



CANCER NEWS

ISSN 0973-9653

Vol 7

No 1

April 2013



**Rajiv Gandhi Cancer Institute
and Research Centre**

A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

www.rgcirc.org

From the Desk of Director Research

Cervical cancer affects women of all ages around the world and is the second most common cancer in women across the globe. This cancer is diagnosed in over 500,000 women every year globally and is the cause of 270,000 deaths globally and over 70,000 in India alone. It is the most common cancer in women in India. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers.

There is no single cause of this cancer, but some factors appear to increase the risk of developing it. The main risk factor for development of cervical cancer is the persistent and recurring infection with a common and contagious virus – the human papillomavirus (HPV). There are many strains of this virus, of which 15 cause cancer. The most common cancer causing types are 16 and 18 – these two are responsible for 70% of cervical cancer globally. Some types of HPV can be passed easily from person to person through sexual contact. These infections are common and usually go away without treatment because the immune system gets rid of the virus. HPV is an important cause of cervical cancer, but not all women with HPV infection develop cervical cancer. Factors such as smoking, multiple pregnancies, and use of birth control pills increase the risk of this disease.

Cervical cancer often goes unnoticed because the symptoms mimic those of other ailments. Early symptoms are vaginal bleeding, occurring between the menstrual periods or an unusual discharge. Regular check-ups involving a pelvic exam and ‘pap smear’ will help early diagnosis of this disease. If found in early stages, it can be successfully treated. The choice of treatment and the long-term outcome depends on the type and stage of cancer. The most common treatment for early stage cervical cancers is radical hysterectomy. The alternative is radiation therapy, which is usually given in combination with chemotherapy.

Cervical cancer can be fully prevented, if there is the required awareness. The cervical screening program encourages regular screening to reduce the number of women who develop or die from cervical cancer. Screening can also detect cervical cancers at an early stage when treatment is most likely to be successful. Such a programme will not be successful if an effective treatment and management programme is not established to run along side it.

This issue of Cancer News profiles the complexities and advancements in the field of cervical cancer, and includes regular articles, such as “Special Feature”, “Guest Article”, “Perspective”, “Watch-Out”, “Research & Development”, “New Technologies”, “Clinical Trials”, “Globe Scan”, “Cancer Control” and “In Focus”.

We appreciate the contribution made by Prof UD Bafna, Head, Dept of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bangalore, for providing the “Guest Article” on “Cervical Cancer- A Guide to Prevention and Management in India”.

Dr D C Doval

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Published by: **Rajiv Gandhi Cancer Institute & Research Centre**
Sector - 5, Rohini, Delhi - 110 085, India

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SPECIAL FEATURE

CERVICAL CANCER – STATUS IN 2013 AND BEYOND

Cervical cancer is unique among common cancers: it has a single known cause, the human papilloma virus (HPV), and highly effective screening and prevention have the potential to virtually eliminate the death from this disease. The wide spread use of PAP smear has helped to reduce US cervical cancer death rate by nearly 70 percent since the 1950. And now the recent introduction of tests to detect HPV and vaccines to prevent HPV infection hold promise to reduce these deaths even further.

Despite this advancement, the cervical cancer burden in developing countries is still high with some 2,50,000 women dying of cervical cancer and 80 % of these deaths occurring in (developing countries) low resource countries where access to preventive vaccines, screening and treatment is limited. Increasing access to these services, remains a top global health priority.

While screening and vaccination remain the first line of defense, researchers are also working to improve treatments for women diagnosed with cervical cancer. In particular, new therapies are urgently needed to prevent recurrence and to eliminate cancer that remains after tumors are surgically removed or treated with radiation.

As we study the timeline of cervical cancer, it was the British Surgeon Ernst Wertheim in 1950 who introduced a new surgical technique, the Wertheim's Radical Hysterectomy, that enabled more than 30 % of cervical cancer patients who underwent the surgery to remain free of cancer after five years. This was considered a monumental feat despite the fact that 15 percent of women died during the procedure which involved removal of the uterus, cervix and surrounding lymph nodes through abdominal incision. This remains the standard treatment till date with various modifications.

Detection of cervical cancer by examining and staining vaginal cell smear was a novel discovery by George Papincolaou in 1928 which remained the gold standard for cancer detection for several decades. It was in 1983-84 that researchers led by Harald Zurhansen were able to isolate stains of human papilloma (HPV) as the likely cause of cervical cancer and that most cervical pre-cancers and cancers contain D & A from HPV-16 or

HPV-18 strains of the virus and these two have been established as the most virulent. In 2008 Dr Zurhansen was awarded the Nobel Prize for Medicine/Physiology for his discovery.

In 1999, the FDA approved a new test to detect the strains of the human papilloma virus (HPV) that are known to cause cervical cancer. The HPV DNA test which identifies the high risk virus types is approved for use in women aged 30 and older in combination with the PAP test, and in women of all ages who have an abnormal PAP test result. Subsequent studies show that HPV testing alone is significantly more sensitive in detecting advanced pre-cancers than PAP test (96 % vs 55 %), but HPV testing accrues results in more false positive results. When combined, the HPV test and PAP tests are found to be 100 % sensitive for identifying women at risk for cervical cancer. For women younger than age 30, however, the PAP test is sufficient and combined screening is not recommended.

It was also in the year 1999 that National Cancer Institute (NCI) issued an alert recommending that physician consider adding chemotherapy to radiation therapy for women being treated for invasive cervical cancer (cancer that has spread within the cervix). The ongoing results from a large clinical trial called the ASCUS-LSIL triage study (ALTS) which was held in 2000-2006, provide important guidance on managing the mild abnormalities that often show up PAP test and help doctors to decide which women need colposcopy and ablative procedures and which one requires more definitive treatment.

The next major advancement was the approval by FDA in 2006 of a cervical cancer prevention vaccine gardasil which prevents infection with HPV 16 and HPV-18 known to cause about 70 % of cervical cancers. The vaccine is approved for girls and young women aged 9 to 26 years. The approval is based on data showing the vaccine is 100 % effective in preventing HPV 16 and HPV 18 related cervical pre-cancers, as well as genital warts. Later the same year the CDC's advisory committee on immunization practices (ACIP) recommended routine HPV vaccination for girls aged 11 and 12; however, state requirements vary. A second vaccine, cervix, was approved in 2009 to prevent infection HPV 16 and HPV 18 in women aged 10 to 25. Presently, both the vaccines are approved for women upto age of 45 years after proper counselling. The cost of the three dose regimen remains a persistent challenge.

In a small study, researchers have shown that two minimally invasive techniques—laparoscopic and robotic radical hysterectomy for early stage cervical cancer are as effective as the traditional radical hysterectomy and lymphadenectomy done in women with cervical cancers. Both the procedures are associated with less blood loss and short hospital stays less than traditional open surgery.

Present Scenario

Presently, cervical cancer is considered to be a sexually transmitted disease associated with chronic infection by oncogenic types of human papilloma virus (HPV). Therefore, the risk factors are the same as those for sexually transmitted disease, including early age at onset of sexual activity (Coitarche), multiple pregnancies, long duration of oral contraceptive use, other STIs including chlamydia and herpes simplex virus and immune suppressed states. Tobacco smoking may be a co-factor for the development of high grade cervical dysplasia in women who have chronic HPV infection.

An interval of epithelial dysplastic changes, typically in the transformation zone, known as cervical intraepithelial neoplasia, precedes the development of invasive cancer. **The reported rate is 70% of cervix cancers. High risk genotypes code for three early proteins (E5, E6 and E7) with cellular growth stimulating and transforming properties.** Progression of carcinoma in situ to invasive cancer ranges from 12% to 22%. The pattern of lymphatic metastasis is predictable and orderly as the rate of para-aortic lymph node metastasis is very rare if the pelvic nodes are uninvolved. The common sites of hematogenous spread include lung, mediastinum, bone and liver.

Most recurrences occur in the first 24 months with a median of 17 months. Clinical staging of cervical cancer by physical examination and limited radiographic methods remains the accepted modality of assessing the disease. Computed tomography (CT) and magnetic resonance imaging (MRI) are used extensively to delineate disease extent and improve treatment planning but do not change the assigned staging. Several studies and meta-analysis have shown an increased sensitivity for MRI compared to CT. However both CT and MRI have low sensitivities for detecting disease in the para-aortic nodes less than 1cm. Positron emission tomography (PET) has emerged as a superior method of imaging nodal disease in cervical cancer. The reported sensitivity is about 84% cervical cancer staging as per FIGO staging 2009. Surgical



Fig 1. Da-Vinci Surgical Robot

findings and radiographically guided biopsies of suspected lesion cannot be used to change or modify clinical FIGO staging. All macroscopically visible lesions are allotted to stage Ib carcinomas. Stage IVa requires biopsy confirmation of bladder or rectal mucosa.

Most of the cervical carcinomas are squamous cell cancer and may also be graded. However treatment protocols do not depend on grade and the histological grade may not correlate with prognosis. Adenocarcinoma accounts for 20% to 25% of cervical carcinomas and is usually associated with HPV 18. Adenosquamous carcinomas appear to be more aggressive and generally get diagnosed at a later stage. Even a small component of small cell carcinoma in a mixed tumor is associated with adverse outcome.

Prognostic Factors

Size of primary tumor, depth of stromal invasion, and lymphovascular space invasion, have been correlated with disease-free survival in patients undergoing Radical Hysterectomy. In patients with stage Ib disease treated surgically with or without RT positive margin status, conveyed a hazard ratio of 3.92 compared to negative margins and is associated with higher recurrence rates.

Lymph node involvement is the most significant negative prognostic factor. Reports emphasize higher 5-year survival rates (90% or higher) among surgically treated patients with no evidence of metastasis in regional nodes, compared to patients with positive pelvic nodes (50% to 60%) or para aortic nodes (20% to 45%). Lymph-Vascular Space Invasion (LVSI) has also proved to be a significant prognostic factor in a surgical pathologic study of 542 patients completed by Gynecologic Oncology Group (GOG). Disease-free survivals were 77% to 89% respectively in patients with or without LVSI.



Fig 2. Robotic Surgery in Progress

General Management

Efficacy of the HPV vaccine has now been established in randomized clinical trials and so primary prevention has become the cornerstone of management of cervical cancer.

Severe dysplasia and carcinoma in-situ have essentially no risk of lymphatic involvement and may be treated with local therapies, such as ablation, cryotherapy and conization. Stage I A carcinoma is usually treated with conization or hysterectomy. The control rate is almost 100%. All macroscopic lesions are stage Ib and this may be divided further into stage Ib1 (lesion < 4cm) and stage Ib2 (lesions confirmed to cervix 4cm) and if limited vaginal involvement is there, it is stage IIa. All these lesions can be treated with Radical Hysterectomy and Pelvic Lymphnode dissection (followed by tailored chemoradiation as indicated by histopathological findings).

Radical hysterectomy can be done either through an abdominal incision or robotically. In cases where fertility

Table: Type III Radical Hysterectomy with Pelvic Lymph Node Dissection for Treatment of Early Stage Cervical Cancer: Robotic vs. Open

	da Vinci (n=50)	Open (n=50)	p-value
Age (years)	47.4	41.9	0.029
BMI (kg/m ²)	28.6	26.1	0.08
Estimated blood loss (ml)	95.4	416.8	<0.0001
OR time (mins)	210.8*	247.8	0.0002
Total lymph nodes	33.8**	23.3	0.0003
Hospital stay (days)	1.0	3.2	<0.0001
Post-operative complications	8.0% (4)	16.0% (8)	0.35

Source: Oral presentation by Dr. John Boggess (UNC) at SGO in March 2008

is desired and disease is early, a Robotic Trachelectomy can also be performed.

The Robotic Radical Hysterectomy, first reported by Sert in 2006, has emerged as a front runner for the management of early cervical cancer. The Da Vinci surgical system offers certain advantages over traditional laparoscopy and laparotomy, like decreased blood loss, an increased lymphnode yield and shorter length of stay (Basil and Pavelka 2011). Major benefits of robotic technology include 3 dimensional, high definition, optics and instrumentation that allows greater range of motion, precision scaling and surgeon autonomy.

Robotic assistance may make lymphadenectomy easier and more comprehensive by overcoming anatomic barriers to the process of stopping uterine cancer. Without increasing patient morbidity and may result in increased use of minimally invasive treatment of uterine cancer. Additionally, hospitals may benefit because of the techniques; advantages, including reduced duration of hospitalization and recovery, an extremely low rate of complication such as infection and ileus.

Radical Parametrectomy

Management of patients who have had a 'simple hysterectomy' for an unrecognized invasive cervical cancer poses a different kind of challenge. While technically difficult, an adequate radical operation after previous simple hysterectomy may be performed for selected patients. This entails removal of parametrial and paracervical tissues along with cuff of vagina and pelvic and para-aortic lymphnode dissection

In an exhaustive review of literature comparing series of patients having radical parametrectomy versus those having postoperative RT the weight average 5-year survival favours RT, (68.7% vs 49.2%). If the postoperative RT approach is chosen, post operative irradiation should be administered immediately after recovery from operation.

Total Pelvic Exenteration

This modality may be considered in a very select group of patients with a limited central recurrence and no metastatic disease following treatment with primary RT or combined surgery and RT. The mortality rate of such a procedure even after careful selection may be 5%. The 5-year survival rate may range from 18% to 40%.

(Dr Rupinder Sekhon, Sr Consultant, Dept of Genito-Uro Oncology; Dr Sudhir Rawal, Director, Dept Surgical Oncology)

GUEST ARTICLE

CERVICAL CANCER – A GUIDE TO PREVENTION AND MANAGEMENT IN INDIA

Introduction

Highest age specific incident rate of around 100 per 100,000 is seen in the 55-59 year age group and the highest age specific mortality rate of 54 per 100,000 is seen in 65-69 year age group in India. 97% of cases are beyond stage 1 as per our data. As the majority of the cases present with advanced stage, the cure rates for these patients are dismal and there is an urgent need to develop a screening test suitable to our country.

Cervical cancer is causally related to Human Papilloma Virus (HPV). The virus is usually transmitted sexually and therefore, cervical cancer is mostly a sexually transmitted disease. Not all the women with HPV infection develop neoplasia and most infections regress spontaneously. Certain other co-factors have been implicated which probably increase the oncogenicity of the HPV. Herpes simplex virus infection, smoking, early age at marriage, women or spouse with multiple sexual partners, multiparity, chronic lower genital tract infection, poor genital hygiene, low socio-economic status have all been implicated.

HPV DNA is found in 93%-99% of invasive cervical carcinoma – 50% have HPV type 16, 10-15% have type 18 and 5-10% have types 45 or 59 (Bosch FX, 1995). A study conducted at the Kidwai Memorial Institute of Oncology, Bangalore, revealed that 15 of 16 patients with CIN III lesion and 19 of 19 patients with invasive carcinoma had HPV E2 gene disrupted. Varying levels of E6 and E7 transcriptions were detected in all the CIN III patients with stronger signals in patients with invasive carcinoma. The women who are infected with HPV, have 4 to >150 times relative risk for developing cervical carcinoma. Prevalence of HPV infection is higher in younger women.

Cervical Cancer Prevention

There has been a regular campaign against cervical cancer for 30 years in India, but this has had little impact on the morbidity and mortality from the disease, with India ranking fourth worldwide. Limited resources and technical manpower do not permit organized screening programs with the Pap test. A wide range of sensitivity and specificity for the Pap test has been reported with a mean of 58% and 68% respectively (meta analysis of 62

studies). The relative insensitivity of conventional cytology means that frequent testing is required for optimal cancer protection. Conventional cytology based screening is very resource intensive, requiring good quality smears, technicians and cytopathologists, adequate laboratory services, well organized screening, diagnosis, treatment and followup procedures to ensure high coverage of the target population. Annual Visual Inspection of cervix with 5% acetic acid, "VIA test" probably suits our general population better than Pap test. There is considerable amount of evidence evolving in our country to favor this test. VIA gives result immediately unlike Pap test. VIA positive women could be managed by cryotherapy in most cases.

A large randomised trial done in India that compared HPV testing, Pap test, VIA and placebo showed HPV testing to be more effective in reducing the mortality due to cervical cancer (NEJM, April 2009). The extremely high NPV (99-100%) of the combination of a negative HPV test and a normal cytologic screen could allow safe widening of the screening interval to 8-10 years. Even one test at the age of 45 years may considerably reduce the cervical cancer incidence. Given that these are expensive tests, their utility as a screening method, is doubtful at present.

The HPV vaccine is a prophylactic vaccine for the prevention of cervical cancer. Both the bivalent (Cervarix) and quadrivalent (Gardasil) vaccine protect against infection of HPV genotypes (HPV-16 and HPV-18) that account for about 70% of HPV-related cervical cancers. Routine HPV vaccination is recommended for females as per the WHO guidelines.

Management of Cervical Neoplasia

CIN I (CIN LR) lesions are usually managed conservatively. If the lesion involves <3 quarters of the cervix then the patient is recalled after 9-12 months. If the lesion has regressed, patient is followed up and if the lesion persists or involves >3 quarter of the cervix then the patient is treated with ablation/LEEP/Cone biopsy. CIN HR (CIN II & III) lesions as diagnosed on colposcopy directed biopsy require excision by conization/LLETZ to rule out invasive cancer. If invasion has been ruled out on the conization specimen and if the cone margins are free, then this procedure is considered therapeutic and patient is advised regular follow-up. If the cone margins are not free then patient is recalled after 3-6 months for a repeat colposcopic examination. If the colposcopy (& Pap test) now reveals that the lesion has regressed, then the patient is placed on regular follow-up. If there is persistence of

the lesion, resection/hysterectomy is advised depending on the desire for conserving fertility.

Managing Invasive Cervical Carcinoma

Following examinations are permitted by FIGO for clinical staging of cervical cancer: Palpation, Inspection, Colposcopy, ECC, Hysteroscopy, Cystoscopy, Proctoscopy, IVP, Chest X-ray, Bone Scan. Following examinations are optional and of value for planning therapy but should not be the basis for clinical staging: Lymphangiography, USG, CT, MRI, Laparoscopy, FNAC of scan detected nodes, PET scan.

USG is almost equivalent to CT but much cheaper and non-invasive. MRI is superior and valuable for determining tumor size, stromal invasion, parametrial extension and LN status and is also safe during pregnancy. PET CT scan is superior for locating distant occult metastasis and may be used selectively in patients with stage II & III cancers to guide in treatment planning.

Carcinoma Cervix Stage IA1: The diagnosis of micro-invasive carcinoma is made either on a conisation or on a hysterectomy specimen. A cervical punch biopsy should not be relied upon for the diagnosis of micro-invasion. When the depth of invasion from the basement membrane is <3mm and the horizontal extent of the lesion less than 7mm, chance of having pelvic lymph node metastasis is less than 1% and the patient can safely be managed by either conization or an extrafascial hysterectomy (Type I Hysterectomy) depending on the desire for fertility.

Carcinoma Cervix Stage IA2: When the depth of invasion of the carcinoma is between 3-5 mm and the horizontal extent <7 mm then the possibility of having pelvic lymph node metastasis is between 0-14%. These patients are usually managed with a type II radical hysterectomy and pelvic lymphadenectomy.

Carcinoma Cervix Stage IB1: Invasive cervical cancers confined to the cervix on clinical examination and with a tumor size <4 cm have equal survival rates with radiotherapy or surgery. Type III radical hysterectomy with pelvic lymphadenectomy is preferred over radiotherapy (especially for lesions <3 cm) as this has several advantages over radiotherapy. Following are the advantages of surgery over radiotherapy (RT):

- Allows accurate surgical staging and planning of further treatment
- Avoids chronic radiation damage to bladder, bowel, vagina
- Sexual dysfunction uncommon

- Ovaries can be preserved
- Radiotherapy could induce second malignancy
- Duration of treatment with RT is 7-8 weeks.

Laparoscopic bilateral pelvic lymphadenectomy is immediately followed, if pN0 at frozen section, by a total lap radical hysterectomy (TLRH) is also feasible and appears to be safe alternative to open radical hysterectomy (Nam JH, Int J Gyn Ca 2004, 2011). Further management after surgery is summarized in the following table:

Node Negative Low risk	Node Negative High risk	Node+
Observe	Small field Pelvic RT	Extended field RT + Weekly cisplatin

High Risk: Tumor > 4 cm, deep stromal invasion, LVSI, + cut margins

Carcinoma Cervix Stage IB2 – III: Survival rates with radiotherapy alone are inferior to concomitant chemo-radiation. There was a worldwide alert on internet, following five large randomized studies showing superiority of concurrent chemo-radiation over radiation therapy alone, that all the patients with stage IB2 – III cervical cancers be managed with concurrent chemo-radiation. Weekly cisplatin 40 mg/m² X 6 cycles is the commonly used CT protocol.

The combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy is essential. EBRT is used to treat the pelvic nodes and parametria, whereas the central disease is primarily treated by the intracavitary implant. Fourfield technique is preferred over two fields as it allows conformal blocking of small bowel, rectum, soft tissues which are outside the target volume. More accurate simulation of treatment fields with CT based treatment planning with improved dose distribution of external beam radiation therapy to the target by linear-accelerator high energy photons, three dimensional treatment planning, conformal blocking techniques and intensity modulated radiotherapy (IMRT) with more than four portals and individual beams of different intensity could result in decreased radiation morbidity and possible therapeutic benefit.

Overall radiation treatment time should be limited to 8 weeks. There is approximately 1% loss of local control for each additional day of treatment. Chemotherapy induced anemia should be simultaneously corrected.

Carcinoma Cervix Stage IV: These patients are usually managed with the intention of palliation only.

(Prof UD Bafna, Head, Dept of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bangalore)

PERSPECTIVE

RADIATION THERAPY IN RECURRENT CARCINOMA CERVIX

Cervical cancer as we all know is one of the potentially preventable cancers. Yet it remains an important cause of morbidity and gynaecological cancer deaths throughout the world. In spite of all treatments, patients of cervix cancer may develop pelvic recurrence, distant metastases, or a combination of both at some point of time during their followups. A 10%-20% recurrence rate has been reported following primary surgery or radiotherapy in women with stage IB-IIA cervical tumors without evidence of lymph node involvement, while up to 70% of patients with nodal metastases and/or more locally advanced tumors would relapse in future (1-4).

Cervical cancer recurrences can be central pelvic, lateral pelvic and extra-pelvic. Central pelvic recurrence develops from the cervix and vagina after primary radiotherapy or from the vaginal cuff and central scar after radical hysterectomy. The relapse can be limited to the vaginal vault alone or can more often involve the bladder and/or rectum. Lateral pelvic recurrence includes parietal and visceral pelvic side wall disease. The former consists of pelvic lymph node metastases and is usually located above the level of the obturator nerve, whereas the latter originates from the paracervix or from scars of the paracervical resection and is placed below the obturator nerve. In patients who develop distant

metastases, the most frequently observed metastatic sites are lung (21%), para-aortic nodes (11%), abdominal cavity (8%), and supraclavicular nodes (6).

It has been seen that majority of the recurrences occur within the first 2 years of diagnosis, and the prognosis remains bleak in such cases, with most patients succumbing to uncontrolled disease (5). Despite improvements in the outcomes of single or combined modality treatment for achieving higher local control of cervical cancer, loco regional recurrences or distant metastasis after initial (surgical or radiation) treatment remain a major therapeutic challenge. *Perez et al.* reported a total pelvic failure rate of 10% in stage IB, 17% in stage IIA, 23% in stage IIB, 42% in stage III, and 74% in stage IVA after radiotherapy alone [5]. The 10-year actuarial incidence of distant metastases was 3% in stage IA, 16% in stage IB, 31% in stage IIA, 26% in stage IIB, 39% in stage III, and 75% in stage IVA [6]

The course of treatment for relapsed cervical cancer depends on the type of treatment previously received and the site of recurrence. Although chemotherapy has been the major treatment modality in the management of patients with recurrent and metastatic cervical cancer, its effectiveness is relatively poor and dismal. Disruption of blood vessels by surgery or high doses of radiation may lead to lower perfusion of the relapsed cancer. Recent phase III trial has documented response rates of 29.1%, 25.9%, 22.3% and 23.4% when cisplatin has been combined with paclitaxel, vinorelbine, gemcitabine and topotecan, respectively [7]. Despite these encouraging results, however, most of the responses are partial and of short duration.

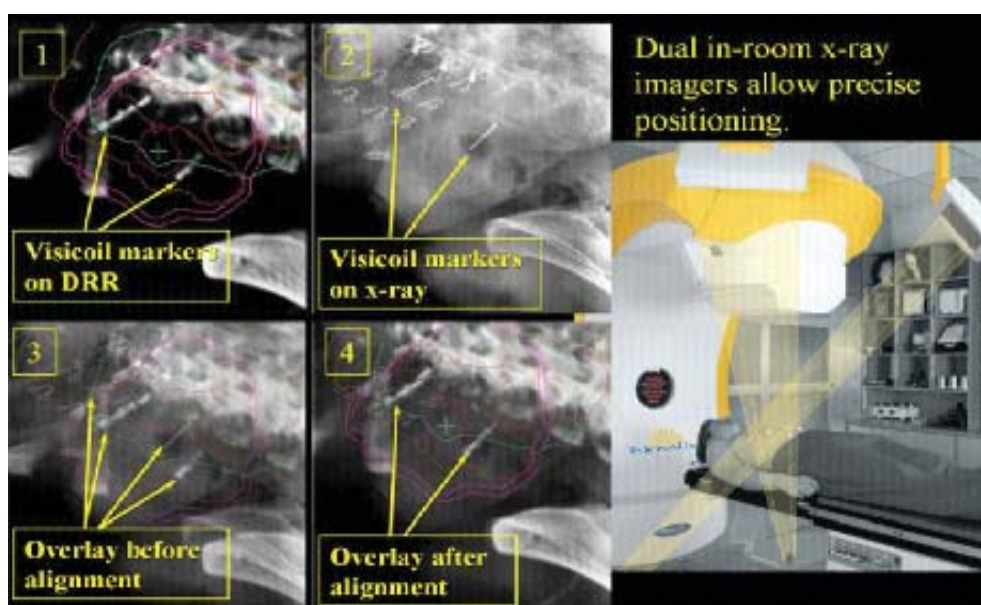


Fig1: Image guided alignment for SBRT and for precision in radiation therapy

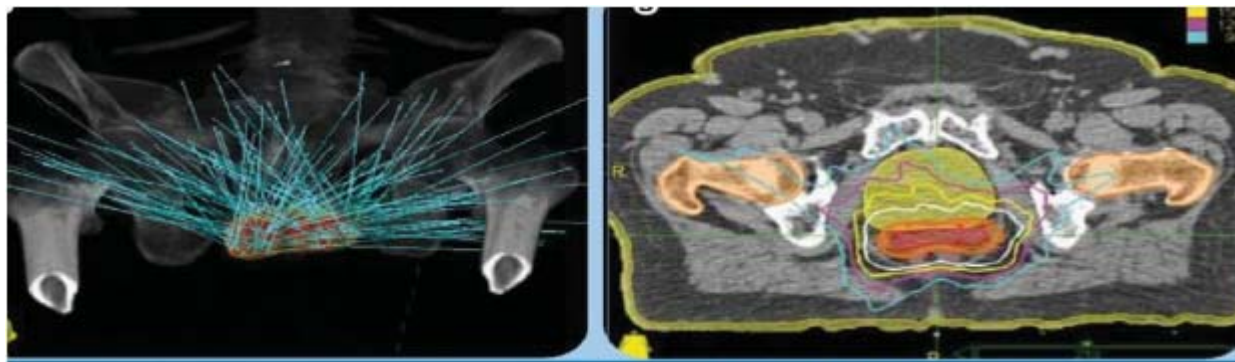


Fig2: Stereotactic body radiation therapy treatment using 136 beamlets converging on a pelvic relapse of previously irradiated

Pelvic surgery (exenteration in many cases) is an option in selected cases of central pelvic recurrence with or without IORT (Intraoperative Radiotherapy). Salvage radiotherapy in the form of tumor directed radiotherapy or brachytherapy has been considered as an option for patients with pelvic recurrence without prior irradiation or with recurrences outside the radiation field. Long term disease free survival has been reported as 40% in many cases.

For those with a history of previous RT and sidewall or nodal recurrences, a combination of surgery and radiotherapy (IM-IGRT, SBRT, brachytherapy or intraoperative radiotherapy) may improve survival for these women who were previously considered incurable. But unfortunately, only few patients are found eligible for surgery because of the lateral location, the proximity of the iliac vessels and the associated surgical morbidity. Relapses in the vaginal vault can be managed with external irradiation plus brachytherapy more effectively than nodal disease which can be treated with external irradiation alone. However, this requires special expertise and technology that may not be available at many centers.

The incidence of isolated para-aortic recurrence after definitive treatment of cervical cancer ranges from

2 to 12% (8). The prognosis of this relapse is usually poor, often being associated with a systemic spread of disease (9). According to recent data, concurrent chemoradiation yields good clinical outcome, especially in asymptomatic patients with an isolated para-aortic failure detected by CT or PET/CT (9).

In recent years, development of three-dimensional radiation therapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) has increased the potential for an improved outcome in selected recurrent cervical cancers. In comparison to conventional EBRT, 3D-CRT and IMRT allow a more precise dose distribution conforming to the target volume and with a steep dose gradient outside the targets, thus sparing OARs and providing an opportunity for dose escalation to the tumor. Concern in dose escalation or in reirradiation has been of tissue toxicity. With more conformality of radiation fields, Mundt et al showed Grade 2 acute gastrointestinal toxicity was 60% vs 91% during radiotherapy for cervical cancer, whereas some patients were previously treated with conventional pelvic radiotherapy. Grade 2 genitourinary morbidity was reduced from 20% to 10% after administration of IMRT, and chronic GI toxicity was 11.1% vs 50.0%, ($p = 0.001$) (10). IMRT also reduces hematological toxicity, because 40% of the total body bone marrow reserve lies within the pelvic bones. This is particularly important for the treatment of recurrent and metastatic disease, especially in patients with a history of irradiation where reirradiation has been made possible.

Stereotactic body radiotherapy (SBRT) is another treatment modality which results in high target dose and steep dose gradients beyond the target, in lesser fractions and therefore, SBRT can deliver higher doses to tumors and causes less normal tissue damage. In recent years, there has been a growing evidence of using stereotactic body radiotherapy for recurrent cervical cancers. This may be particularly useful for patients with recurrent

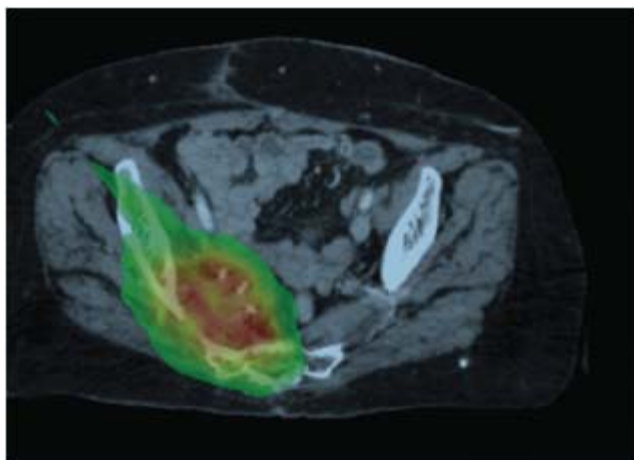


Fig3: Dose Distribution in SBRT for Pelvic Recurrence

cervical cancer involving the pelvic side wall, who are traditionally unfit for exenteration and usually receive palliative chemotherapy when the primary therapy was (chemo-) radiation or surgery plus adjuvant irradiation.

Deodato et al reported a case series of SBRT in recurrent gynecological cancer. 11 patients (12 lesions) were given a dose of 30 Gy in five fractions. After a median follow-up of 19 months, 7 patients (63%) experienced local and/or distant progression of disease. The 2-year local progression-free survival was 81.8%, while the 2-year metastases-free survival was 54.4%. Acute and late toxicities were grade 2 or less (11). Despite the growing interest, there is very limited clinical data in the literature on SBRT for recurrent cervical cancer. Most reports have small sample sizes. No definite “optimal” SBRT single fraction dose and total dose have been achieved. Further studies on dose–response relationship are needed to evaluate the effectiveness and toxicity in recurrent cervical cancer.

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(Dr Swarupa Mitra, Consultant, Dept of Radiation Oncology)

WATCH - OUT

Composition for Treatment of Cervix Cancer

Shin, et al. of SNUR&DB Foundation, Korea have been awarded US patent No. 8377899 on 13 February 2013 for their invention entitled “Composition for treatment of cervix cancer”. Cervix cancer is one of the most frequent malignant tumors in women. Incidence of invasive cervix cancer is slowly decreasing, but it is still one of the most frequent cancers in the developing countries. Clinical and molecular epidemiological studies say human papilloma virus (HPV) infection is the major cause of cervix cancer. HPV is a small DNA virus composed of approximately 8000 nucleotides and causing benign and malignant tumors. The present invention relates to a composition for the treatment of cervix cancer, more precisely a composition for the treatment of cervix cancer comprising the first active part containing human papilloma virus (“HPV”) specific siRNA as an active ingredient and the second active part containing an anticancer agent as an active ingredient. The composition for the treatment of cancer of the present invention has better anticancer effect than the single therapy of the HPV specific siRNA or the anticancer agent, and has an advantage of reducing side effects by using the anticancer agent at a low concentration.

(www.uspto.com, March 10, 2013)

Micrnas in Cervical Cancer

US patent no. 8361714 has been awarded to Beaudenon-Huibregtse, et al of Asuragen, Inc. (USA) for their invention “Micrnas differentially expressed in cervical cancer and uses thereof” on 29th January 2013. The present invention concerns methods and compositions for identifying a miRNA profile for a particular condition, such as cervical disease, and using the profile in assessing the condition of a patient. Cytological examination of cervical smears with Papanicolaou staining (Pap smear) is the screening method universally accepted for early detection of cervical cancer and its precursors. The invention relates generally to the field of molecular biology. More particularly, it concerns methods and compositions involving microRNA (miRNAs) molecules. Certain aspects of the invention include applications for miRNAs in diagnostics, therapeutics, and prognostics of cervical cancer.

(www.freepatentsonline.com, March 10, 2013)

RESEARCH & DEVELOPMENT

Cervical Cancer Brachytherapy

A team of scientists in Norway has studied the dosimetric impact of interobserver delineation variability (IODV) in MRI-based cervical cancer brachytherapy. MR images of six patients were distributed to 10 experienced observers worldwide. They were asked to delineate the target volumes and the organs at risk (OARs) for each patient. Two types of reference contours were created. For each patient, the standard deviation (SD) for the 10 observers was calculated. For rectum and bladder, the mean relative SD for D2cc was 5-8% while sigmoid was at 11%. For the whole treatment, the IODV in HR-CTV caused an uncertainty of $\pm 5 \text{ Gy} \alpha/\beta = 10$ (1SD). The corresponding figure for OARs was $\pm 2-3 \text{ Gy} \alpha/\beta = 3$. For the target volumes, the dosimetric impact of IODV was smallest for the GTV and HR-CTV, while IODV had an even smaller impact on the bladder and rectum.

(Radiother Oncol, Feb 22, 2013)

Mobile Lipid Resonances in Cervical Cancer

A study was conducted in the UK to characterise the major saturated and unsaturated lipid peaks in histologically normal cervical epithelium and stroma, dysplastic epithelium (low-grade cervical intraepithelial neoplasia, CIN) and cancer tissue samples using diffusion-weighted (1)H high-resolution magic angle spinning MRS, to determine whether mobile lipid resonances (MLRs) distinguish tissue types and to test for a correlation between MLRs and the number of cytoplasmic lipid droplets. Diffusion-weighted spectra of tissue biopsies were acquired and lipid droplets were visualised. Linear discriminant analysis separated 'no cancer' from 'cancer' based on the intensities at 0.9, 1.3, 2.2 and 2.8 ppm [area under the curve (AUC)=0.939, $p < 0.001$], 'low-grade CIN' from 'cancer' based on the intensities at 0.9, 4.1, 4.3 and 5.3 ppm (AUC=0.987, $p < 0.001$) and 'no cancer' from 'low-grade CIN' based on intensities at 0.9, 2.2 and 4.3 ppm (AUC=0.984, $p < 0.001$). On average, there were more droplets visible in low-grade CIN and cancer-containing tissues. MLR combinations indicative of average lipid structure efficiently separated tissue classes and increased lipid resonances correlated with increased numbers of cytoplasmic lipid droplets.

(NMR Biomed, Feb 17, 2013)

NotI-Microarrays in Cervical Cancer

Researchers at the Russian Academy of Sciences, Russia have investigated the genetic and epigenetic alterations in cervical carcinomas. In total, 48 paired normal/tumor DNA samples, specifically enriched in NotI sites, were hybridized to NotI-microarrays. Thirty genes, including tumor suppressors or candidates and genes previously unknown as cancer-associated (ABHD5, C3orf77, PRL32, LOC285375, FGD5 and others), showed methylation/deletion in 21-44% of tumors. The genes were more frequently altered in squamous cell carcinomas (SCC) than in adenocarcinomas (ADC, $p < 0.01$). A set of seven potential markers (LRRN1, PRICKLE2, VHL, BHLHE40, RBSP3, CGGBP1 and SOX14) is promising for discrimination of ADC and SCC. Bisulfite sequencing analysis confirmed methylation as a frequent event in SCC. High downregulation frequency was shown for RBSP3, ITGA9, VILL, APRG1/C3orf35 and RASSF1 (isoform A) genes (3p21.3 locus) in SCC. Thus, the data revealed novel tumor suppressor candidates located on chromosome 3 and a frequent loss of epigenetic stability of 3p21.3 locus in combination with downregulation of genes in cervical cancer.

(Epigenetics, Mar 2013)

Surgical-Pathological Factors in Cervical Cancer

A new study has evaluated the surgical-pathological risk factors by weighting the magnitude of significance of multiple risk factors correlating to survival and treatment response in cervical cancer. Multivariate analysis was performed for survival outcomes on 540 stage IA2-IIB cervical cancer cases. Hazard ratio (HR) in each risk factor was determined. Survival curves and postoperative treatment response (concurrent chemoradiotherapy (CCRT) vs radiotherapy alone) were evaluated based on the extent of HR-weighted scores. HR for risk factors relating to disease-free survival (DFS) were: lymphovascular space invasion 3.95, nodal metastasis 3.88, adenocarcinoma 3.40, large tumor 2.36, positive margin 1.99, deep stromal invasion 1.29, and parametria invasion 1.21. Hazard ratio-weighted scores were negatively correlated to DFS. Tumors with larger score offset the benefits of CCRT over radiotherapy alone for postoperative adjuvant treatment ($P < 0.001$). Surgical-pathological risk factors, therefore, provide valuable information for survival and management of early-stage cervical cancer.

(Br J Cancer, Mar 5, 2013)

NEW TECHNOLOGIES

APTIMA® HPV 16 18/45 Genotype Assay

The US Food and Drug Administration has approved Hologic's APTIMA HPV 16 18/45 Genotype Assay for use on TIGRIS® DTS® System to identify human papillomavirus (HPV) RNA from high-risk genital HPV genotypes 16, 18 and/or 45. The APTIMA HPV 16 18/45 Genotype Assay is an *in vitro* nucleic acid amplification test for the qualitative detection of E6/E7 viral messenger RNA (mRNA) of HPV types 16, 18 and 45 in cervical specimens from women with APTIMA HPV Assay positive results. The test results may be used to determine the need for additional follow-up and diagnostic procedures in women with age ≥ 30 years and ≥ 21 with borderline-cytology results and positive test results by APTIMA HPV Assay. The genotype assay is the first test to be approved by FDA for genotyping HPV types 16, 18 and 45 which are associated with about 80% of all invasive cervical cancer worldwide. The new test would help the healthcare professionals better assess a patient's risk of subsequently developing cervical cancer. It is expected to get commercialized during the first quarter of fiscal year 2013.

(U.S. Food and Drug Administration, Nov 1, 2012)

Avastin for Recurrent and Metastatic Disease

The cancer drug Avastin may extend the lives of patients with aggressive cervical cancer, a new study finds. The study included 452 women with recurrent, advanced or persistent cervical cancer who were not curable with standard chemotherapy. The drug was administered intravenously with their chemotherapy treatment. The dose was given one day every three weeks until the disease progressed or intolerable toxicity occurred. It was found that the patients treated with chemotherapy alone had a median survival of 13.3 months while those who received Avastin had a median survival of 17 months. The survival difference between the two groups was highly significant. However, the patients who received the drug experienced more side effects than those who did not. The researchers state that these findings may change the way patients are treated and improve the outcomes for women who previously had very limited treatment options.

(HealthDay News, Feb 8, 2013)

New Technology for Screening

With the introduction of organized cervical cytological screening programs, the incidence of cervical cancer had been significantly reduced. The researchers at Zhengzhou University, China, have determined a new technology with unique advantages for cervical cancer screening. The cervical specimens collected in PreservCyt were processed for ThinPrep cytological test, the new technology test and human papillomavirus detection. The concordance between new technology test and ThinPrep cytological test was 96.34% with 931 positive and 148 negative cases. The sensitivity and the specificity of the new technology were 99.04% and 82.22%. In the 124 positive cases of new technology, human papilloma virus DNA test was positive in 87.9% and negative in 12.1% cases. The sensitivity and the negative predictive values of the new test were 98.57% and 95.45% respectively, when compared to the histopathological diagnosis. If the new technology is used as screening test, it may be a quick screening test and does not depend on the subjective judgment of clinicians.

(Int J Gynecol Cancer, Dec 2012)

Prognostic Marker for Early-Stage Cervical Cancer

Scientists at Sun Yat-sen University, China have investigated that the gene forkhead box M1 (FOXM1) promotes tumor cell invasion and correlates with poor prognosis in early-stage cervical. The FOXM1 transcription factor plays essential roles in regulating the proliferation, differentiation and transformation of cells. The FOXM1 gene and protein expression profiles were determined by quantitative polymerase chain reaction, Western blotting, gene transfection, short hairpin RNA interference (RNAi) and invasion assays etc. The FOXM1 expression was found to be significantly up-regulated at both mRNA and protein level in early-stage cervical cancer compared to those in cervical intraepithelial neoplasia and normal cervical tissues. The increased expression of FOXM1 increased migration and invasion of cancer cells whereas RNAi-mediated knockdown of FOXM1 had the opposite effect. The upregulation of FOXM1 also increased the matrix metalloproteinase-2 (MMP-2), MMP-9 expression and activated the Akt/glycogen synthase kinase-3 α /Snail pathway which results in the promotion of migration and invasion of cervical cancer cells. The study suggests that FOXM1 may act as a prognostic marker and a new potential target for cervical treatment.

(Gynecol Oncol, Dec, 2012)

GLOBE SCAN

First 3-D Image

Cervical cancer is caused by so-called “high-risk” human papilloma viruses (HPV), of which type 16 (HPV 16) is the most dangerous. After infecting a healthy cell, HPV must stimulate it to multiply in order to reproduce itself. The viral proteins E6 and E7 cause cell proliferation and the development of cervical cancer, which is why they are known as “oncoproteins.” For the first time, researchers have solved the three-dimensional structures of E6 proteins in type-16 human papilloma virus and its type 1 bovine equivalent (BPV1). The complete structure of an E6 protein—which is very tricky to produce in the laboratory—had remained unsolved for almost 30 years. The three-dimensional structure of the E6 protein capturing its target reveals the exact molecular mechanism of its carcinogenic activity. It also explains the protein’s remarkable ability to act as a viral terrorist and hijack many of the functions of the infected cell. This breakthrough is crucial for cervical cancer treatment, as it should make it possible to identify and improve medication to prevent the protein from causing tumors.

(France: *Science*, Feb 8, 2013)

Cervical Cancer after Recovery

Patients with histologically confirmed cervical intraepithelial neoplasia (CIN) grade 1-3 who have completed a 2-year follow-up period with three negative cytological test results, show an incidence of invasive carcinoma of 35.1 per 100,000 women years. Their risk for invasive cancer is 4-fold the risk in healthy women who had a negative primary test result. It has been proposed that this group should be kept in long-term, frequent follow-up. The author argues that if cervical cancer develops in these women, the treatment and diagnostics of CIN might have been incorrect. If the thickness of the electrosurgically excised tissue strips is insufficient, more deeply situated parts of the cervical crypts may be left behind in the stroma. After healing, cervical carcinoma may develop beneath a normal surface if these parts of the crypts contain intraepithelial neoplastic cells. This carcinoma is not amenable to early diagnosis. Before deciding on a more intense follow-up, there is need to investigate the quality of the diagnostics and treatment in this group of women.

(Netherlands: *Ned Tidschr Geneesk*, Jan 2013)

New Test for Detection

Since the introduction of organised screening in Sweden in the 1960s, the number of women being diagnosed with and succumbing to cervical cancer has fallen dramatically. However, despite intensive screening, 250 women still die from cervical cancer each year in Sweden, and 500 more develop the disease. The sensitivity of the current test is low, which means that cell samples must be taken at least every three years. A large number of tests must also be repeated because of unreliable results, something which causes anxiety among patients and additional costs for the health service. Around 70 per cent of all cervical cancer cases are caused by two specific virus types, known as HPV 16 and HPV 18. The authors have developed a method that identifies proteins of these oncogenic viruses in cells, enabling a more objective interpretation of the test results. This method can hopefully produce a more reliable diagnosis in uncertain cases and reduce the number of missed cancer cases, as well as the number of women who have to be re-called because of cell samples that are difficult to interpret.

(Sweden: *Science Daily*, Nov 23, 2012)

Metabolic Syndrome and Cervical Cancer

The metabolic changes present in the metabolic syndrome (MetS) have been associated with increased risk of pancreatic and colon cancers; however, there is little information about the association between MetS and cervical cancer risk. A case-control study was performed using data from the National Health and Nutrition Examination Survey (NHANES) between 1999-2010. Women 21 years of age and older, of which an estimated 585,924 (2.3% of the sample) self-reported a history of cervical cancer (cases), were identified. About half (48.6%) of cases and 33.2% of controls met criteria for MetS. Logistic regression analysis showed increased odds of history of cervical cancer among women with MetS (OR = 1.9; 95% CI 1.06, 3.42; P value 0.05) for the risk of history of cervical cancer among women with MetS while adjusting for other known risk factors (high number of lifetime sexual partners, multiparity, history of hormonal contraceptive use, and history of smoking) (AOR = 1.82; 95% CI 1.02, 3.26; P value 0.05). In this US surveyed population the authors found increased odds of history of cervical cancer among subjects with MetS.

(USA: *ISRN Oncol*, Jan 21, 2013)

CLINICAL TRIALS

HPV Vaccination in Adolescent Females

A phase III (PATIRICIA) trial was held by the researchers of University of Kuopio Hospital, Finland, to determine whether the HPV vaccine types could be replaced with other high risk HPV types. A total of 4,808 adolescent females were included in the trial and randomized into 2 groups. One group received ASO4-adjuvanted HPV16/18 virus like particle vaccine and another group received hepatitis A virus (HAV) vaccine. HPV infection was assessed after vaccination every 6 months for 4 years for genital oncogenic HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 58, 59, 66, 68, 70 as well as low risk HPV types. Study revealed that risk for acquisition of any genital HPV types is neither found in HPV DNA negative HPV16/18 vaccinated women compared to the base line HPV DNA negative HAV vaccinated women nor in HPV16/18 vaccinated baseline HPV16/18 positive women compared to baseline HPV16/18 negative women. Increased risk of getting infection with HPV types 39, 45, 59, 68 was found in HAV vaccinated, HPV18 positive women. This result is suggestive of replacement of HPV type after 1-4 years of vaccination with HPV 16/18 type.

(*Int J Cancer*, Dec 2012)

Nab-Paclitaxel for Advanced Cervix Cancer

Researchers of the Arizona Cancer Center performed phase II trial in women with metastatic or recurrent cervix cancer after first-line of treatment. Total 37 patients were enrolled in the study, of which 35 patients were eligible and evaluable for response and tolerability. All the eligible patients had received one prior chemotherapy regimen and 27 of them had prior radiation therapy with concomitant cisplatin. Nanoparticle, albumin-bound paclitaxel (nab-paclitaxel) was administered at 125 mg/m² IV over 30 minutes on days 1, 8 and 15 of each 28-day cycle and the median number of cycles were 4. Results showed that 10 of the 35 patients had a partial response and another 15 patients had stable disease. The median progression-free and overall survival were 5.0 and 9.4 months, respectively. The only grade 4 event was neutropenia in 2 patients (5.7%), and Grade 3 neurotoxicity was reported in 1 (2.9%) patient and both resolved following dose reduction. The study concludes that Nab-paclitaxel has considerable activity and moderate toxicity in the treatment group.

(*Gynecol Oncol*, Dec 2012)

CANCER CONTROL

Recommendations on Screening for Cervical Cancer

The Canadian task force on preventive health care has come up with revised guidelines for cervical cancer screening. Recommendations are presented for screening asymptomatic women who are or have been sexually active. They do not apply to women with symptoms of cervical cancer, previous abnormal screening results (until they have been cleared to resume normal screening), those who do not have a cervix (due to hysterectomy), or who are immunosuppressed. The recommended guidelines are:

- For women aged <20, no routine screening for cervical cancer.
- For women aged 20 to 24, no routine screening for cervical cancer.
- For women aged 25 to 29, routine screening for cervical cancer every 3 years.
- For women aged 30 to 69, routine screening for cervical cancer every 3 years.
- For women aged 70 who have been adequately screened (i.e. 3 successive negative Pap tests in the last 10 years), it was recommended that routine screening may cease. For women aged 70 or over who have not been adequately screened, it was recommended continued screening until 3 negative test results have been obtained.

(*Canadian Medical Association Journal*, Jan 8, 2013)

Tubal Ligation and Cervical Cancer

Women who have a tubal ligation, the surgical tying or severing of fallopian tubes to prohibit pregnancy, have less frequent Pap smears, which puts them at an increased risk for cervical cancer, according to research from the University of Oklahoma Health Sciences Center, USA. The researchers used a questionnaire to identify factors associated with the cancer, including the frequency that the women went for Pap tests. It was discovered that women who have had a tubal ligation were not as likely to have regular Pap tests. In all age groups, women with tubal ligation were more likely to have had no Pap screening in the previous five years compared to women using other forms of contraception. The importance of screenings in women, including the Pap test, is stressed to prevent cancer.

(*Medical News Today*, Jan 16, 2013)

INFOCUS

CARCINOMA CERVIX: SOME BASICS OF PATHOLOGY

Cervical cancer is second only to breast cancer in its incidence worldwide. Age-standardized incidence rates (ASIR) range from about 10 per 100,000 in most developed countries to more than 40 (and up to 100) per 100,000 in many developing countries.

The cervical cancer, which is predominantly of the squamous cell type but also includes adenocarcinomas of different subtypes is causally related to human papilloma virus infection (HPV) and is a prime example of multistep carcinogenesis. Knowledge of these two essentials has allowed a vaccination and a screening strategy to combat with the menace of cervical cancer. While vaccination has been a recent introduction, the identification of precursor lesions through cytological screening has contributed to significant reduction in cervical cancer related mortality.

Sexually transmitted human papillomavirus (HPV) is the most common etiological agent of cervical carcinoma, with about 70% caused by high-risk HPV 16 and 18. Approximately 10 other HPV genotypes cause the remaining 25% to 35% of cervical cancers.

The products of two early HPV genes, E6 and E7, play a major role in cervical carcinogenesis (Figure 1). HPV preferentially infects the basal cells in the cervical transformation zone, an area of active cell turnover. Integration of viral DNA in the genome disrupts most of the viral genes except two of the early genes, viz, E6 and E7, which continue to be expressed and their proteins immortalize the human keratinocytes and accord them

proliferative advantage and ability to accumulate further genetic alterations, leading to cancerous transformation. Interaction of these genes with cellular proteins involving the tumor suppressor proteins TP53 and pRB, respectively leads to a rapid degradation of the cellular proteins via the ubiquitin pathway. The net effect of loss of p53 and RB proteins is an unstable genome and freed E2F protein which pushes the cell through cell cycle and also activates transcription of “p16 protein”, an important marker for identification of cervical dysplastic changes.

From amongst the horde infected, only a few progress to high grade dysplasia and cervical cancer, with several host and environmental factors contributing to HPV persistence and progression to cervical neoplasia. These include individuals with multiple sexual partners, early age of first intercourse, early childbearing, multiple pregnancies, cigarette smoking, HIV infection, immunodeficiency states, and oral contraceptive use.

Those who develop cervical neoplasia undergo a stepwise progression starting from preinvasive lesions that can be detected by screening and cured with complete excision (Figure 2).

Pap smears are routinely done for screening of cervical lesions. Widespread adoption of Pap screening has resulted in early detection of cervical cancer precursors, with established guidelines for management of abnormal results. Accurate histologic and cytologic classification of HPV mediated lesions has important implications for guiding patient management.

The rate of progression to invasive cancer from CIN is usually slow, taking years to decades. This long natural course provides an opportunity for screening to effectively detect this process during the preinvasive phase, thus allowing early treatment and cure. Because many of these preinvasive lesions (especially LSIL) would have

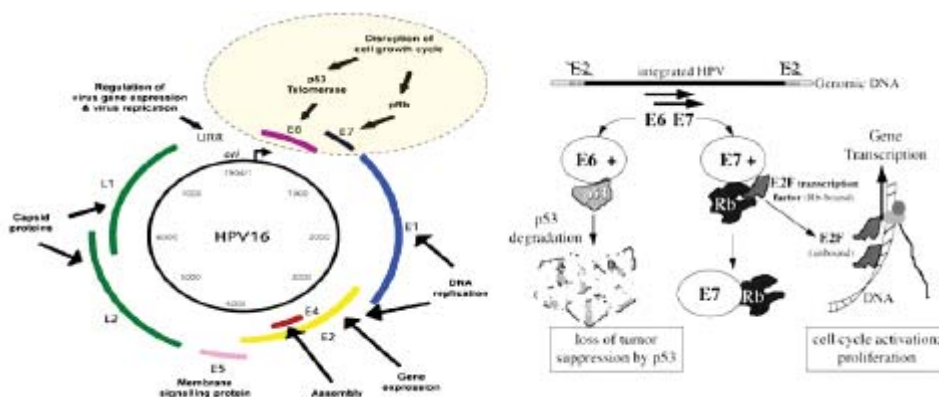


Figure 1. Interaction of HPV proteins with tumor suppressor proteins with ultimate effect of cellular proliferation and inactivation of p53, the guardian of genome protein

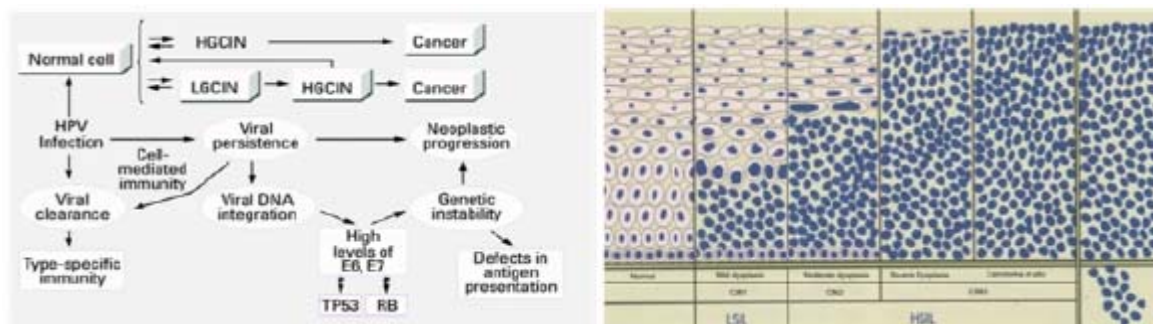


Figure 2. Mechanisms of human papillomavirus [HPV] carcinogenesis.

LG = Low grade, HG = High grade, CIN = Cervical intraepithelial neoplasia, RB = Retinoblastoma gene. [Adapted from WHO]

never progressed to invasive cancer, screening also runs the risk of leading to treatment for women who do not need to be treated.

Although cervical cancer mortality increases with age, the prevalence of CIN is highest among women in their 20s and 30s. Mortality is rare among women younger than 30 years; HSIL is rare among women older than 65 years who have been previously screened. About 70% of ASCUS and CIN 1 lesions regress within 6 years, while about 6% of CIN 1 lesions progress to CIN 3 or worse. In about 10% to 20% of women with CIN 3 lesions, the lesions progress to invasive cancer.

Case-control studies have found that the risk of developing invasive cervical cancer is three to ten times greater in women who have not been screened. Risk also increases with long duration following the last normal Pap test, or similarly, with decreasing frequency of screening. Screening every 2 to 3 years, however, has not been found to increase significantly the risk of finding invasive cervical cancer above the risk expected with annual screening.

Based on the data generated through these studies, current guidelines recommend initiating Pap testing three years after first intercourse and not later than the age of 21 years, and continuing it every one to two years until age 30, and later at one- to three-year intervals until age 65-70 or indefinitely.

The accuracy of Pap test has been an issue of concern with clinicians and women groups. A single test has sensitivity of 55% to 80% for detecting high-grade lesions. However, the progression being slow, it is believed that false negative cases will get detected during subsequent screening raising the sensitivity of a program of regular Pap testing to far higher and acceptable levels.

While conventional screening of vaginocervical smear has been effective in reducing cancer related mortality significantly, efforts have been made to enhance the sensitivity of testing by using liquid based cytology and

HPV testing. As, yet there is no evidence to favor liquid based cytology as a superior modality. HPV DNA testing has been sought by women groups and some clinicians on false belief of improving the sensitivity of cervical cancer screening. However, carcinogenic HPV infections are very common, particularly in young women, and the majority get cleared on their own within 1 to 2 years. Such being the case, over referrals and undue stress to one harboring self-clearing infection is a serious concern.

HPV testing, therefore, has been approved for use in two contexts only (1) as a second test following an equivocal cytology result of ASCUS; and (2) for primary screening in conjunction with cervical cytology for women aged 30 years and older.

The histological diagnosis of dysplasia unexpectedly is also fraught with difficulties and interobserver variations of interpretations compromising accurate diagnosis that directs appropriate management triage, the goal of cervical biopsy. Various immunohistochemical and molecular assays are now available as ancillary studies in the workup of difficult squamous and glandular lesions. *p16* protein over-expressed because of freeing of E2F manifests as diffuse, strong, cytoplasmic and/or nuclear staining in squamous and glandular lesions associated with high-risk HPV infection. Atypical immature metaplastic lesions that are *p16* positive have been shown to have a higher incidence of subsequent HSILs. ProEx C is a recently developed immunohistochemical assay that targets the expression of topoisomerase II and minichromosome maintenance protein-2, two genes that have been shown to be over-expressed in cervical cancers. The assay is a nuclear stain that is positive in cervical dysplasia and has been validated in cytologic specimens for the detection of HSIL.

Histological Types of Cervical Cancer

The World Health Organisation (WHO) recognizes two main histological types of invasive cancer that is,

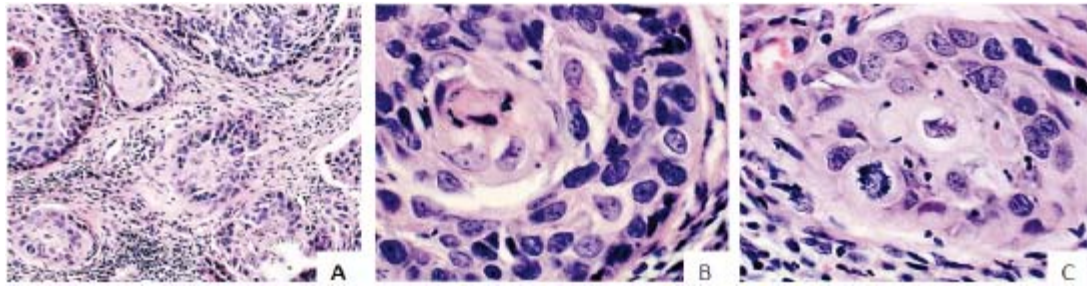


Figure 3. Invasive keratinizing squamous cell carcinoma (histology): A. Round nests of cancer cells invade stroma in which inflammatory cells are visible; B. Invasive well differentiated squamous cell carcinoma exhibiting keratinization of tumor cells in the centre. C. High dry view of nuclear atypia and mitosis.

- **Squamous carcinoma** (which constitute about 85% of all cases); and
- **Adenocarcinoma** (which constitute about 10-12% of all cases).

Several other types of carcinoma, eg, adenosquamous carcinoma, adenoidcystic carcinoma, metastatic carcinoma, make up the remaining 3-5% of all cases.

Squamous carcinomas are further typed according to whether they are keratinising or non-keratinising carcinomas. Keratinising carcinomas may be well differentiated or moderately differentiated and are composed of large tumor cells. The non-keratinising carcinomas (poorly differentiated carcinomas) may be of large cell or small cell types (Figure 3)

Adenocarcinomas are less commonly found and although each type is histologically distinct, it is not uncommon for two or more histological forms of adenocarcinoma to be present in a single tumor. The frequent coexistence of glandular and squamous

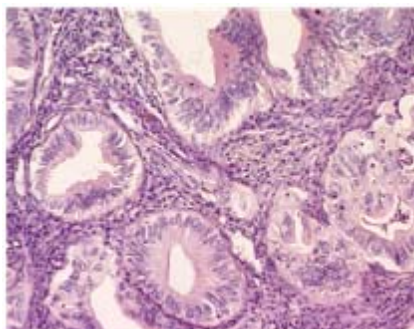


Figure 4. Adenocarcinoma of cervix - well differentiated. Note tumor cells are forming glands. The neoplastic glands are crowded and penetrate beyond the stroma of the cervical epithelium into the fibromuscular wall of the cervix. Observe the cellular atypia and crowding.

carcinoma suggests that they may have a common origin in the reserve cells of the cervix as well as a common etiology. The most frequent type of adenocarcinoma to be found in the cervix is the endocervical type of mucinous adenocarcinoma. Three grades of endocervical carcinoma are recognized—well—differentiated, moderately differentiated, and poorly differentiated—depending on

the similarity of the tumor cell to the glandular epithelial lining of the endocervix (Figure 4)

Key Points & Conclusion

1. Cervical cancer is a sexually transmitted disease caused by HPV 16 and 18 along with a few other high risk HPV strains (90%).
2. There is possibly no cervical cancer outside this group despite HPV being detected in 90% cases only.
3. Pap smear is a satisfactory screening modality, especially when employed regularly in a structured screening program.
4. Liquid cytology accords no benefit but adds to the cost of screening.
5. HPV DNA testing in early age group is controversial because despite finding high risk strains, most women will eliminate the infection in 1 to 2 years without any consequences. Cost is also a consideration.
6. Histological evaluation for dysplasia is at times difficult to diagnose and grade. Use of p16 and ProEx C immunostaining is rewarding.
7. There is a whole gamut of other carcinoma types besides squamous carcinoma and even these are causally associated with HPV infection.

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(Dr Anurag Mehta, Director Laboratory Services)

RGCON - 2013 HIGHLIGHTS

Rajiv Gandhi Cancer Institute and Research Centre, (RGCI&RC) held its 12th Annual International Conference from 15th to 17th February 2013 at Hotel Eros - (Hilton), Nehru Place, New Delhi. Like every year, this year too RGCI&RC adhered to its tradition of academic excellence. In keeping with the rapid changes in the management of colorectal cancers, the theme of the conference was very aptly chosen as “**Changing Scenario in Colorectal Cancer**”.

The first day, 15th February, was dedicated to live surgical workshops and video workshops during the morning and afternoon. The operation included Robotic LAR / APR by Dr Byung-Soh Min from Korea; Lap colectomy/LAR/APR operated by Dr Sung Bum Kang, from Korea, Intersphincteric Resection by Dr Yoshito Akagi from Japan; and Peritonectomy and HIPEC by Dr Shivendra Singh from RGCI&RC. They were complemented by an interactive panel discussion by eminent surgeons from all over the country and abroad. Following this, there was a live video presentation from “Institut Mutualiste Montsouris, Paris” by Dr Brice Gayet, Paris.

Inauguration

The formal inauguration of the conference was held in the evening at 5.30 pm. This was indeed a glittery, spectacular session. The dias was adorned by the presence of the Chief Guest, Mr. Sriprakash Jaiswal, Central Minister of Coal, and the Special Guest, Dr V. Shantha,

and other dignitaries as Mr. Rakesh Chopra, Chairman RGCI&RC; Mr DS Negi, CEO, RGCI&RC; Dr AK Dewan, Medical Director, Dr DC Doval, RGCI&RC; and Dr Sunil Gupta, Organizing Secretary of RGCON 2013. The inauguration was auspiciously marked by the lighting of the lamp as per the Indian customs and release of the souvenir by the Special Guest, Dr V Shantha, Chairman, Cancer Institute, Adyar, Chennai, Padmashree, Padma Bibhushan, IARC award winner for her work for the development of Cancer Registries in India, Nazli- Gad-EL-Mawla Award-Cancer Control in Resource Poor Country, Brussels, and Ramon Magsaysay Award for Public Service. In a very ceremonious moment, the LIFE TIME ACHIEVEMENT AWARD was presented to Dr V Shantha for her relentless service to the ailing patients of cancer and her dedication and devotion to her profession and humanity. Like every year, the prestigious Dr P.S.Raman Memorial Award for the best paper published in 2012 was announced and awarded to Dr Gauri Kapoor, Senior Consultant, Department of Pediatric Hematology and Oncology, RGCI&RC, for her paper entitled "Experience with High Dose Methotrexate Therapy in Childhood Acute Lymphoblastic Leukemia in a Tertiary Care Cancer Centre of Developing Country".

Evening session was a brain storming session on Emerging Molecules in Colorectal Cancer which included lectures by foreign delegates followed by a very interesting panel discussion. The lectures, delivered on very new molecules like Bevacizumab by Dr Herbert I Hurwitz, USA; Cetuximab by Dr Heinz-Josef Lenz, USA; Regorafenib by Dr Andrea Sartore Bianchi, Italy; and



(L to R: Dr D C Doval, Chairman RGCON- 2013; D S Negi, CEO; Mr Rakesh Chopra, Chairman; Dr V Shantha, Cancer Institute (W.I.A) Chennai; Dr A K Dewan, Medical Director; Dr S K Gupta, Organizing Secretary; RGCON- 2013)



Clock-wise: (1). Life Time Achievement Award being Presented to Dr V Shantha; (2). Dr V Shantha Addressing the Audience (3). Mr. Sriprakash Jaiswal, H'ble Union Minister of Coal, Govt. of India (4). Dr S H Adwani with Organizing Team

Aflibercept by Dr Will Steward, UK; were indeed very enlightening.

The 2nd Day of the conference promised a plethora of topics including epidemiology, hereditary colorectal cancers, screening and the recent advances in imaging and their implications in colorectal cancer management.

Dr Andrea Sartore Bianchi, Italy, spoke in great detail on Role of Biomarkers in colorectal cancer and it's implications, a topic that interests all colorectal oncologists alike. A never ending topic of debate for all oncosurgeon is "Surgery of the Primary: Lap/SILS/Robotic/Open Colectomy – Which is Oncologically Sound?" This debate was very expertly addressed by various speakers putting forward their opinion in support of their favourites, Lap Colectomy by Dr Sung Bum Kang, Korea; SILS Colectomy by Dr G Srikanth, Bengaluru; Robotic Colectomy by Dr Byung-Soh Min, Korea; and Open Colectomy by Dr E. Hemant Raj, Chennai.

Dr Heinz-Josef Lenz, USA, in his inimitable style held the attention of the audience with his talk on 'Role and the impact of molecular markers on treatment decisions in the metastatic setting'. Dr Peter Gibbs from Australia, presented his views on First Line Therapy – SIRFLOX and FOXFIRE.

Curative intent treatment for colorectal liver metastasis- State of the art-colorectal liver metastasis was discussed by various specialists who presented their respective evidences. 'Perspective of Medical Oncologist' was presented by Dr Heinz-Josef Lenz, USA; Surgeon's Perspective by Dr KR Prasad, from UK; Perspective of Radiation Oncologist by Dr Swarupa Mitra, Delhi; and Interventional Radiologist's Perspective by Dr MC Uthappa, from Bengaluru. A Glimpse into the Future of New Radiation Techniques for Rectal Cancer by Dr B Ajai Kumar from Bangluru.

One of the highlights of RGCON 2013 was the number of debates. Debates were very well moderated by panels of chairpersons encouraging exchange of opinion with the house as well. The scientific contents, and hospitality were immensely appreciated by everyone present. The conference came upto the expectations of providing a comprehensive and up-to-date multidisciplinary perspective on epidemiology, biology, diagnosis, management and future directions of colorectal cancers.

(Dr Swarupa Mitra, Consultant, Dept of Radiation Oncology; Dr Sunil Gupta, Sr Consultant, Dept of Medical Oncology; Dr Shivendra Singh, Sr Consultant, Dept of Surgical Oncology)



**Rajiv Gandhi Cancer Institute
and Research Centre**

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BREASTCON 2013

EMERGING TRENDS AND FUTURE DIRECTIONS MANAGEMENT OF EARLY BREAST CANCER

Under the Aegis of
**The Association of Surgeons of India
Indian Association of Surgical Oncology
Indian Society of Oncology**

Date: 13th - 14th April 2013

Venue: India Habitat Centre, Lodhi Road, New Delhi - 110003, India

INTERNATIONAL FACULTY

- | | |
|--|---|
| ■ Prof. Ismail Jatoi
University of Texas, U.S.A. | ■ Dr. Jayant Vaidya
Whittington Hospital, U.K. |
| ■ Prof. Robert Mansell
Cardiff University, U.K. | ■ Prof. Giovanni Paganelli
European Institute of Oncology, Milan, Italy |
| ■ Dr. Amit Goyal
Royal Derby Hospital, Derby, U.K. | ■ Prof. Christine Brezden-Masley
University of Toronto, Canada |

KEY TOPICS

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| ■ Recent Advances in Breast Imaging | ■ Neoadjuvant Chemotherapy and Breast Conservation |
| ■ Surgical Considerations in Breast Conservation | ■ Hormonal Therapy in Early Breast Cancer |
| ■ Breast Oncoplasty : state-of-the-art | ■ APBI, IORT & IART |
| ■ Targeted Therapy in Breast Cancer | ■ Survivorship issues in Breast Cancer |
| ■ Management of The Axilla | ■ Update on In-situ Cancers |

HIGHLIGHTS OF THE CONFERENCE

- Plenary Sessions and Key Note Addresses
- Panel Discussions and Case Capsules
- Master Video Session
- Meet the Professor Session
- Posters and Oral Presentations



ORGANIZING COMMITTEE

- | | | |
|---|---|--|
| Dr. D. C. Doval
Chairman - Organizing Committee
Director - Research & Medical Oncology | Dr. Kapil Kumar
Organizing Secretary
Sr. Consultant - Surgical Oncology & Chief of Breast Services | Dr. Ullas Batra
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|---|---|--|

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DD / Cheque to be made in favour of **Rajiv Gandhi Cancer Institute**, Conference Account, payable at Delhi

LAST DATE FOR ABSTRACT SUBMISSION - 15th MARCH 2013

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