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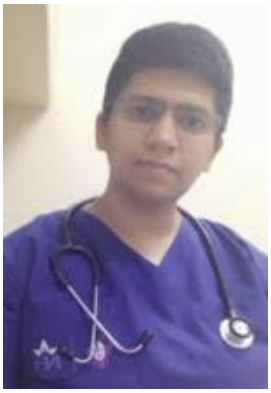
HFRT in Glioblastoma Multiforme during Covid-19 Pandemic

A reasonable alternative ?

Dr. Manisha, Dharamshila Narayana Superspeciality Hospital



Brain tumors is the tenth most prevalent cancer in India with an incidence of approximately 28,000 each year[1]. Glioblastoma multiforme (GBM) is one of the most common malignant neoplasms and it generally has a poor prognosis with the median overall survival (OS) being <18 months despite advances in its management[2,3]. The current standard treatment of GBM radiotherapy 60 Gy in 30 fractions, with 1.8–2.0 Gy per fraction, over a period of 6 weeks with concurrent temozolomide (TMZ) followed by adjuvant temozolamide 6-12 cycles[3].

Hypofractionated radiotherapy aims at delivering a higher dose per fraction,>2 Gy per fraction resulting in reducing the overall treatment time considerably and inhibiting tumor repopulation. The last quarter of year 2019 was marked by beginning of wave of the SARS Covid-19 infection and it was soon declared a pandemic by WHO by March 2020[4]. The virus has affected a sizeable population of all sectors of the society including the health sector.

In view of the severity of the outbreak and considering the fact its vaccines are still in their preliminary phase and no effective treatment is available, the standard treatment protocols are now being modified to decrease the risk of exposure of patients to this highly contagious and deadly virus. The cancer patients, being already immuno-compromised, serve a high risk population for mortality due to Covid-19[5]. The European association of Neuro-Oncology also advised considering hypo-fractionated radiotherapy schedules to limiting the number of visits to the hospital in tumors, where it is feasible without affecting outcome[6].

The role of hypofractionated radiotherapy is well established in prostate and breast cancer but its role is CNS tumors is still investigational. HFRT over 1-3 weeks is already a standard of care for patients with poor prognostic factors like advanced age (>65-70 years) or poor performance status[7]. For young patients with a good performance status but with associated CDC-identified risk factors for increased COVID-related morbidity and mortality risk/benefit ratio should be assessed in a multi-modality tumor board. In such scenarios, HFRT (40 Gy/15#) holds the promise of radiobiologically escalating the dose and potentially improving local control and its role should certainly be evaluated in the era of covid-19 pandemic[9].Similarly, palliative HFRT regimens of 34 Gy/10 fractions or 25 Gy/5 fractions can be considered in frail patients with extremely poor PS[8,10]. The risk & benefits of the final treatment protocol should be explained to the patient and proper informed consent should be obtained.

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Can HPV vaccine reduce the incidence of cervical cancer - the preventable death?

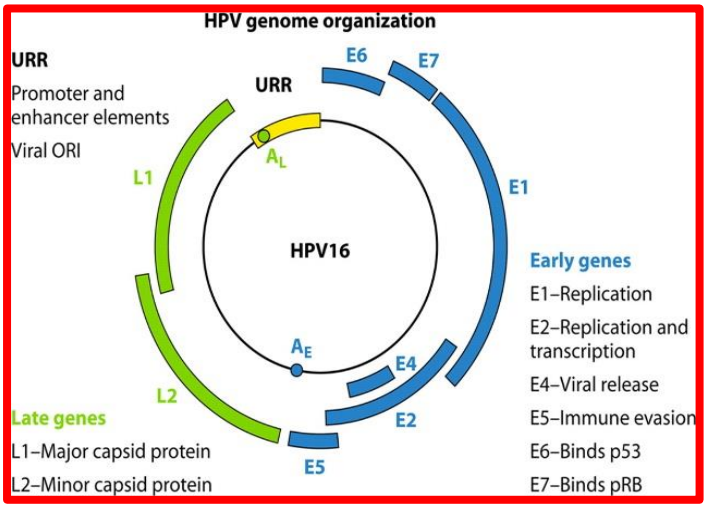
Dr. Indu Bansal Aggarwal, Dharamshila Narayana Superspecialty Hospital

Cervical cancer is the most easily detectable and preventable cancer in women, yet it is the 4th most common in incidence and cancer mortality worldwide. It is the most common diagnosed cancer in 28 countries & the leading cause of cancer death in 42 countries. Globally around 13.1/100,000 women are diagnosed with cervical cancer each year. The most chilling truth is that inspite of the fact that its most preventable and easily detectable cancer, yet in India more than 200 women die every day, 8 women die every hour and every 7 min a women loses her life because of cervical cancer. Can we do something to prevent it?

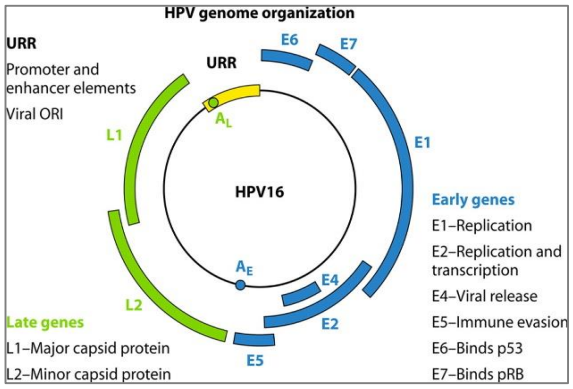
Viral infections constitute 15-20% of all human cancers and a total of 98.7% of all cervical cancers are HPV positive. At 4 years after the first intercourse more than 50% young population are inflicted with HPV and by age 50 yrs 80% women would have contracted HPV infection. Young women <25 yrs are at greatest risk of HPV infection and 2nd peak occurs in age > 55 yrs due to changes in immune function with menopause. Women infected with HIV have more than twice the risk of HPV infection as compared to non HIV (64%vs 28%).

High grade precancerous lesions are estimated to take 10 yrs to progress to cervical cancer. Routine screening with Pap smear can detect most of the cancers in precancerous stage making it curable. 40-50% of cervical cancers are diagnosed in women who undergo routine cervical cytology. 4 out of 5 women are diagnosed with cancer who had not been tested with Pap smear in years.

Remember, HPV infection is the main cause for cervical cancer and it is preventable. It enters through cervical micro-abrasions during sexual intercourse and majority are asymptomatic and 90% infections heal within 2 years but in 0.8% cases, high risk HPV types persist, reach deeper layers and can transform into cancer over a number of years. It takes about 7-10 years for 1st infection to transform to cervical intraepithelial neoplasia (CIN 3) yrs & further 10 yrs for conversion to full blown cervical cancer.



Human Papillomavirus is a double stranded DNA of papilloviridae family. More than 100 types of HPV infection have been identified, 40 % colonize genital tract and 15 types are found to be carcinogenic. High-risk HPV DNA is found to be present in 99.7% of cervical cancers. High-risk types are 16, 18, 31, 33, 35, 39,45, 51, 52, 56, 58, 68, and 59 and potential high-risk are types 53, 66, 70, 73, and 82.



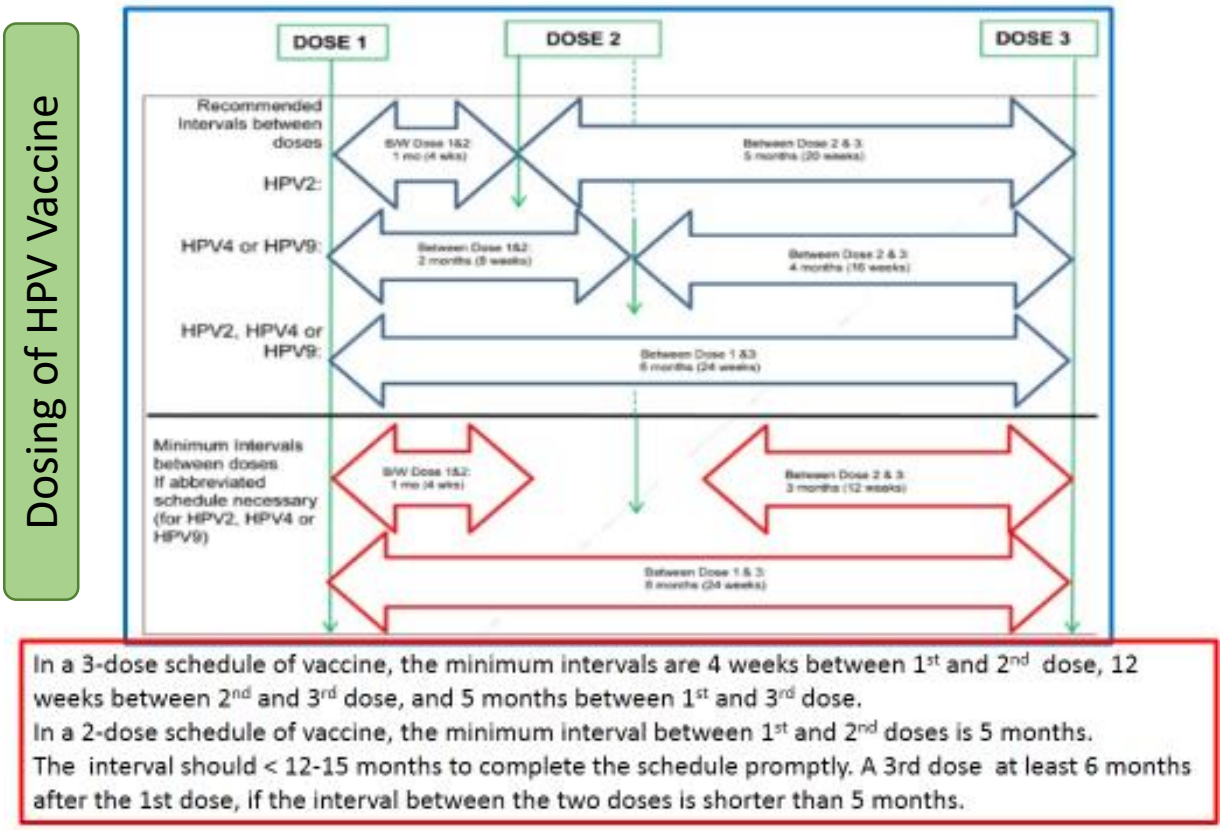
Out of these, HPV16 and 18 are the most virulent high-risk genotypes, and cause about 70% of all invasive cancers. Cervical cancers caused by HPV 16 and 18 appeared earlier than that caused by other types and HPV18 and 45 are implicated in more aggressive cervical adenocarcinomas. Types 6 and 11 are associated with 90% of anogenital warts.

HPV virus has promoter and enhancer elements, 6 early proteins, 3 regulatory proteins (E1, E2, and E4) and 3 onco-proteins (E5, E6, and E7) which lead to viral replication & cell transformation and 2 structural proteins L1 and L2 that compose the capsid of virus. Because we know the structure of virus, so thankfully we have a HPV vaccine to prevent cervical cancer. The prophylactic vaccines have been made using HPV virus like particles (VLP) to generate neutralising antibodies against major capsid proteins L1 and L2. These also protect against anal, vulvar, vaginal cancers, ano-genital warts and vulvar, vaginal, cervical and anal intraepithelial neoplasias. Therapeutic vaccines are in pipeline that can potentially eliminate pre-existing lesions and malignant tumors by generating cellular immunity against HPV infected cells that express early viral proteins as E6 and E7.

HPV vaccines are type specific- meaning thereby that they are effective only against the type of HPV which is available in vaccine. These are prophylactic vaccines and hence are effective before any sexual infection. They are not therapeutic and hence do not treat any existing infection. There are 4 types of HPV vaccine- Monovalent, Bivalent (Cervarix), Quadrivalent (Gardasil) and Nanovalent (Gardasil-9). Monovalent vaccine is against only HPV 16 and is in trial phases. Nanovalent is against 9 types of HPV and is available as Gardasil-9. It's not yet available or approved in India. The details of each vaccine are summarised below.

S .No.		Cervarix (2HPV)	Gardasil (4HPV)	Gardasil-9 (9HPV)
1.		Bivalent	Quadrivalent	Nanovalent
2.	**Manufacturer**	GSK	Merck	Merck
3.	**Year of license**	Oct 2009	June 2006	Dec 2014
4.	**Composition**	Least antigenic load, has adjuvant ASO4	Aluminum hydroxide adjuvant	Twice antigenic and aluminum load than Gardasil
5.	**HPV types**	16,18	6, 11, 16, and 18.	6,11, 16,18,31,33,,45,52, & 58
6.	**Sex**	Females, males (not FDA)	Females, males (Not FDA)	Females, males (Yes FDA)
7.	**Age**	9-26	9-26 F, M 9-26	9-26F, 9-21M
	27-45 yrs	FDA –No, EMA -yes	FDA –No, EMA yes	FDA - Yes EMA yes
8.	**Contraindications**	Hypersensitivity to latex	Hypersensitivity to yeast	Hypersensitivity to yeast
9.	**Protection against**	Cervical cancer	Anal, cervical, vulvar, vaginal cancers, ano-genital warts, vulvar, vaginal, cervical and anal intraepithelial neoplasia	Anal, cervical, vulvar, vaginal cancers, ano-genital warts, vulvar, vaginal, cervical and anal intraepithelial neoplasia
10.	**Dosage**	0.1 and 6 month period	0,2 and 6 month period	0, 2 and 6 month period
11.	**Site of administration**	Deltoid	Deltoid, anterolateral part of thigh	Deltoid, anterolateral part of thigh
12.	**Available as**	Prefilled syringe	Single dose vial, prefilled syringe	Single dose vial

The ideal age for vaccinating young girls is at 11-12 years of age (on time) although vaccination can start at 9 years of age (early vaccination and we can start priming the parents at this time). If someone is not vaccinated till 11 or 12 years of age then catch up vaccination can be done till 26 yrs of age before any sexual exposure. Expanded vaccination can be given till 45 years of age as it might prevent against those HPV infections which the female has not contracted yet. If the child is less than 14 years of age then 2 doses (O, 6 months) spaced at least 5 months apart are enough. If the time interval between 2 doses is less than 5 months, then it's preferable to give a third dose at least 6 months from the 1st dose. If the child is more than 14 yrs of age, then 3 doses are recommended at 0, 1, 6 months or 0, 2, 6 months as per the manufacturer guidelines. In a 3-dose schedule of vaccine, the minimum intervals are 4 weeks between 1st and 2nd dose, 12 weeks between 2nd and 3rd dose, and 5 months between 1st and 3rd dose. If due to any reason, any dose is missed then we don't have to start all over again but the missed dose can be given upto 1 and half year. It's better not to continue the vaccination if a female gets pregnant but it can be administered to lactating females. There is no evidence to abort the pregnancy if female gets pregnant shortly after the vaccination.



In a 3-dose schedule of vaccine, the minimum intervals are 4 weeks between 1st and 2nd dose, 12 weeks between 2nd and 3rd dose, and 5 months between 1st and 3rd dose.
In a 2-dose schedule of vaccine, the minimum interval between 1st and 2nd doses is 5 months.
The interval should < 12-15 months to complete the schedule promptly. A 3rd dose at least 6 months after the 1st dose, if the interval between the two doses is shorter than 5 months.

The vaccine is administered intramuscularly in arm or anterolateral aspect of thigh. The child should be made to lie down at least for 15 minutes after the shot as rarely fainting or syncopal attacks have been reported. Most common side effects include - injection site redness, swelling or itching, anaphylactic reaction to any component of injection, fever, nausea, gastroenteritis, appendicitis, diarrhoea, but very rarely Venous thromboembolic events and Guillan- Barre syndrome have also been reported.

The vaccination coverage of at least 50 % can provide a 68% reduction in HPV 16 and 18 and around 60% reduction of anogenital warts. If we are able to achieve HPV vaccination coverage of at least 70% in women, it would be considered as optimum and cost effective.

Please remember that as the vaccine does not prevent against all strains of HPV so regular screening has to be continued as per age specific guidelines. Also education of children against harms of unhealthy sexual practices and importance of genital hygiene can't be underestimated.

So let's all join hands and take a pledge to eradicate cervical cancer from India. I feel only monovalent approach of vaccination is not enough. A bivalent approach of screening and vaccination is absolutely essential. Better still would be at least a quadrivalent approach of sexual education, screening, vaccination and treatment of detected cases. The best approach of all would be a Nanovalent approach of sexual education, screening, vaccination, treatment of all detected cases, reduction of cost of vaccine and its free availability, robust surrogates to test its efficacy, maintenance of cold chain, emphasis of vaccination of adolescent girls before sexual exposure rather than vaccination of both boys and girls and development of non-type specific and therapeutic vaccines. I am sure we can win over cervical cancer soon.

Covid 19 pandemic and cancer prostate- weighing, readjusting and harmonizing radiation treatment

Dr. Shruti Agarwal, Maulana Azad medical College, Delhi

The world is experiencing an outbreak of a novel coronavirus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2)[1]. WHO has declared 2019 novel coronavirus disease (COVID-19), caused by SARS-CoV-2, a public health emergency of international concern. Patients with cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy or surgery[2,3] thus these patients are at increased risk of Covid 19 infection and poor prognosis.

Prostate cancer is the most common cancer in men worldwide and one of the most common cancers treated within radiation oncology departments[4]. So, patients with prostate cancer represent that population which needs to be managed efficiently for radiation especially when there is paucity of staff and resources during pandemic.

A framework is recommended deemed as "RADS" framework[5] which stands for Remote visits, and Avoidance, Deferment, and Shortening of radiotherapy. Remote visits refers to telemedicine, that is video calls/ phone calls to be taken instead of in person visits.

For very low-, low-, and favorable intermediate-risk disease, treatment is avoided until after pandemic-related restrictions have been lifted. Radiation therapy can be deferred for Patients with unfavorable intermediate-risk, high-risk, very high-risk, postprostatectomy, clinical node-positive, oligometastatic, and low-volume M1 and these patients can be put on androgen deprivation therapy (ADT) for time being. If treatment is deemed necessary then shortest fractionation schedule should be adopted without compromising toicity and efficacy. SBRT and ultrahypofractionation are considered with dose

schedule of 8Gy for 5 fractions over 2-5 weeks. Palliative care shall also follow the same principles of RADS framework with careful weighing of pros and cons of radiation.

These recommendations could be designed as prostate cancer is distinct from other malignancies as its prognosis is generally favourable. It's a slow growing tumor with alpha/beta ratio <3 so hypofractionation works well. Also the use of ADT, helps patients to delay radiation therapy for some months.

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Cancer and the COVID-19 pandemic: A Catch 22 situation?

Dr. Vinay Samuel Gaikwad, Paras Hospitals, Gurugram

Cancer. A devastating pandemic accounting for around 13% of deaths (7 million) globally. 16 million new cancer cases being detected each year. Its treatment invariably damages the body's immune system. It could be surgery, radiation therapy, chemotherapy, or a bone marrow transplant; each modality increasingly detrimental to our body's immunity, and therefore our body's ability to fight off infection. Add to this the psychological trauma a person must endure to get through it all. This may all sound rather devastating, but there's more.

Throw into this miserable concoction, a pinch of another pandemic of questionable curability (read COVID-19), and there you have it. A recipe fit to satiate the apparently ravenous appetites of the Gods of Pandemonium and Suffering. If a patient with cancer is infected with the novel corona virus, their chances of death are around 3.5-6%. The universe appears to have designed these diseases to kill. But is there an escape, or are we stuck between the devil and the deep sea?

Out of this mire of pessimism arises a waft of positivity, a breath of reassuring fresh air. This is the gush of the goodness of the human essence. The ability of Homo sapiens to come together, to forget differences and to fight. To survive. To overcome. Dear fellow humans, nothing is beyond the power of our collective determination to thrive amidst adversity. We have done it before and we will do it again. And again.

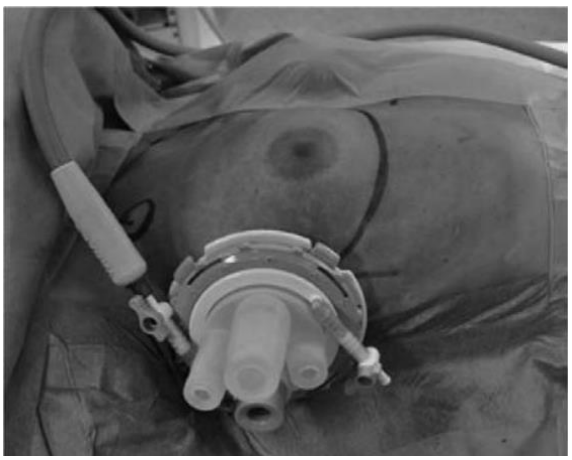
We, as oncologists, are ready to guide and counsel our cancer patients regarding the best possible way forward. Whether one is newly detected, currently undergoing treatment, or a previously treated patient, there is a viable solution. It may be a tightrope walk but, more often than not, there is a way to balance our way out. So, hold your heads high my friends. Neither cancer nor viruses (or a potential combination of the two) can sink our eternal spirit.

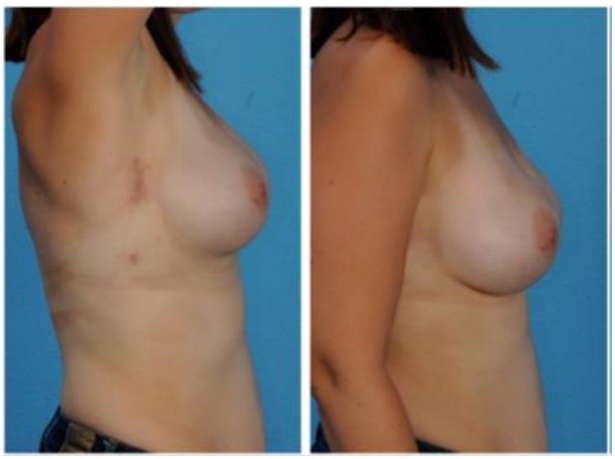
Robotic Mastectomy: Hope or Hype?

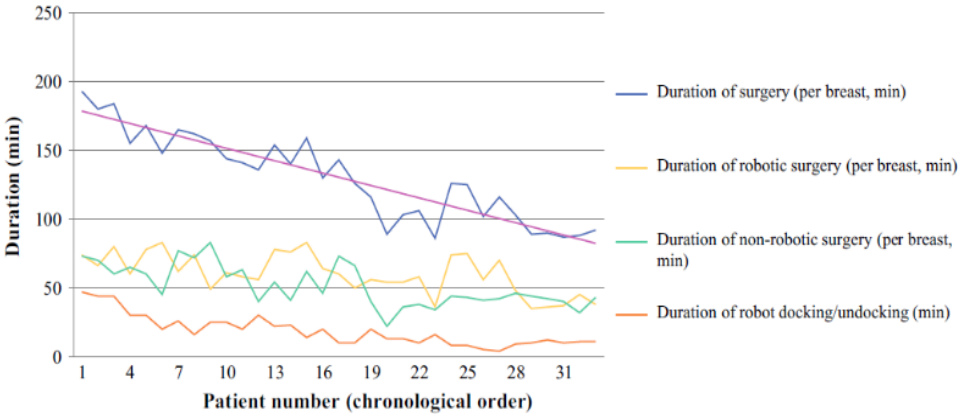
Dr. Shubham Jain, Consultant, Surgical Oncology, Max Institute of Cancer Care, Saket, Lajpat Nagar & Panchsheel Park

Nipple-sparing mastectomy (NSM), which preserves the nipple areolar complex (NAC) and skin flaps during mastectomy, is being increasingly performed in newly diagnosed early breast cancer patients and for risk reducing mastectomies due to better cosmetic outcome, higher patient satisfaction, and maintained oncologic safety. Absolute contraindications to NSM include advanced breast cancers, heavy nodal disease or NAC involvement. Relative contraindications to NSM include hard smokers (>20 cigarettes/day), uncompensated diabetics, and women with large (breast cup size larger than D or breast mastectomy weight > 600 gms) or ptotic breasts ≥ grade 2 as the aesthetic outcomes may be suboptimal.

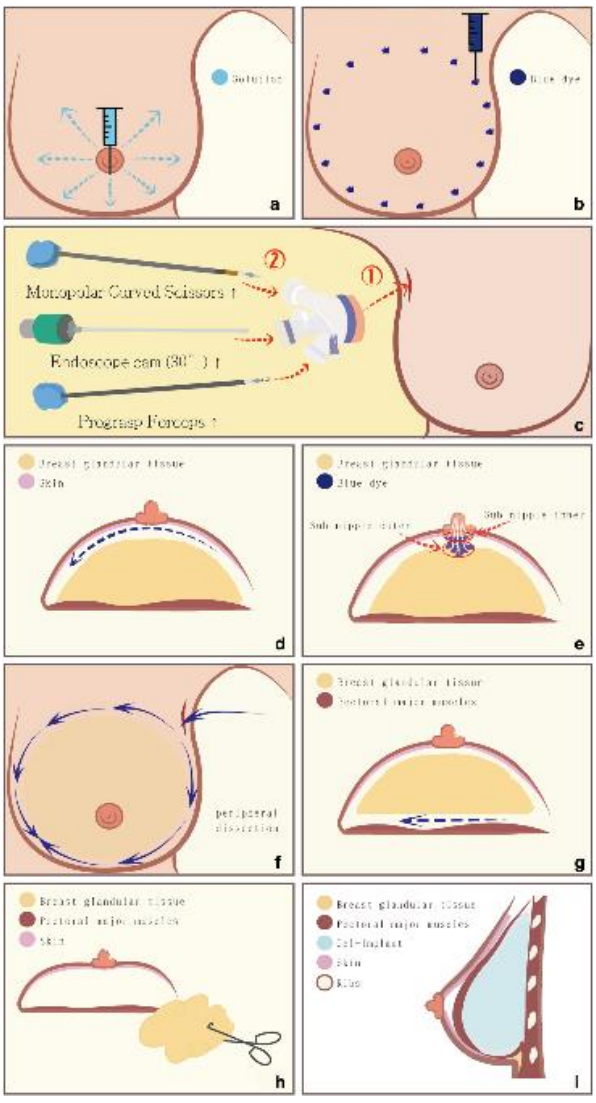
Minimal invasive surgery has become the main stream of operations, and new surgical innovations of NSM, like endoscopic nipple sparing mastectomy (E-NSM) or robotic nipple sparing mastectomy (R-NSM), are emerging and being applied in the surgical treatment of breast cancer. E-NSM, which is performed through small axillary and/or peri-areolar incisions, is associated with small inconspicuous incision and good cosmetic outcome. Conventional E-NSM is performed with two separate incisions over axilla and peri-areolar regions. E-NSM with areolar incision, just like NSM with areolar related incision (NAC ischemia/necrosis rate: range 7%-81.8%), is associated with increased NAC ischemia/necrosis (reported ranged: 9.1-19%). New technique modifications of E-NSM are emerging focusing on single axillary incision NSM, which spare the peri-areolar incision and thereby decrease the compromise of bloody supply from mastectomy skin flap, is reported to have low NAC necrosis rate (0%). However, the 2-dimensional endoscopic in-line camera produces an inconsistent optical window around the curvature of the breast skin flap, and the internal mobility is limited and the dissection angles are inadequate with traditional endoscopic rigid tips instruments through single access. Due to the limitations of endoscopy instruments and technique difficulty, neither conventional E-NSM nor single access E-NSM has gained widespread use.







R-NSM was first reported by Toesca et al, from European Institute of Oncology, Milan, Italy in October, 2015. This technique introduces da Vinci surgical platform through a small extra-mammary axillary or lateral chest wound, easily hidden in the axilla and incorporates 3-dimensional (3D) imaging system and flexibility of robotic arm and instruments, thus having the potential to overcome the technique difficulty of E-NSM. Significant reduction in post-operative pain and hospitalization periods may be other potential benefits. However, they increased duration of operating time and the additional costs related to the operation to be the major hurdles in applicability. With more frequent use, these are expected to come down. They later reported on the safety and feasibility of the technique as well with no early local failures at 19 month follow up and acceptable complication rates.



Sarfati et al, from Gustave Roussy, France, too reported on the safety, feasibility and reproducibility of R-NSM with immediate prosthetic breast reconstruction (IPBR). They observed a consistent decrease in the operative duration and were able to complete the entire procedure in approximately 85 minutes, towards the end of their study. They did not have any major/minor mastectomy skin flap or NAC necrosis in their study.

Lai et al, from Changhua, Taiwan have also reported on the safety and feasibility of R-NSM and immediate reconstruction with Gel implants and autologous latissimus dorsi flap, with good cosmetic results, even in patients with positive axillary nodes, requiring axillary dissection and adjuvant radiotherapy.

In the US, however, apart from a few initial reports of R-NSM being performed in New York and New Jersey, the procedure has taken a back seat, and is strictly being offered on a trial basis, mainly because of an FDA safety communication raising caution when using robotically associated surgical devices in women's health including mastectomy and other cancer related surgeries. This came following the results of LACC trial, which reported inferior survival in cervical cancers offered radical hysterectomy through minimally invasive (laparoscopic and robotic) approach.

On-going research into robotic surgery for breast cancers include

- A prospective superiority trial evaluating patients' satisfaction comparing R-NSM and immediate robotic breast reconstruction vs. conventional open technique, being conducted at Milan, Italy. 82 patients have been enrolled into the study, which is expected to complete in December, 2019. The results are eagerly awaited.
- A Taiwanese prospective 3-arm trial evaluating surgical (clinical and aesthetic) outcomes and cost effectiveness of R-NSM compared with E-NSM or conventional NSM in the management of breast cancer. The trial is currently recruiting and an estimated 180 participants are to be enrolled into the trial.
- An international, multicentre, pooled analysis of estimated 300 participants using prospective or retrospective studies to evaluate the surgical and oncological outcomes after R-NSM and immediate reconstruction.

To summarize, R-NSM seems a safe and feasible surgical option available for patients. However, till more mature oncological outcomes get reported and the cost of technology becomes more affordable, widespread use may be limited.

Electrochemotherapy

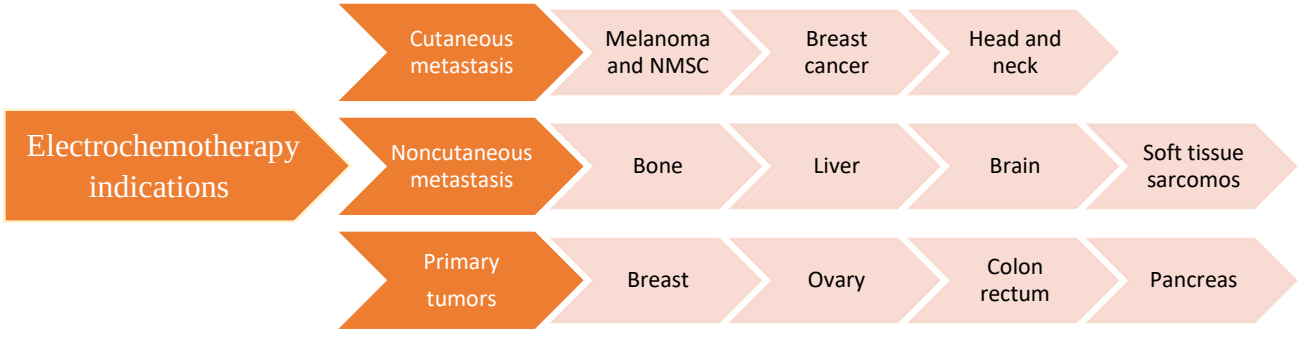
Review and management of a challenging case

Dr. Manish Kumar Gaur, Dr. Deo SVS . Department of Surgical Oncology, BRA-IRCH & NCI, AIIMS, New Delhi.

Introduction

Electrochemotherapy (ECT) is a new non-thermal tumour ablation modality which delivers non-permeant drugs with intracellular targets inside the cell. It is based on the local application of short and intense electric pulses that transiently increases the permeability of the cells in tissues. ECT can be utilised as an alternative modality or as a palliative treatment after standard therapies (such as surgery, radiotherapy, and chemotherapy) to improve the quality of life for selected patients.

The concept, pre-clinical and clinical studies – started in the 1990s. The first clinical trial of ECT was published in 1991 on head and neck squamous cell carcinoma nodules[1]. However, the clinical experience is limited mostly in European centres. Mostly tried tumours include skin cancers/ cutaneous metastases of different tumours/ few solid tumours- recurrent and complex situations including squamous cell carcinoma, malignant melanoma, basal cell carcinoma, skin metastasis, Kaposi sarcoma, tumours of the breast, kidney and salivary gland. The current and potential indications of the ECT are shown in the figure below.

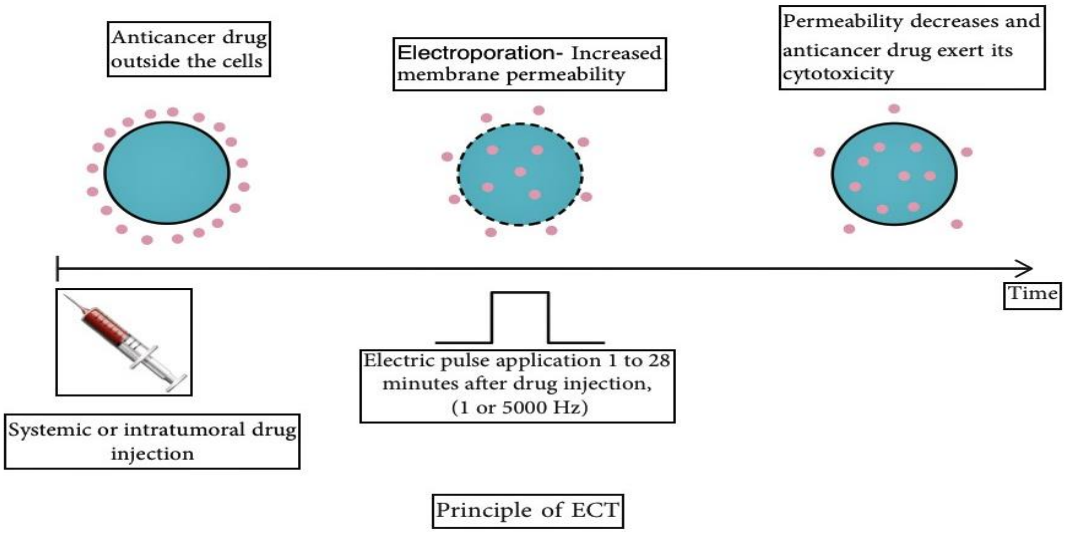


Various indications of ECT

Principles and Practice of ECT

The first version of the standard operating procedure (SOP) for ECT was developed and validated by the European Standard Operating Procedures for ECT (ESOPE) in 2006[2]. Recently, a new version of SOP has been published by a Pan-European expert panel from various specialties[3].

In this procedure, chemotherapy is injected into the tumour or bloodstream and electric pulse is delivered to send the nonpermeable chemotherapy into the cancer cells by making them temporarily permeabilize – "Electroporation". This results in cancer cell necrosis and cell death.



Principle of ECT

ECT is performed with the help of an electrical pulse generator and different types of electrodes. It involves the application of eight, 100µs, pulses at 1 or 5000 Hz frequency and specified electric field (V/cm) with a median duration of 25 minutes. Various electrodes used in ECT are shown in the figure.

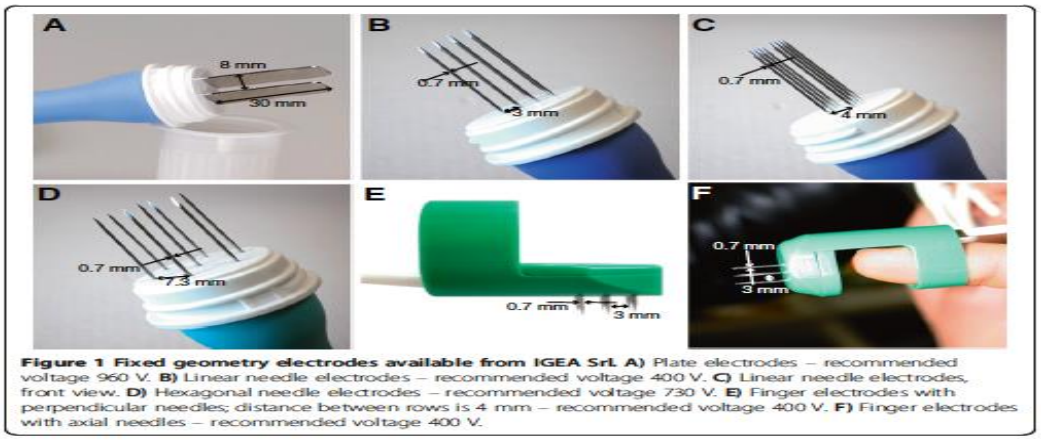


Figure 1 Fixed geometry electrodes available from IGEA Srl. A) Plate electrodes – recommended voltage 960 V. **B)** Linear needle electrodes – recommended voltage 400 V. **C)** Linear needle electrodes, front view. **D)** Hexagonal needle electrodes – recommended voltage 730 V. **E)** Finger electrodes with perpendicular needles; distance between rows is 4 mm – recommended voltage 400 V. **F)** Finger electrodes with axial needles – recommended voltage 400 V.

Chemotherapy agents

Only Bleomycin and Cisplatin have been identified to date for ECT in cancer and routes are either Intralesional or Intravenous. For intratumoral application, however, the pulses need to be delivered from 1 min to 10 min after drug injection.

Dose calculation for Intra-tumoral Bleomycin

One unit (U) contains 0.56-0.66 mg of bleomycin and 1 unit (U) is equivalent to 1000 international units (IU)[4]. Measure the lesions to calculate the volume and concentrations of bleomycin that will have to be prepared as shown in the table

Dose calculation for Intra-tumoral Bleomycin

Tumour volume ($V = ab^2\pi/6$)	$V < 0.5\ cm^3$	$0.5\ cm^3 < V < 1\ cm^3$	$V > 1\ cm^3$
Bleomycin dose (concentration 1000 IU/ml)	1 ml (1000 IU) / cm^3 of tumour	0.5 ml (500 IU) / cm^3 of tumour	0.25 ml (250 IU) / cm^3 of tumour

Challenges in the management of skin cancers in Xeroderma Pigmentosum(XP)

The treatment of skin cancer in Xeroderma patients is full of challenges due to multifocal lesions, unclear lesion edges, large lesions with high recurrence risk and poor surgical risk. The goal of treatment is the complete eradication of the tumour while preserving important anatomical structures in terms of function and aesthetics and the principle lies in early detection and early intervention. There are various treatment options ranging from traditional surgical like wide excision with margins to non-surgical including radiotherapy, topical like 5 FU, Imiquimod, Ingenol mebutate and Diclofenac, oral therapy includes retinoids; targeted therapy includes Cetuximab, Gefitinib; Immunotherapy includes Anti-PD 1 antibody (Cemiplimab).

Despite having so many options, the management of skin cancers in this setting is highly challenging in view of young age, field cancerization, multiple cancers, critical area involvement - aesthetic & functionally, post multiple treatment settings and multiple modalities. Patients are referred to oncology centres at later part of disease course, in recurrent cancers, advanced invasive malignancies and not amenable for simple surgical/medical treatments. Various treatment options at comprehensive cancer centres include major ablative surgical resections, radical radiotherapy, systemic chemotherapy and targeted therapy which results in loss of organ/ function, cosmetic & functional disfigurement, acute & long term morbidity of therapies, high recurrence rates and difficulty in repeating same treatment modalities. Thus, there is a need for a treatment modality which is simple, less toxic, less invasive, the feasibility of re-treatments and effective.

ECT in XP

The literature on ECT for management of skin cancers in Xeroderma Pigmentosum patients is limited to one short communication only[5].

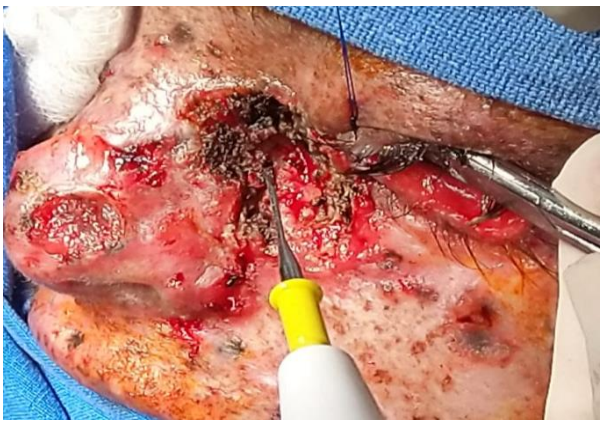
Our experience with ECT in XP

We performed ECT in an 8years old boy, who was apparently normal at birth and diagnosed clinically as a case of Xeroderma Pigmentosum at 5years of age. He had 5x5cm ulcerated plaque over the parietal region of the scalp for which wide local excision and rotation flap followed by radiation therapy (54Gy/30#) to the scalp was done in 2017. The final biopsy was basi-squamous carcinoma. He developed multiple lesions over the face in a short span of time. He had lesions over the scalp, infraorbital nodules both sides, dorsum of the nose, which were suggested of basal cell carcinoma, squamous cell carcinoma, metatypical BCC. Radiofrequency excision of pedunculated lesion at scalp was performed in 2018 and multiple radiofrequency ablation sittings were tried for hyperkeratotic lesions over the face. Also, excision of infraorbital nodules was done. He was now left with a refractory ulcer at the medial canthus of the left eye. A trial of cryotherapy was used for this lesion but it did not respond.

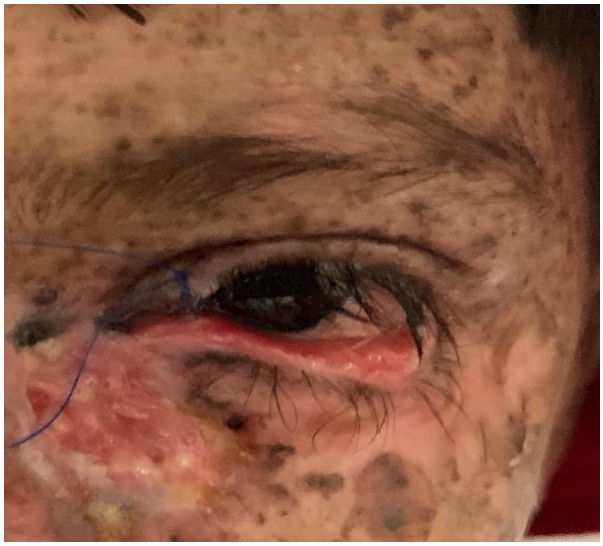
Thereafter, the case was referred to the department of surgical oncology for management of the same. On clinical examination of the face, he had crusted plaque of 2x2cm at the medial canthus of the left eye, involving part of the lower eyelid, root of nose and extending to nasolabial fold. Apart from this, he had plaque over the tip of the nose. The infraorbital lesions and scalp lesions were healed.

An attempt was made for eye and vision salvage in view of young age and post multiple modalities of treatment. We tried novel treatment in this case – Electrofulguration and Electrochemotherapy was performed in September 2019. We used intralesional Bleomycin 2000 IU followed by 8 electrical pulses of 1Hz and 1000V each lasting for 100 micro sec using linear electrodes. He had a dramatic response to ECT and the lesion healed completely in a week. He is doing well after 8 weeks of the procedure.

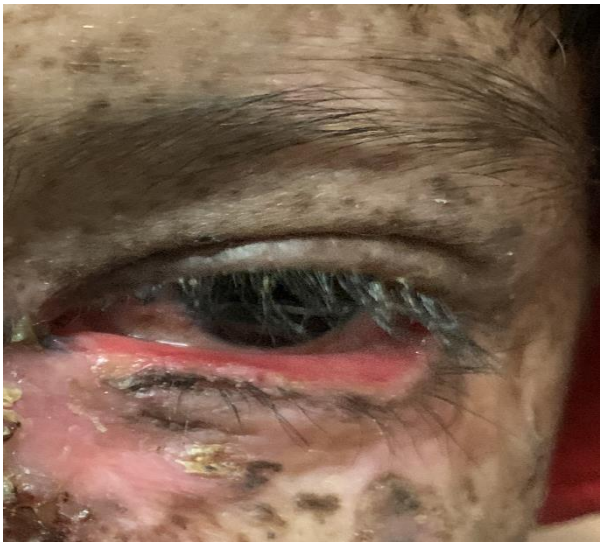
The electrical pulse generator with electrode



Intraop pictures of the treated lesion



2 weeks post ECT



4 weeks post ECT

Conclusion

Electrochemotherapy is a novel ,simple and promising treatment modality for skin cancers or cutaneous metastases. Skin cancers associated with Xeroderma are challenging to treat. Various options ranging from prevention, simple dermatological interventions to surgical & medical options with varying degrees of success. There is a need for simple, effective, low morbidity and low-cost intervention which can be repeated. ECT is emerging as a promising intervention for cutaneous malignancies & skin metastases.

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Essentials of Cancer Prevention: Primary, Secondary and Tertiary Approaches

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Global cancer burden is on the rise and it is estimated that by the year 2030 there could be 27 million people with cancer translating to more than 17 million cancer deaths each year. Although, the death rate from cancer had fallen by 27% over the past 25 years, it still remains a leading cause of death worldwide. It has been postulated that about 42% of cancer cases and 45% of cancer deaths are linked to modifiable risk factors and could be prevented by adopting certain prevention strategies. Prevention of cancer comprise of a wide range of activities aimed at reducing the risks or threats of the disease and can be divided into primary, secondary and tertiary methods.

Primary Cancer Prevention aims to prevent the disease before it ever occurs. This is achieved by preventing the exposure to hazards that causes cancer, altering the unhealthy behaviours pertaining to diet and life-style as well as genetic screening. There are both modifiable and non-modifiable risk factors associated with the incidence of various cancers. Examples of primary cancer prevention of modifiable risk factors include smoking cessation, maintaining a healthy body weight, physical activity, etc. More than 4 in 10 cancers as well as cancer deaths are linked to modifiable risk factors that can be altered as part of primary cancer prevention. The modifiable risk factors for primary prevention include:

1. Cigarette smoking: Smoking is the number one preventable cause of cancer. It causes almost all cases of lung cancer and accounts for 30% of all cancer deaths. Smoking increases the risk for cancers of the upper airway, stomach, mouth, tongue, liver, cervix, bladder etc. Prevention strategy for this risk factor is to quit smoking. For non-smokers, the prevention strategy is to avoid second hand (environmental tobacco smoke) and third hand smoke (residual nicotine and other chemicals left on indoor surfaces by tobacco smoke). Further, no form of smokeless tobacco is a safe substitute for cigarettes.

Any type of tobacco (chewing, oral, or spit tobacco; snuff or dipping tobacco; dissolvable tobacco) contains more than 60 harmful chemicals and causes mouth, tongue, cheek, gum, esophagus and pancreatic cancer. Proportion of tobacco related cancers relative to all sites of cancers ranges between 24.4%-65.2% for males and 6.9%-42.3% for females (Three-Year Report of Population Based Cancer Registries 2012-2014, Indian Council of Medical Research).

Smoking cessation has major and immediate health benefits for men and women of all ages as quitting smoking decreases the risk of lung and other cancers. Compared with smokers who continue to smoke, the lung cancer mortality is lower for individuals who quit smoking by age 50 years and even lower for individuals who quit smoking by age 30 years. Never smokers have the lowest cumulative lung cancer mortality. Similarly, the risk of getting bladder cancer, pancreas cancer and cervical cancer is 2-3 times more in smoker men and women as compared to non-smokers.

2. Excess body weight: Being overweight or obese is one of the most important risk factors for a number of cancers such as bowel, breast, kidney, stomach, uterine etc. Excess body weight is thought to be responsible for about 8% of all cancers as well as about 7% of all cancer deaths in the United States. Prevention strategy for this risk factor is to maintain a healthy body weight (BMI 18.5 to 24.9 kg/m2).

3. Drinking alcohol: Drinking alcohol is related to increased risk of mouth, throat, esophagus, breast, colon and liver cancers. Even a little bit of alcohol consumption increases the risk of developing cancer. It is responsible for about 5.6% of all cancers and about 4% of all cancer deaths in the United States. Prevention strategy for this risk factor is to avoid consumption of alcohol.

4. Eating red/processed meat and imbalanced diet: The intake of red or processed meat should be limited to small quantity. Diet low in dietary fiber and calcium as well as sugary drinks and processed foods (high in added sugar, or low in fibre, or high in fat) should be avoided as much as possible. As an effective prevention strategy, focus should be on eating more of vegetables, fruits, whole grains, and pulses such as beans.

5. Physical inactivity: This is responsible for 2.9% of cancer cases and 2.2% of deaths in the United States. About one third of fatal cancer cases could be prevented by better nutrition and physical activity. Adults should get moderate to vigorous activity for 30 to 45 minutes, 5 or more days a week. Children and adolescents should get 60 minutes a day of moderate to vigorous physical activity at least 5 days a week. Vigorous physical activity has shown to reduce the risk of breast and colon cancer.

6. Ultraviolet (UV) radiation from the sun: This is responsible for almost 5% of cancer cases and 1.5% of deaths in the United States. As an effective prevention strategy, focus should be to keep out of the sun, especially in the middle of the day and to wear protective clothing, sunglasses, hat and use of sunscreen creams/lotions.

7. Cancer-associated infections: A small portion of cancers are thought to be linked to infections. Six cancer associated infections include helicobacter pylori, hepatitis B virus (HBV), hepatitis C virus (HPC), human herpes virus type 8 (HHV8), human immunodeficiency virus (HIV), and human papilloma virus (HPV). As an effective prevention strategy, focus should be to get vaccinated at the right time and undergo regular organized screening.

8. Others: This include occupational risk factors such as exposure to asbestos, heavy metals etc.; environmental risk factors such as arsenic contamination, aflatoxins in food, indoor air pollution and immunosuppression. As an effective prevention strategy, focus should be to take precautionary measures to avoid these exposures.

There are certain non-modifiable risk factors that are responsible for certain familial cancers. These biological risk factors occurs in families due to the presence of gene mutations that increases the risk of developing a particular cancer. For example, a woman with

a positive family history has about two to three times more likelihood of developing breast cancer than a woman with no family history. The various types of familial cancer are as follows:

Familial adenomatous polyposis (FAP)

FAP is a rare inherited condition and can lead to < 1% of all bowel cancers in the general population. Regular bowel screening, generally by colonoscopy, is recommended to commence between the age of 10 to 15 years.

Hereditary non-polyposis colorectal cancer (HNPCC)

HNPCC is a rare inherited bowel cancer syndrome that is responsible for <5% of all bowel cancer cases. Regular bowel surveillance is recommended for those who have inherited the gene change

Hereditary breast and ovarian cancer (BRCA1 and BRCA2)

About 5% of breast and ovarian cancers are due to an inherited faulty gene. Removal of both breasts in patients with BRCA mutations is generally accepted prevention strategy in reducing the risk of breast cancer. Similarly, removal of both ovaries can prevent ovarian cancer. Oral contraceptives and tubal ligation should be considered in women who wish to retain ovarian function.

Melanoma

Less than 5% of all melanoma is due to an inherited faulty gene. People with familial melanoma should avoid sun exposure and perform regular self-examinations to look for skin changes.

Further, genetic tests are available for estimating the lifetime chance of developing various cancers such as breast cancer, ovarian cancer, colon cancer, thyroid cancer, prostate cancer, pancreatic cancer, melanoma, sarcoma, kidney cancer and stomach cancer.

Secondary Cancer Prevention aims to reduce the impact of cancer by detecting it at the earliest possible state in order to offer a definitive treatment. This is achieved by checking for the presence of cancer in population as risk (screening) as well as testing for cancer even if there are no symptoms (early detection). The screening recommendations for various cancers by National Comprehensive Cancer Network (NCCN) is as follows:

Breast Cancer

For women between 20–40 years of age:

- Clinical breast exam (CBE) every 1–3 years and periodic breast self-examination (BSE) are recommended

For women > 40:

- Annual mammogram (MMG) & CBE & periodic BSE are recommended

Cervical Cancer

Pap test within 3 years of vaginal intercourse, but starting no later than 21 years of age; continue annually with conventional cervical cytology or every 2 years using liquid-based cytology .At ≥ 30, women with 3 consecutive normal Pap tests, screening intervals can increase to every 2–3 years. Screening can cease at age 70 with 3 or more consecutive normal Pap tests within the previous 10 years. Continue screening despite age if history of cervical cancer, diethylstilbestrol (DES) exposure, or immune-compromised states. Human papillomavirus (HPV) positive women continue screening at the discretion of their healthcare providers.

Colorectal Cancer

Average risk (age ≥ 50, no history of adenoma, inflammatory bowel disease, or family history of colon cancer):

• Colonoscopy every 10 years is preferred or fecal occult blood test (FOBT) annually and flexible sigmoidoscopy every 5 years or double contrast barium enema (DCBE) every 5 years

Prostate Cancer

Risk/benefit discussion and offer baseline prostate-specific antigen (PSA) testing and digital rectal exam (DRE) at 40:

• PSA ≥ 0.6 ng/ml, or African American, or positive family history: Screen with PSA and DRE annually

• Otherwise, repeat PSA and DRE at age 45. PSA ≤ 0.6 ng/ml: Begin annual screening at age 50

• PSA > 0.6 ng/ml: Perform annual follow-up

Tertiary Cancer Prevention aims to soften the impact (symptoms, morbidity) of ongoing cancer that has lasting effects. This is achieved by helping patients manage the long-term problems in order to improve as much as possible their ability to function, quality of life and life expectancy.

The saying “an ounce of prevention is worth a pound of cure” is very relevant in context of cancer prevention and early detection. In order to achieve a meaningful degree of prevention and protection from cancer, a combination of primary, secondary and tertiary interventions are needed and should be adopted by the population at large. Having a cancer is nothing to be afraid of and by taking an active role in the screening, diagnosis and treatment of this aggressive disease a person can improve his/her chances of survival along with a better quality of life.