscess .
Tab Amoxicillin (625mg)+ Clavulinic acid TDS (5-10 days depending upon the severity)
NOTE : Incision and drainage should not be done for breast abscess at PHC level

Referral criteria: Any breast lump especially lumps which are hard, fixed to skin/ surrounding structure with or without asymmetry and skin ulceration,

peaud'orange appearance, satellite skin nodules and axillary lymph nodes should be referred to a higher centre for diagnostic evaluation and follow up. Lumps with proliferative disease with or without atypia should be referred to higher centre for excision biopsy.

Follow up:

Follow up of benign lumps can be done at PHC level till they develop cancer in the later stages of life. This will be useful for patients who are able to afford mammogram and ultrasound investigation expenses.

Cervical cancer

Cervical cancer is the 3rd common cancer in Kerala among women. According to population based cancer registry of RCC we are seeing a declining trend for cervical cancer in Kerala for the past 3 decades. Now the incidence of this cancer is 8.1/100,00 population and it is not a major public health problem and population based screening is not cost effective and is not needed in Kerala. However early detection can be done through camps and clinics. It is a preventable cancer and curable cancer if detected and treated early.

Etiopathological factors

The primary cause of cervical precancer and cancer is persistent infection with one or more of oncogenic Human Papilloma Virus(HPV). Majority of these infections will resolve by itself. A minority of HPV infection persists and causes cervical precancer which progress to cancer within 10-20 years later. Strain number 16, 18 of HPV is the major cause of precancerous conditions and cancers of cervix. Early marriage/early coitus, increased parity, increased number of MTP's, poor nutrition & multiple sexual partner relations are found to be other risk factors for cervical cancers.

Dignostic Criteria of Ca Cervix

Post-menopausal bleeding if occurs; usually it is due to Ca cervix or endometrial carcinoma. Patient should be referred to good diagnostic centre for Pap smear and if negative should be referred to gynaecologist for fractional curettage and USG abdomen and pelvis.

Other minor symptom includes post coital bleeding. Our past experience with diagnostic colposcopy and biopsy showed that majority of this is due to HPV infection. Other symptoms include blood stained discharge PV , sometimes foul smelling and blood stained water discharge which is due to malignancies.

Management

All CIN 1 can be kept under 6 monthly follow up if patients are with good compliance. Otherwise cold coagulation or cryotherapy can be done. CIN 2 &CIN 3 should be referred to higher centres with facility for LEEP (Loop Electro Surgical Excision Procedure), colposcopy, colpo directed punch biopsy etc. Patients with ASCUS (Atypical Squamous cells of Undetermined Significance should be subjected to 6 monthly pap smear and colposcopy if available. Majority of the ASCUS & ASC-H are due to HPV infection. But rarely it could be due to high grade lesions like CIN 2,CIN 3, malignancy etc. Majority of CIN 3 reports are wrong and harbor invasive cancers on further diagnostic evaluation and hysterectomy for such patients are very dangerous. Patient with AGUS (Atypical Glandular epithelium with Undetermined Significance) should be subjected to fractional curettage.

Treatment

In case of bleeding during examination, observe, as most would stop spontaneously. In case the bleeding is persistent, pack the vagina tightly with sterile ribbon gauze.

Post-coital bleeding/foul smelling discharge

First line management

Ciprofloxacin 500mg BD X 5 days and candid V6 tablets X 6 DAYS (If whitish curdy discharge is present)for vaginal application.

Miconazole,betamethasone cream (if there is itching, local application over the vulval parts)

If no response prescribe

Clindamycin +miconazole vaginal pessary (for mixed infection) for 7 days and Ciprofloxacin + Tinidazole BD X 5 days (If there is Trichomonas vaginalis and gram negative organisms as indicated by frothy yellowish/greenish discharge).

Patient should be told about allergic reaction to these medicines.
If symptoms persist, refer to higher Centre to rule out malignancy/CIN changes .

NOTE: If government kits are available,use it as desired.

Referral criterion
Granular cervix/exophytic/proliferative/infiltrative growth with profuse bleeding on touch has to be referred to cancer treating centres/gynaecologists in higher centres.
Evaluate the lesion with p/v , p/s and PAP smear and biopsy to find out whether it is low grade (CIN-1, ASCUS,HPV flat lesions) or high grade lesions (CIN 2 and CIN 3 lesions).All high grade lesions should be referred to gynaecologist in higher centres.

Primary Prevention
Primary prevention of cervical cancer by HPV vaccination is the logical solution to this cancer. Both bivalent and quadrivalent vaccines are licensed in India and either of two brands (Guardacil or Cervarix) can be used but the same brand should be used for the entire series.

Screening
Since cervical cancer is not a major public health problem, population based screening is not effective. So early detection especially of symptomatic women through pap smear, VIA (visual inspection using 4% Acetic acid /VILI (visual inspection using Lugol's iodine) or HPV testing can be used as a diagnostic test. To sum up, primary prevention through vaccination and opportunistic cancer detection through camps and early cancer detection clinics will help to reduce the cervical cancer incidence to some extent. This is feasible, cost effective and affordable.

APPENDIX -2

CERVICAL SMEAR

Cervical smear is a reliable means for the diagnosis of cervical cancers and precancers,but it fails to provide much information about the status of the endometrium.

The cervical smear must be obtained under direct vision after introduction of the speculum. Under no circumstances speculum should not be moistened with medical jellies, since the foreign material may contaminate the smear. If there is no difficulty in introducing the speculum a few drops of normal saline solution may be used to moisten it.

Collect smear from the squamo columnar junction by scraping the external os 3-4 times using a wooden Ayre's Spatula. One end of the spatula is somewhat longer than the other so that it fits in the external os and reaches the endo-cervical canal. The scraper is rotated under pressure; the longer one being used as a pivot within the external os. The material is spread on a slide and fixed immediately.

Pap smear kit

Patient preparation for Gynaecological smears

1. The patient is instructed to avoid the use of douches, vaginal medications or spermicides, 48 hours prior to testing. A 24 hour abstinence from sexual intercourse should be maintained.
2. Smears should not be taken from menstrual bleeding because of contamination with blood, endometrial cells, debris and histiocytes. It is better to take Pap smear 2 weeks after the first day of LMP.

Basic Equipments needed

1. Sterilised bivalve cuscos speculum
2. Ayre's spatula
3. Clean glass slides
4. Couplin jars with fixative
5. Glass marking pencil
6. Cytology requisition form with all relevant details of the patient
7. Normal saline

NOTES