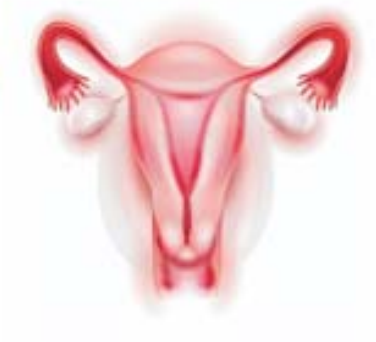
REGIONAL CANCER CENTRE, BULLETIN

Vol (2) Issue (1) April 2010

JIPMER - Cancer Update



FOCUS - GYNAECOLOGICAL CANCERS

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Editorial

Greetings to you all…

It is a pleasure interacting with you again through this bulletin. As many of you aware that due to continuing advances in the science of oncology we decided in November 2009 to conduct Continuing Medical Education (CME) programmes quarterly to share the knowledge and experience of various specialties dealing with all branches of Oncology and that our first CME on Colorectal Cancer was a big success. We were overwhelmed by the response then, which has vindicated our decision about the need for regular CMEs. The consistent evolution of our understanding of biology, pathophysiology and the response of cancer cells to multimodality treatment besides the rapid developments in the technology of radiation therapy have equipped us better in dealing with the disease. However, it is an irrefutable fact that the definitive cure for cancer still eludes us all.

The topic chosen for this CME is Gynaecological Malignancies and the timing cannot be more opt with so much developments happening in the country towards gender justice. This CME is designed to foster discussions on the management principles, the challenges and the latest developments in the science of gynaecological oncology so as to provide the delegates a comprehensive review of the subject. The junior faculties are encouraged to present the latest research and developments that are taking place in gynaecological oncology and the senior faculty from JIPMER, other medical colleges & hospitals in Puducherry and from Chennai will be sharing with us their wisdom and their sound personal clinical experience. I believe the interactions will hone the skills of the young physicians as well as students and equip them to face the future clinical challenges. This way the CME will be useful in connecting the dots of the past to the matrix of the future.

This bulletin includes the articles presented during the CME. This issue will also serves as a record of some of the latest developments in the gynaecological oncology at this point of time. I congratulate the authors and the entire editorial team who sifted through all the articles, making it as a quality reference material.

My best wishes to the young team of CME programme for taking their time off from their busy schedule and making all the efforts for another successful CME.

Dr. K. S. Reddy
Director RCC

Hereditary Gynaecological Cancers

(Dr. P. Reddi Rani, Professor of Obstetrics & Gynaecology, JIPMER)

Summary

Hereditary predisposition to breast and ovarian cancer, most commonly due to gem line mutations in $BRCA_1$ and $BRCA_2$ has been recognized for many years which are transmitted as an autosomal dominant disorder. The hall marks of hereditary cancer syndromes include multiple affected family members, early age of onset and the presence of multiple and or bilateral primary cancers. The two important hereditary cancers in gynaecology are Hereditary Breast / Ovarian Cancer (HBOC) and Lynch / Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC). Genetic testing which plays a role in defining the risk requires careful counseling to discuss the limitations of testing itself and available management strategies. Prevention options include screening, chemoprevention and risk reducing surgery. In premenopausal women undergoing risk reducing bilateral salpingo-oophorectomy (rrBSO), quality of life may be affected due to menopausal symptoms. Short term HRT after rrBSO may not affect the reduction in breast cancer risk. Needs more research in this field.

Keywords – BRCA mutations, Hereditary Syndromes, Ovarian Carcinoma, Risk Reducing Surgery

Introduction

Over the past few years knowledge of genetic susceptibility to breast and ovarian cancer has increased substantially. Most of the genes involved in malignancies regulate cell division and differentiation. Majority of malignancies are acquired due to exogeneous exposure to carcinogenic agents, only few are inherited and familial.

Testing for mutations in the $BRCA_1$ and $BRCA_2$ genes is becoming increasingly available to women who are believed to have an elevated risk of familial predisposition to breast and ovarian cancer. Approximately 10% of ovarian cancers are believed to be familial and 90% of these hereditary ovarian cancers can be accounted for mutations in $BRCA_1$ and $BRCA_2$ mutations[1]. The risk of ovarian carcinoma due to mutations in $BRCA_1$ estimated to be 28 to 44% by 70 years of age compared with the general population risk of 1.8%[2]. The risk of ovarian carcinoma by age 70 with $BRCA_2$ mutations estimated to be 27%, lower than for $BRCA_1$ and also occurs after age 50[3].

Genetic factors

Inherited mutations in the $BRCA_1$ and $BRCA_2$ genes are responsible for most hereditary ovarian and breast cancers. Family history is an important factor in assigning an individual woman's probability for developing these cancers. Patients with one first degree relative with ovarian cancer have approximately 5% risk and patients with two first degree relatives with ovarian cancer have a 7% risk[4].

Women with $BRCA_1$ and $BRCA_2$ mutations have a 60 to 85% cumulative life time risk (to 70 years of age) of invasive breast cancer and a 15 to 65% cumulative life time risk of invasive epithelial ovarian cancer[5]. Hereditary ovarian cancer syndrome is defined as women with at least two first degree relatives with ovarian cancer who have a life time probability as high as 25 to 50% of developing ovarian cancer[6].

Two distinct clinical syndromes associated with hereditary ovarian cancer have been identified. They are HBOC and HNPCC. HBOC accounts for 85 to 90% of all hereditary cancers identified. The vast majority of these cases are associated with mutations of $BRCA_1$ locus. $BRCA_1$ is a tumour suppressor gene that acts as a negative regulator of tumour growth. Inheritance of a cancer predisposing mutant-allele of $BRCA_1$ is followed by loss of inactivation of the wild-type allele which results in non regulation of cell growth and progression towards malignancy. In women with $BRCA_1$ mutations the risk of ovarian cancer begins to rise in late 30s and early 40s. For women with $BRCA_2$ mutations the ovarian cancer risk does not begin to rise until approximately 10 years later[7].

HNPCC or Lynch II syndrome is also an autosomal dominant genetic syndrome where there is a predisposition to the site specific colorectal cancer with the predilection for the proximal colon, early age of onset. One of the DNA mismatch receptor genes places the carrier at a high risk of multiple adenocarcinomas. There is a life time risk of colorectal cancer of up to 60% in women, 40 to 60% risk of endometrial cancer and a 10% risk of ovarian cancer[8].

Preventive options

The various options available for women at high risk for hereditary cancers are:

1. Screening
2. Chemoprevention
3. Risk reducing surgery

Screening

It is very important to identify women with hereditary risk of cancer. A directed family history is the most important initial screening in the evaluation. If a woman's family history indicates the possibility of a hereditary cancer syndrome, it is worthwhile to have a genetic counsel / or other genetic professional develop a thorough and accurate cancer pedigree.

Family structures with a 10% or greater probability of detecting a Germline BRCA mutation[9].

- Breast cancer diagnosed before age 50 in 2 or more related women.
- Breast cancer diagnosed before age 50 in one women, ovarian cancer at any age in 1 or more additional related women in family.
- Breast cancer diagnosed after age 50 in 1 or more women, with ovarian cancer in 2 or more additional relatives.
- Ovarian cancer in 2 or more relatives.
- Male breast cancer with any family history of breast or ovarian cancer.

Cancer risks in individuals with deleterious BRCA mutations

Mutations of $BRCA_1$ and $BRCA_2$ are associated with increased risk of female breast and ovarian cancer including fallopian tube and primary peritoneal cancer. The prevalence of germ line BRCA mutations in population based studies indicates $BRCA_1$ mutations in approximately 4 to 5% of ovarian cancer patients and 1 to 2% in $BRCA_2$ mutations. But in cases with family history of these diseases there is increased incidence. Family cancer risk assessment clinics have identified mutations in either $BRCA_1$ or $BRCA_2$ in 21% to 73% of individuals undergoing testing. Risk estimates vary widely among series[10].

For women who do choose to undergo screening the National Breast Cancer guidelines[11] are to offer Transvaginal ultrasound (TVUS) and then combine TVUS with CA 125 measurement after the menopause. Ovarian cancers are difficult to detect in early stage as CA 125 levels are elevated in only half of the patients with ovarian epithelial cancer and also it is elevated in non-neoplastic conditions also. TVUS lacks sensitivity and specificity. There is no reliable method of screening for ovarian cancer.

In women with HNPCC who choose not to undergo risk reducing surgery should have TVUS commending at age 30 to 35 years or at five years younger than the youngest affected family members with the addition of CA 125 at menopause. Endometrial sampling is required in those with abnormal uterine bleeding or in women who have a thickened endometrium on TVUS. It is not clear whether these measures can reduce the incidence or mortality from endometrial or ovarian cancer in this group.

The Society of Gynaecologic Oncologists education resource panel developed guidelines through a series of meetings and conferences. The guidelines for whom genetic risk assessment recommended include

1. Patients with greater than approximately 20-25% chances of having an inherited predisposition to breast and ovarian cancer[12].
    - Women with a personal history of both breast and ovarian cancer
    a) Women with ovarian cancer and a close relative with breast cancer at ≤50 years or ovarian cancer at any age.
    b) Women with ovarian cancer at any age who are of Ashkenazi Jewish ancestry
    c) Women with breast cancer at ≤ 50 years and a close relative with ovarian or male breast cancer at any age.
    d) Women with Ashkenazi Jewish ancestry and breast cancer at ≤40 years.
    e) Women with a first or second degree relative with a known $BRCA_1$ or $BRCA_2$ mutations.

*Peritoneal and fallopian tube cancers should be considered as part of the spectrum of hereditary breast / ovarian cancer syndrome.

* Close relative is defined as a first, second or third degree relative

2. Patients with greater than approximately 20-25% chances of having an inherited predisposition to endometrial, colorectal and related cancers[12].
    - Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria[13] as listed below
    a) At least 3 relatives with a Lynch / HNPCC associated cancer in one lineage
    b) One affected individual should be a first degree relative of the other two
    c) At least 2 successive generations should be affected
    d) At least 1 HNPCC – associated cancer should be diagnosed before age 50.
    - Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50.
    - Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50.
    - Patients with colorectal or endometrial cancer with evidence of mismatch repair defect
    - Patients with a first or second degree relative with a known mismatch repair gene mutations

In patients with greater than 5-10% chance of having an inherited predisposition to breast and ovarian cancer and also in patients with inherited predisposition of 5-10% to endometrial, colorectal and related cancers, genetic risk assessment may be helpful[12].

Chemoprevention

Though combined oral contraceptive pills (OCP) reduce the ovarian risk in general population the effect on BRCA mutation carriers is unclear. There is a possible 40 to 50% reduced risk of ovarian cancer with previous use of OCPs in women at high risk for ovarian cancer[14]. The reduced risk is greater for use longer than 5 years and persists for long term over 20 years after ceasing use. There are concerns regarding a possible small increased risk of breast cancer due to OCP use in women with $BRCA_1$ mutations but not for those with $BRCA_2$ mutations[15].

Risk reducing surgery - Management of women with hereditary ovarian cancer risk

Risk reducing bilateral salpingo-oophorectomy (rrBSO) is more frequently employed particularly in women who have completed child bearing and are nearing menopause. The risk of ovarian cancer from families with hereditary ovarian cancer syndrome is sufficiently high to recommend prophylactic oophorectomy in these women at age 35 years or after child bearing completed. Most women with $BRCA_1$ and $BRCA_2$ mutations who develop ovarian carcinoma do so after age 45. Finch et al[16] in their study of women with a BRCA mutation undergoing risk reducing BSO showed an 80% overall reduction in ovarian, fallopian tube and primary peritoneal cancer compared to whom who did not have surgery. BRCA mutations are associated with an increased risk of fallopian tube carcinoma and complete removal of both tubes and ovaries is indicated.

An important concern regarding prophylactic oophorectomy is the possibility of subsequent peritoneal carcinomatosis which has been documented in 2 to 11% of women who have undergone the procedure[17]. An analysis of 12 families in which at least two women had ovarian cancer demonstrated that prophylactic oophorectomy reduced the risk of ovarian peritoneal cancer by 50% but in some instances it was due to missed microscopic diagnosis of ovarian carcinoma which later presented as peritoneal carcinomatosis, stressing a proper histological

evaluation of prophylactically removed ovaries to diagnose microscopic disease[18]. It is also essential to perform peritoneal washing and inspect upper abdomen at the time of surgery to diagnose occult cancer.

Age for rrBSO

The mean age at diagnosis of ovarian cancer is 52 years in $BRCA_1$ and 62 years in $BRCA_2$ mutation carriers. The diagnosis of hereditary ovarian cancer before the age of 30 years is rare but rises significantly after age 35 for $BRCA_1$ carriers and almost a decade later for $BRCA_2$ carriers. There is a greater reduction in breast cancer risk in women having rrBSO before age 40 (70%) compared to those after age 40 (40%). Since the benefit diminishes with age, it is recommended that rrBSO should be performed when child bearing is completed or by age 35[19].

HRT after rrBSO

An important concern in women with mutations of $BRCA_1$ and $BRCA_2$ are problems of premature menopause which may affect the quality of life and also the long term risk of osteoporosis. Role of HRT is controversial as it can contribute to the risk of developing breast carcinoma. Unopposed estrogen is associated with increased risk of endometrial carcinoma in women who are not hysterectomized and combination of estrogen and progestogens increases the risk of development of breast cancer. Rebbeck et al[20] in their study found that short term HRT after rrBSO did not affect the reduction in breast cancer risk achieved by rrBSO.

Tubal ligation

It lowers the risk of ovarian cancer among BRCA carriers by up to 60% and is an option for those women who do not wish to undergo rrBSO but who have completed their families[21].

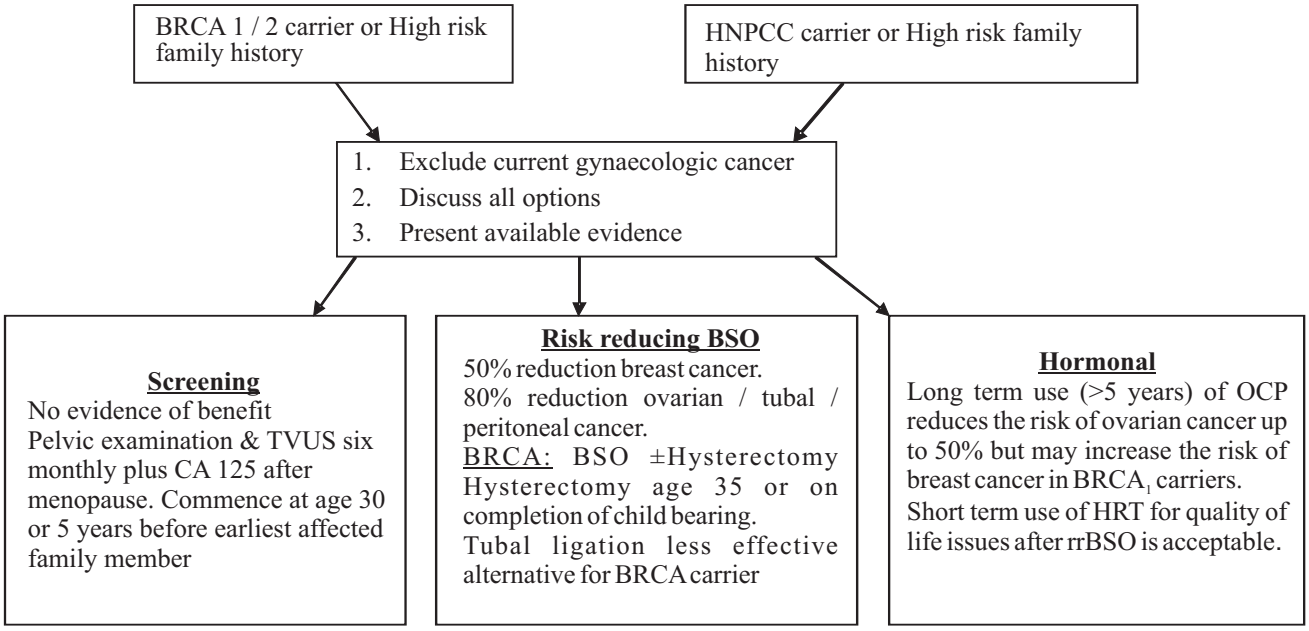
Hysterectomy

The addition of hysterectomy to rrBSO is recommended for women at risk of endometrial carcinoma (HNPCC). Hysterectomy is controversial in BRCA carriers but benefits may include that HRT with unopposed estrogen can be given without concern for endometrial carcinoma.

Conclusion

Counseling, screening, chemoprevention and risk reducing surgery are preventive approaches in carriers of BRCA mutations. Combination of intense surveillance and risk reducing surgery in carriers of BRCA mutations may allow the diagnosis of breast, ovarian and endometrial cancer at an early stage.

Algorthim for the management options for high risk women[8]



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HPV Vaccine

(Dr. K.S.Reddy, Professor and Head, Dept. of Radiation Oncology, RCC, JIPMER)

Summary

The cervical cancer remains as the commonest cause of cancer death among women in developing countries which may be due to lack of access to screening and management and follow up abnormal cervical pathology. Human Papilloma Virus is the commonest aetiological factor and 70% of invasive cervical carcinoma is due to HPV 16 and 18. The Quadrivalent HPV vaccine protects against HPV types 6, 11, 16 and 18. Administration before the initiation of sexual activity gives greatest health benefits. A 3 dose regimen 0, 2 and 6 months is recommended in all adolescents 11 to 12 years. It is approved from age 9 to 26 years who have not yet been vaccinated. A comprehensive approach is necessary incorporating vaccination, screening, early treatment and follow up to prevent cancer cervix and its related morbidity and mortality.

Introduction

Cancer cervix is a preventable condition by cervical screening programme which is well developed in developed countries where mortality is reduced by 50% but in developing countries with poor resources, screening services are not available to all and remained as an important cause of mortality and morbidity. It has been estimated that without further preventive measures death from cervical cancer are predicted to jump up four fold to over a million a year by 2050 as a result of explosion in HPV infection across the world[1]. There is a need for primary prevention. HPV vaccine is coming up as a primary preventive measure which has the obvious advantage even in developed countries avoiding the cost of screening and avoiding the false positive diagnosis which causes anxiety and unnecessary investigations.

Cervical cancer: Burden of disease

Cervical cancer is the commonest genital tract cancer in women of developing countries in low socioeconomic group and due to lack of screening procedures. Globally it comprises approximately 12% of all cancers in women and second most common on cancer in women world wide. In developing countries it accounts for approximately 15% of all cancers and in developed countries 4% of all cancers[2]. The estimated life time risk of cervical cancer is 3.67% and the life time cervical mortality risk is 1.26%[3].

HPV Infection

Human papilloma virus infection is a highly prevalent sexually transmitted infection responsible for significant morbidity and mortality. Molecular studies have shown that HPV DNA is present in almost all (99.7%) cervical cancers. HPV 16 and 18 are the most common HPV types found in cervical cancer and are responsible for approximately 70% of these cancers 50.5% due to HPV 16 and 13.1% due to HPV 18[4]. More than 100 types of HPV have been identified, among which at least 15 are high risk types which are responsible for both high grade and low grade cervical lesions and cervical cancer. Viral proteins E_6 and E_7 which prolong cell replication promote genetic instability and progression to cancer.

Low risk types 6 & 11 cause genital warts and low grade cervical lesions, laryngeal papillomas but they do not cause cervical or other HPV related cancers. Most studies suggest that the prevalence of HPV infection occurs among those younger than 25 years who are sexually active and the peak incidence of cervical cancer occurs around age 50 years. 90% of HPV infections are cleared, persistent infection are usually due to high risk leads to cervical cancer. There is a prolonged latent phase of 20-30 years which allows for screening of the cervix to detect precancerous abnormalities.

Common HPV types associated with HPV related disease[4]

	HPV Types	Manifestations
High risk	16, 18, 31, 33, 45	Low grade cervical changes High grade cervical changes Cervical cancer Anogenital and other cancer
Low risk	6, 11	Benign Low grade cervical changes Condylomata acuminta genital warts

Factors that put women at risk of HPV infection[5]

- Young age (Peak 20-24 years.)
- Lifetime number of sexual partners
- First sexual intercourse at early age
- Male partner sexual behaviour
- Smoking
- Oral contraceptive use
- Uncircumcised male partner

Due to the obligatory role of HPV infection in the development of cervical neoplasia, a vaccine to immunize against HPV infection would be a valuable strategy for the primary prevention of cervical cancer. Addition of HPV vaccine which is targeted against 70% of oncogenic HPV types to cervical screening programme may provide a cost effective option for further reducing the burden of the disease[6]. Use of quadrivalent HPV vaccine, in conjunction with Pap screening would also be expected to have an impact on the overall population through herd immunity. Successful clinical trials with prophylactic HPV vaccination have raised the hope that the common gynecological conditions like cervical cancer, cervical dysplasias genital warts and anogenital cancers can be prevented through vaccination.

Quadrivalent vaccine

Development of immunogenicity to HPV involves presentation of the L I protein on the HPV viral capsid to the immune systems. Virus like particles (VLP) which are empty viral capsids can be synthesized and are immunogenic of the HPV vaccines. Currently being developed the quadrivalent vaccine (Gardasil) containing HPV types 6, 11, 16 and 18 is the first vaccine FDA approved for the use in the prevention of anogenital cancers, precancers or warts related to HPV infection. It consists of a mixture of four types of viral DNA – free virus like particles derived from the L I capsid proteins of HPV types 6, 11, 16 and 18.

Who should receive the HPV vaccine?

Girls of ages 11 to 12 years, most of whom have not started sexual activity are the primary targets of immunization. The vaccination is also recommended for 13 to 26 years old girls and women. The FDA approved the vaccine for females aged 9 to 26 years. Even adults who have been sexually active for years may not have been exposed to all high risk HPV covered by the vaccine. A working group on HPV prevention[7] concluded that any sexually active person may benefit from vaccination and should have the opportunity to receive the vaccine. Adolescents are particularly vulnerable to HPV because the squamous columnar cell junction of cervix is more exposed than the adult cervix in whom only smaller area of cervical ectopy comprised of columnar epithelial cells are exposed. In a randomized double blind placebo controlled trial[8] of more than 20,000 young women aged 16 to 26 years, it was found that the vaccine was highly effective in preventing cervical dysplasia of any grade and external genital lesions related to HPV types 6, 11, 16 and 18. These women were followed up for an average 2 years. In an another prospective planned combined analysis of four randomized controlled trials[9] based on sexually active women aged 16 – 26 years who received either three doses of vaccine or placebo it was found that there was no case of CIN 2 or 3 or cervical adeno carcinoma in situ in the vaccine group (n = 8487) compared with 53 cases in the placebo group (n = 8460) during average 20 month follow up period. According Sanders et al[10] vaccination of the entire US population of 12 year old girls would prevent more than 200,000 HPV infections, 100,000 abnormal pap tests and 3300 case of cervical cancer. Vaccines work best before an individual has been exposed to HPV infection. The advisory committee on immunization practices of the CDC11 recommended that the vaccine be administered routinely to 11 and 12 year old girls and to non vaccinated females aged 13 to 26 years. It can be started in girls as young as 9 years.

Dosing and administration

It is a non-infectious vaccine, should be refrigerated at 2 to 8°C and should not be frozen. The vaccine is prophylactic and not meant to treat individuals already exposed to HPV and it does not protect against strains of HPV other than types 6, 11, 16 and 18. It is administered in 3 stages (0, 2, 6 months). The quadrivalent vaccine contains 20, 40, 40 and 20 g of VLP for HPV types 6, 11, 16 and 18 respectively comes as single dose vial containing 0.5 ml. It is not recommended for use in pregnant and lactating women. It will not protect against other sexually transmitted infections. It is highly effective with good safety profile.

After HPV vaccination neutralizing antibodies are secreted from memory B cells and bind to their target HPV type preventing infection before it occurs thereby blocking the initial step towards the development of cervical cancer. HPV antibodies generated by vaccination may wane with time, although current data indicate that immune responses persist through 5 years. The need for booster immunization to maintain protection against infection will only become apparent after prolonged periods of follow up[12].

Adverse reactions

These include pin, swelling and erythema at the infection site but no serious reactions have been reported.

Contraindications

- Persons with a history of immediate hypersensitivity to yeast or any vaccine component.
- Not given in pregnant women due to limited amount of data in this setting.

Limitations of vaccine

It will not eliminate cervical cancer for several reasons.

- Women may be already infected with high risk HPV types 16 & 18
- Though highly efficacious, they are not 100% effective
- Some oncogenic types are not included in the vaccine.

An important limitation in developing countries is the cost of the vaccine and reaching the targeted population.There is also hypothetical risk of reduction in safer sex practices and in screening modalities because of HPV vaccination. Quadriple vaccine promises to save lives but won't replace the pap test. It significantly reduces the incidence of cervical pathology. Screening with pap smear should continue because of the potential effects of HPV serotypes not covered by the vaccine. At present cervical screening recommendations remain unchanged for HPV vaccine recipients as it can prevent only 70% of cervical cancer. Education plays a very important role for the acceptance of vaccine. It is necessary to explain adolescents and their parents about the full benefits of HPV vaccination.

A comprehensive approach is necessary to prevent cervical cancer which incorporates vaccination, screening and early treatment. Cervarix is a bivalent vaccine against HPV 16 and 18 which is recently approved by FDA.

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An Introduction to Fertility Sparing Surgery in Gynaecological Malignancies

(Dr. Papa Dasari, Dept., of Obstetrics and Gynaecology, JIPMER, Puducherry)

Management of Gynaecological malignancy in the elderly and in those who finished their fertility is not met with so much controversy and expertise as that in women who desire to preserve their fertility. In developing countries like India women's social life depends on their fertility potential more so when they are not employed and or illiterate. This is very much evident while treating patients with infertility. Though the primary aim of management of malignancy is preservation of life, fertility preservation is equal to preservation of life in some situations for some women. In this article a brief outline about the possibilities and options available for fertility preservation is discussed.

One should think of fertility preservation while treating Childhood Gynaecological malignancies, Adolescent Gynaecological malignancies and malignancies in young nulliparous /uniparous women. A multi Institutional retrospective investigation (1965-2000) which identified 52 patients of epithelial ovarian cancer in stage IA-IC treated with unilateral adnexectomy and adjuvant chemotherapy reported 98% survival at 5 years and 93% survival at 10 yrs. Of the 24 patients who attempted conception 17 conceived (71%) which resulted in 26 term deliveries without any congenital anomalies and 5 spontaneous abortions. The authors concluded that fertility sparing surgery can be safely undertaken in Stage I epithelial ovarian cancer[1].

Epithelial ovarian neoplasms are uncommon in pediatric and adolescent patients, accounting for approximately 20% to 30% of ovarian tumors in adolescent females and women younger than 25. Tumors of low malignant potential (LMP) account for a significant proportion of epithelial neoplasms in this patient population[2]. Tumours of low malignant potential have excellent prognosis when treated surgically conservatively. An analysis of 38 patients (Stage I -89%; Stage II-3% ;Stage II-8%)) with low malignant potential treated by fertility sparing procedures like unilateral salphingo-ovariotomy and cystectomy without any adjuvant treatment were reported by Rao and collegues. There was no mortality but recurrences were observed in 16% and 13% delivered live foetuses at a median follow up of 26 months. The authors concluded that fertility sparing surgery has a risk of reccurrence in contralateral adnexa and it should be offered to well motivated patients. Recurrences may be due to microinvasion which may be missed on initial pathological report. In a retrospective clinic pathological review of 126 serous and mucinous low malignant potential tumours 11% showed microinvasion. However, microinvasion in these group of tumours did not seem to worsen prognosis on long term follow up.[4] Among the malignant germ cell tumours in patients with a median age of 22 years the survival rate was reported to be 97% for dysgerminomas and 67% for non-dysgerminomas in a recent study and fertility sparing surgery was found to be as effective as radical surgery in all eligible patients[5].

A five year cumulative pregnancy rate of 52.8% was reported in a large series of patients who underwent vaginal radical trachelectomy with bilateral pelvic lymphadenectomy for early

stage invasive carcinoma cervix.(Stage I A 2 and B1 with less than 2cm in diameter and less than 10 mm invasion) [6]. When vaginal approach is not possible due to distorted anatomy abdominal approach can also be underdaken in selected patients under laparscopic guidance[7].The complications following these procedures like increased risk of spontaneous abortions, preterm labour and infertility need to be explained.

Phase II multicentre study of fertility sparing treatment for stage IA endometrial carcinoma and atypical endometrial hyperplasia in 28 young women with high dose medroxy progesterone acetate revealed a cure rate of 67% and a pregnancy rate of 46% and reccurrence rate of 47% over 3 year follow up period.[8]

Lissoni Andrea and collegues reported on fertility sparing surgery in uterine leiomyosarcoma in which the diagnosis was made on histopathological examination of myomectomy specimens of 8 young nulliparous women between 19-32 yrs of age. The patients were subjected to strict follow up and were evaluated by pelvic examination, hysteroscopy, USG, CT, MRI and X-Ray chest. At median follow up of 48 months 2 patients delivered at term spontaneously and the third patient had recurrence diagnosed at caesarean section, who died later despite chemotherapy . Two patients had hysterectomy after 16 and 24 months and were found to have leiomyoma at histopathology. The authors concluded that fertility sparing surgery in cases of uterine leiomyosarcoma may be offered selectively to young nulliparous women desiring pregnancy and definitive surgery i.e., hysterectomy should be undertaken soon after the fertility function is over.[8]

Fertility sparing surgery is an option in unilateral involvement of ovary in several subtypes of ovarian cancer viz., tumours of low malignant potential, malignant ovarian germ cell tumours, ovarian sex-cord stromal cell tumours and early stage epithelial ovarian cancers and it can be followed by chemotherapy. Fertility sparing surgery for invasive cervical cancer includes conisation for stage A1 and A2 and Radical trachelectomy for stage A2 and B1 with small lesion. Ovarian transposition can be undertaken for women undergoing chemoradiation. Hormonal therapy can be considered for women with early stage endometrial cancer of low grade [9]. In advanced gynaecologic malignancies cryopreservation of normal ovarian tissue and in-vitro fertilisation with surrogacy allows one to have their own biological child in the present day of Assisted Reproductive Technology. The options include Oocyte cryopreservation, Embryo cryo preservation, ovarian tissue cryo preservation, ovarian suppression and ovarian transposition. The oncologist has an important role in discussing these options before planning the definitive treatment[10]. The care of patients requiring fertility sparing therapy is challenging and complex and is a multidisciplinary approach involving Gynecological Oncologists, Reproductive Endocrinologists, Perinatologists, Psychiatrists and finally Radiation Oncologists.

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Endometrial Hyperplasia and its relationship with Endometrial Carcinoma

(Dr Pampa.Ch.Toi, Assistant Professor, Department of pathology, JIPMER)

One of the most important causes of abnormal uterine bleeding is endometrial hyperplasia. This deserves special mention because of its relationship with endometrial carcinoma. Endometrial hyperplasia if left untreated can develop significant mortality and morbidity .Apart from carcinoma of the cervix, endometrial carcinoma is one of the commonest gynaecological malignancies and early diagnosis is important.

In endometrial hyperplasia there is proliferation of endometrial glands with alteration of the gland stroma ratio.The clinical significance of this condition is that, it is a precursor of endometrial cancer. The current and common classification of endometrial hyperplasia as accepted by the World Health Organization and the International Society of Gynaecologic Pathologists characterizes the glandular architecture pattern and presence or absence of nuclear atypia. There are divided into four groups, simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia and complex hyperplasia with atypia.Various studies have found that lesions with varying degree of complexity and atypia when left untreated progressed to adenocarcinoma. About 29% of complex hyperplasia with atypia, 8% of simple hyperplasia with atypia, 3% of complex hyperplasia and only 1% of simple hyperplasia may progress to endometrial carcinoma. It has been found that concurrent carcinoma occurs in 17-52% of atypical hyperplasia.

The aetiopathogenesis of endometrial hyperplasia and endometrial carcinoma are almost similar and molecular studies have shown that both share specific molecular genetic alteration. Endometrial hyperplasia results from continuous estrogen stimulation that is unopposed by progesterone.This maybe due to endogenous or exogenous estrogen.The endogenous source are due to chronic anovulation (polycystic ovary syndrome) or perimenopause, obesity, functioning granulosa cell tumors of the ovary. Exogenous source includes prolonged administration of estrogenic substances (estrogen replacement therapy). Other risk factors are nulliparity, early menarche, late menopause. The exact role of estrogen in transformation of the normal endometrium to hyperplasia is not known, however molecular studies have shown some genetic alterations in such cases.

Endometrial carcinomas are classified broadly into TypeI and Type II. The Type I carcinoma (endometrioid carcinomas) are associated with endometrial hyperplasia.

A common genetic alteration found in a significant number of hyperplasias and related endometrial carcinomas is inactivation of the PTEN tumor suppressor gene.Endometrial hyperplasias are associated with microsatellite instability and defects in DNA mismatch repair genes.This feature is also seen in cancers adjacent to endometrial hyperplasias. A PTEN gene mutation with loss of expression of the PTEN protein is an early event in this progression while mutations of K-ras and mismatch repair genes occur later.

Mutations in the PTEN tumor suppressor gene have been identified in 30% to 80% of endometrioid carcinomas and in approximately 20% of endometrial hyperplasias, both with and without atypia. Its main function in tumorigenesis, is dephosphorylation of the lipid molecule phosphatidylinositol - trisphosphate (PIP_3), which blocks the phosphorylation of AKT, a central factor in the phosphatidylinositol 3-kinase (PI3K) growth-regulatory pathway. When PTEN is inactive, AKT phosphorylation is enhanced, and it stimulates protein synthesis and cell proliferation and inhibits apoptosis. It has been shown that loss of PTEN, resulting in the activation of AKT, can lead to phosphorylation of the estrogen receptor in a ligand (estrogen)-independent manner. Thus, loss of PTEN function may activate pathways normally activated by estrogen. Endometrioid adenocarcinomas, which are estrogen-dependent, account for 80 percent of all endometrial cancers and contain K-ras mutations (20 percent of cases), microsatellite instability (20 to 30 percent), and mutations in the PTEN gene (83 percent) Endometrioid adenocarcinoma appears to arise from endometrial hyperplasia with atypical hyperplasia as an intermediate step.

Endometrial hyperplasia is a pathologic diagnosis and, therefore, cannot be made without an endometrial tissue sample. The diagnosis of endometrial hyperplasia should be suspected in women with heavy, prolonged, frequent (i.e less than 21 days), or irregular uterine bleeding. Irregular uterine bleeding in perimenopausal women, or any bleeding in postmenopausal women, is the most common clinical symptom of endometrial neoplasia. Such bleeding is usually (80 percent) due to a benign condition However, given the real risk of endometrial hyperplasia or carcinoma, abnormal uterine bleeding, especially postmenopausal bleeding, requires further evaluation.

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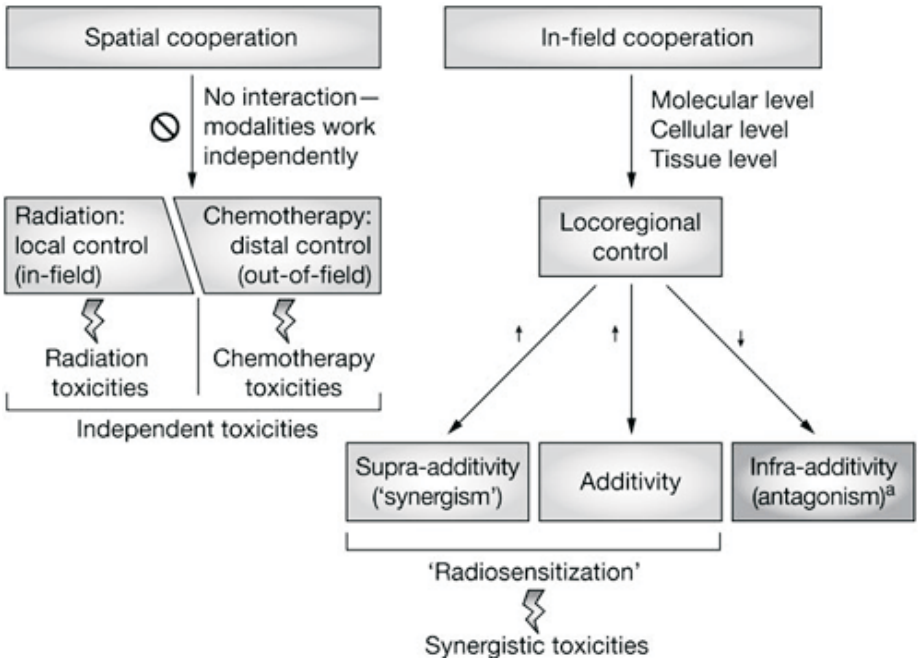
Concurrent Chemo-Radiotherapy in Carcinoma Cervix

(Dr. Gunaseelan. K, Assistant Professor, Department of Radiation Oncology, RCC, JIPMER.)

Carcinoma cervix is the commonest malignancy seen in Asian women and constitutes approximately 30% of all cancers. It is also the leading cause of female cancer mortality in India. Nearly 50% of the patients present with advanced stages (FIGO Stage III/IV). The main stay of treatment has traditionally been radical radiation therapy and over decades the survival rates have achieved a plateau of 30 - 45% at 5 years. In developing countries the socioeconomic problems, illiteracy, late presentation and irregular follow-up have further compromised our survivals. Over the last decade there have been studies on the use of chemo-radiotherapy in carcinoma cervix. This article discuss about the rationale, impact on survival and toxicities associated with the use of concurrent chemo-radiation in carcinoma cervix.

The clinical rationales support the use of chemotherapy delivered concurrently with radiation is firstly, chemotherapy can act as a radiosensitizer, improving the probability of local control and survival, by aiding the destruction of radioresistant clones. Second, chemotherapy given as part of concurrent chemoradiation may act systemically and potentially eradicate distant micrometastases. The term spatial cooperation also support the use of chemotherapy delivered concurrently with radiation whereby radiotherapy acts locoregionally, and chemotherapy acts against distant micrometastases. (as shown in figure below)



Rationale for adding chemotherapy to radiation - Spatial and in-field cooperation are the two idealized types of cooperation between radiation and chemotherapy. Both mechanisms can contribute synergistically to clinical benefit.

This cooperative effect requires the agents to have non-overlapping toxicity profiles in order that both modalities can be used at effective doses without increasing normal tissue effects. However, few chemotherapeutic agents meet this criterion, because limited single-agent activity or toxicity-driven dose reductions preclude the delivery of systemic dosing schedules. Many trials of concomitant chemoradiotherapy, however, have demonstrated decreased incidence of distant metastases compared with radiation alone. This evidence could indicate that chemotherapy delivered at radiosensitizing doses has some systemic spatial cooperative effect, or that the improved local control of chemoradiotherapy decreases subsequent metastases.

However, Synchronous administration of radiation and cytotoxic chemotherapy will enhance acute radiation reactions within all tissues included in the treatment volume, resulting in more severe acute symptoms. Impact on chronic radiation injuries is less predictable. Anxiety regarding normal tissue tolerance, both immediate and late, has delayed extrapolation of successful chemoradiation strategies for anal cancer to the larger volumes of vulnerable tissues routinely irradiated in the treatment of cervical cancer.

Multiple clinical trials have investigated the sequential use of neoadjuvant chemotherapy followed by conventional radical radiation therapy for patients. In several of these studies, patients treated with neoadjuvant chemotherapy followed by radiation had worse survival probability than did patients treated with radiation alone. This has been attributed to selection of cross-resistant tumor clonogens as well as delay in initiation of the potentially curative therapy.

In dramatic contrast to the manifest failure of sequential chemotherapy and radiation, the large majority of recent prospective, randomized controlled trials investigating radiation and synchronous chemotherapy have demonstrated improvements in both local control and survival. Data from five phase III randomized clinical trials sponsored by the National Cancer Institute have shown that the addition of concurrent cisplatin-containing chemotherapy to radiation results in a reduction in risk of recurrence by 21%. Four of these trials pertained to women with locally advanced cervical cancer, stages Ib2 to IVa. The fifth studied high-risk postoperative patients stages Ib to IIa with cancer extension to parametrium, surgical margins, or regional lymph nodes (as shown in table below)

Study	Regimen	Overall survival	Toxicity	Pelvic Recurrence	Distant Mets
Keys	XRT (75Gy to point A)	74(3yr)	10	24	16
	XRT+CP	78	37	11	12
Peters	XRT (75Gy to point A)	77(3yr)	3	17	16
	XRT+CP+FU	87	50	6	10
Whitney	XRT+HU (80Gy to point A)	50(5yr)	31	30	21
	XRT+CP+FU	62	13	25	18
Rose	XRT+HU (80Gy to point A)	47(3yr)	22	30	4
	XRT+CP	65	23	19	-
	XRT+CP+FU+HU	65	28	20	3
Morris	XRT (85Gy to point A)	58(5yr)	2	35	33
	XRT+CP+FU	73	49	19	14

The optimal drug regimen is uncertain. Four of these trials had an experimental arm containing 5-fluorouracil (5-FU); however, the Gynecologic Oncology Group (GOG) prospectively compared weekly cisplatin with continuous-infusion 5-FU and terminated the study (GOG protocol 165) when it became clear that no possibility existed that the 5-FU arm might ultimately prove superior. Weekly cisplatin at a dose of 40 mg/m^2 for six doses has become the most commonly used regimen for concurrent chemotherapy with radiation for advanced cervical cancer.

However, the National Cancer Institute of Canada (NCIC) prospectively compared radiation alone with radiation plus weekly cisplatin in 259 patients with squamous cancers with bulky (≥5 cm) stage Ib2 to IIa, or smaller tumors with positive nodes, and patients with stages IIb to IVa cancers. The study was designed to have an 80% probability of detecting a 15% survival difference at 5 years. Although patients receiving the cisplatin regimen did marginally better, the study failed to find a statistically significant difference.

The Radiation Therapy Oncology Group (RTOG) prospectively compared radiation alone administered to extended volumes (pelvis plus paraaortic nodes) with pelvic radiation with three synchronous cycles of 5-FU and cisplatin, with one cycle administered synchronously with intracavitary brachytherapy. The population of 403 patients composing the study population were identified and selected with entry criteria similar to those of the NCIC study (except that nonsquamous cancers were included). The relative risk of recurrence was 0.48 (90% confidence interval) in the chemoradiation arm compared with radiation alone.

Further complicating this issue are the three additional prospective, randomized studies that have found relapse-free survival benefit from the synchronous administration of epirubicin with radiation, mitomycin-C with radiation, or 5-FU plus mitomycin-C with radiation, and a fourth prospective randomized trial that failed to detect benefit from synchronous administration of cisplatin, vincristine, and bleomycin with radiation compared with radiation alone.

Most studies have demonstrated that the use of combined chemotherapy and radiation therapy has been associated with statistically significant increase in gastrointestinal and hematologic toxicity that, although significant, has been tolerable. Data suggest that synchronous administration of chemotherapy potentiates radiation effect in cycling, immediately responding cell systems, in both cancer and normal tissue. Thus both immediate normal tissue reactions and side effects are potentiated. Importantly, an increase in catastrophic late complications such as bowel obstruction, fistula formation, or second malignancies, has not been seen.

Over 19 randomized trials have been published addressing the issue of chemo-radiotherapy. However, heterogeneous data, poor randomization, inadequate number of patients, sub-optimal radiotherapy, non-uniform use of chemotherapeutic drugs, its sequencing and poor documentation have not yet provided the evidence to substantially alter the practice. Hence, meta-analysis of these trials was undertaken to further evaluate the role of chemo-radiotherapy in carcinoma cervix.

The first meta-analysis published by Cochrane Collaborative Group of 4580 randomized patients (19 randomized trials) suggested that chemo-radiation did show an absolute survival benefit improvement both in progression free and overall survivals by 16% and 12% respectively ($p<0.0001$). The survivals were significantly better with Cisplatin based concomitant chemo-radiation ($p<0.0001$). Incidentally, the distant metastasis rates were also significantly lower in chemo-radiation ($p<0.0001$). However, all these benefits were seen only in early stages. In addition, acute grade 3/4 hematological and gastro-intestinal toxicities were higher with chemo-radiation (additional 8% and 5% respectively). The data was insufficient to report on late toxicity.

The second meta-analysis of 9 randomized trials, recently published by the Canadian Group to evaluate only cisplatin based concomitant chemo-radiation confirms the improvement in overall survival (4year survival data) in advanced stages, bulky IB tumors (prior to surgery) and high risk early disease (post-surgery). Although acute grade 3/4 hematological and gastro-intestinal toxicities were higher in chemo-radiation, they were short-lived, with only 2 deaths and the remaining resolved with medical treatment. There was no significant increase in the late toxicity from the data available.

Both the Cochrane and Canadian meta-analysis have to a large extent tried to address the role of concomitant chemo-radiation, but Carcinoma Cervix Stage III accounted for only 30-35% and moreover evaluation with optimal radiation schedules and comparison of late toxicities still remains unanswered. What is more important is that the cisplatin is relatively inexpensive and is available worldwide. This means that cisplatin-based chemo-radiation is affordable in the developing countries where carcinoma cervix still forms the major cancer. However, the role of chemo-radiation in Carcinoma Cervix Stage IIIB in a developing countries including India still remains unexplored. Given the preponderance of evidence, which now suggests that synchronous radiation with radiopotentiating chemotherapy favorably affects probability of cancer-free survival, clinical research into the optimal drugs and schedule of administration is likely to play a central role in clinical investigation for the foreseeable future.

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Surgical Management of Lymph Nodes in Gynaecological Cancer

(Dr. R.Aravind, Assistant Professor, Dept. of Surgical Oncology, JIPMER)

Management of regional lymph nodes in gynaecological cancer has been a subject of several retrospective studies, randomized and non randomized trials. This article attempts to review available literature and provide evidence based inferences with regard to management of lymph nodes in the most common gynecological cancer subsites with special emphasis on the role of surgery.

Cervical Cancer

Stage wise frequency of metastasis to pelvic and para-aortic lymph nodes in cervical cancer is shown in Table 1.

Table1

Stage	Pelvic	Para-Aortic
IA1	0-0.5%	4-7%
IA2	7-9%	4-7%
IB	12-20%	~7%
IIA, B	35%	15-20%
III	35%	25-30%
IV	50%	25-30%

Extent of Lymphadenectomy in Early Stage Cervical Cancer

IA2, IB1, Non Bulky IIA (≤4cm)

Complete pelvic lymphadenectomy from mid common iliac artery proximally to the deep circumflex iliac vein distally,is indicated at the time of radical hysterectomy for these group of patients. High Risk patients should receive adjuvant chemoradiotherapy. An SWOG trial showed an overall (81% vs 71%) and Progression free survival (80% vs 60%) benefit for patients receiving Pelvic RT +CDDP+5FU versus those receiving Pelvic RT alone. These patients either had pelvic node metastasis, positive surgical margins or parametrial invasion.

As shown in the table above, about 7-10% of these patients will harbor occult metastasis in the para-aortic nodes. In a study by Sakuragi et al, multiple pelvic lymph nodal metastasis and common iliac nodal metastasis were independent risk factors for para-aortic lymph node metastasis. In a trial conducted by the RTOG, high risk cervical cancer patients (IB/IIA>4cm) were randomly assigned to receive pelvic RT alone vs Pelvic and Para-Aortic RT before brachytherapy. There was a statistically significant absolute survival benefit (67% vs 55%) for patients receiving extended field RT. There was no consistent method used to evaluate the para-aortic nodes. Morris et al published the results of an RCT of pelvic RT +5FU +CDDP vs Pelvic and Para-Aortic RT in high risk cervical cancer patients (IIB –IVA, IB,IIA with tumor >5cm or Pelvic node positive). Patients with Para-aortic lymph nodes involvement were excluded on basis of lymphangiogram or surgical staging. The estimated 5yr overall survival was 73% in chemoRT arm vs 58% in RT alone arm (p=0.004).

PreTreatment Surgical Staging in Locally Advanced Cervical Cancer

Although the FIGO staging system does not account for pelvic and para aortic lymph node involvement into the staging criteria, both FIGO and NCCN encourage using imaging methods

to define cancer extent to facilitate treatment planning in individual patients. CT and MRI have been investigated by GOG and ACR Imaging Network and found to be suboptimal in evaluating depth of cervical stromal invasion, parametrial invasion or lymph node metastasis. The role of PET has been evaluated in several studies and found to be useful in primary lymph node staging in locally advanced cervical cancer but it's role in early stage cancer with small tumor volume and CT/MRI defined node negative patients is limited.

In a GOG retrospective study of pooled patients who participated in one of three phase III trials, patients who were histologically confirmed to be paraaortic lymph nodes (PALN) negative had significantly better prognosis when compared with patients defined as PALN negative based on radiologic imaging.

As of date the only RCT comparing pretreatment surgical staging versus imaging for Stage IIB to IVA, cervical cancer showed a poorer outcome in the surgical arm. It has been shown in several studies that extraperitoneal lymph node dissection carries less risk of complications than the transperitoneal route. Recent studies have confirmed the safety and efficiency of laparoscopic staging also. In a study by Cosin et al, 266 patients with cervical cancer underwent staging extraperitoneal pelvic lymph node (PLN)+PALN lymphadenectomy prior to RT and node positive patients received extended fields of RT. Patients who underwent resection of nodes with gross metastases or microscopic metastases had equivalent survival, while patients who had unresectable nodes had a poor survival. Hacker et al also reported in a study the benefit of resecting bulky positive lymph node metastasis prior to radiotherapy.

In conclusion, while surgical staging is an integral part of radical hysterectomy performed for early stage cervical cancer, the benefits of routine pre-treatment surgical staging for patients with locally advanced cervical cancer scheduled to receive chemoradiotherapy remains controversial and needs to be addressed by further phase III studies. However, retrospective studies show that patients with bulky positive lymph node metastasis have a survival equivalent to those with microscopic metastases, if these bulky nodes are completely resected prior to RT.

Endometrial Cancer

Seventy five percent of patients with endometrial cancer are diagnosed with Stage I disease. About 10% of these women harbor pelvic lymph node metastases. While 20% of women with deep myometrial invasion and/or poorly differentiated tumors develop PLN, only 5% with superficial myometrial invasion and well differentiated tumors have PLN metastases. Kitchener et al published the results of an RCT comparing standard surgery (TAH + BSO + peritoneal washing for cytology + palpation of PALN) vs standard surgery + pelvic lymphadenectomy for patients pre-operatively thought to have disease confined to the uterus. This study did not find any evidence of disease free or overall survival benefit for the lymphadenectomy group. Panici et al reported the results of an RCT comparing systematic pelvic lymphadenectomy versus no lymphadenectomy for patients with Stage I endometrial cancer. They did not find any overall survival or disease free survival benefit for patients in the lymphadenectomy arm. A Cochrane meta-analysis published in January 2010 recommended against routine systematic pelvic lymphadenectomy in Stage I patients with endometrial cancer. Todo et al reported results of a retrospective study of pelvic + para-aortic lymphadenectomy vs Pelvic lymphadenectomy alone in endometrial cancer patients with intermediate or high risk of recurrence. In this study, the authors found a statistically significant improved overall survival in intermediate/high risk patients who underwent PALN+PLN vs PLN lymphadenectomy.

In conclusion, it is clear that PLN lymphadenectomy provides no benefit in low risk stage I endometrial cancer patients (who constitute the majority), while further phase III data are needed to address the issue of PALN +PLN lymphadenectomy in High risk patients.

Ovarian Cancer

FIGO has indicated that PLN +PALN sampling is an integral part of ovarian cancer surgery. In a RCT of systematic PLN+PALN vs random removal of nodes in ovarian cancer confined to the pelvis (Stage I and II), 22% were upstaged to Stage IIIc in the systematic lymphadenectomy group vs 9% in the sampling group. Systematic lymphadenectomy was associated with an improvement in progression free and overall survival but it was not statistically significant. The trial was not adequately powered to detect a survival difference. Panici et al reported an RCT of systematic PLN+PALN vs resection of bulky nodes alone in patients with Stage III/IV ovarian cancer who were optimally cytoreduced (<1cm). The addition of systematic lymphadenectomy prolonged progression free survival but did not have any benefit on overall survival probably because of the dilution effect of effective platinum based 1st line /2nd line chemotherapy. The incidence of PLN,PALN and both PLN+PALN were, 13%,17% and 35 % respectively.

In conclusion, systematic lymphadenectomy in early ovarian cancer provides accurate staging information and helps avoid unnecessary postop chemotherapy. The therapeutic role is still debatable. In advanced ovarian cancer, systematic lymphadenectomy improves progression free survival but does not improve overall survival. However, there is no doubt that gross nodes have to be resected in order to achieve optimal cytoreduction, in all stages.

Vulvar Cancer

Risk of lymph node metastasis increases with increasing stage. Patients with tumors <2cm with <1mm stromal (IA) invasion are the only patients for whom a wide excision is satisfactory treatment.

For patients with IB and II patients without suspicious groin nodes, an RCT by the GOG showed that groin dissection with or without postop RT was superior to groin irradiation alone in respect to progression free and overall survival. Ipsilateral groin dissection is indicated in patients with lateral tumors while patients with midline tumors should receive bilateral groin dissection.

For patients with two or more positive nodes following groin dissection, adjuvant pelvic and groin RT is superior to pelvic lymphadenectomy alone, according to a GOG study. Berek and Hacker have shown node size >10mm is a predictor of poorer outcome. Similarly extracapsular spread is associated with a poorer outcome. The current recommendation is that patients with $\geq$ 3 micrometastasis in the groin, node size >10mm, extracapsular spread or bilateral microscopic spread should receive adjuvant pelvic and groin RT.

Intraperitoneal Chemotherapy for Treatment of Ovarian Cancer

(Dr. D. Biswajit, Assistant Professor, Dept. of Medical Oncology, JIPMER)

Introduction

The most common route of ovarian cancer spread is within the peritoneal cavity. The benefit of administering chemotherapy directly into the peritoneal cavity is supported by preclinical and pharmacokinetic data. Compared to intravenous (IV) treatment, intraperitoneal (IP) administration permits a several-fold increase in drug concentration to be achieved within the abdominal cavity. There is now a growing body of evidence showing a survival advantage for IP cisplatin as compared to IV administration of platinum along with intravenous taxane-based chemotherapy in women with optimally cytoreduced (to <1.0 cm) stage III epithelial ovarian cancer. The publication of results from the most recent of these trials, Gynecologic Oncology Group (GOG) trial 172, led the US National Cancer Institute to issue a Clinical Alert in January of 2006, strongly encouraging the use of IP chemotherapy in this subset of patients. However, while the use of IP chemotherapy is gaining acceptance, it is not universal, largely due to the greater toxicity associated with this approach.

Importance of Initial Surgical Cytoreduction

Despite the regional advantage of IP chemotherapy, penetration into tumor tissue is limited to a few millimeters of tumor on the peritoneal surface layers and these approaches are best suited to patients with minimal residual disease after surgical cytoreduction.

Indications and Contraindications

IP chemotherapy is indicated for women with optimally debulked (to ≤ 1.0 cm) stage III epithelial ovarian cancer. The benefit of IP chemotherapy is uncertain in the setting of early stage disease, stage IV disease, and in patients who have residual tumor greater than 1 cm in diameter.

Contraindications to IP port placement include patients at poor surgical risk, active peritonitis or sepsis, and the presence of extensive intraabdominal adhesions, which prevent adequate distribution of instilled chemotherapeutic agents.

IP Catheter and Port — The drug delivery device, Bardport venous access catheter, as an example, should be a fully implantable port attached to a single lumen venous silicone catheter of large size (9.6 French [Fr]) so that it does not kink and obstruct flow (as shown in picture) [7] .

Timing — The IP access device can be placed at the time of initial laparotomy performed for diagnosis, staging, and cytoreduction, as long as a thorough discussion with the patient about the potential benefits and toxicities associated with this approach has taken place prior to surgery

Location — While there have been no studies comparing different IP chemotherapy port locations, the most commonly recommended site is two to three fingerbreadths above the right or left costal margin in the midclavicular line.

Procedure for chemotherapy administration — IP chemotherapy infusions have been given in the operating room or as early as 24 hours postoperatively. The fluid shifts which surround aggressive surgical debulking make renal toxicity a major concern. During GOG 172, the average delay of chemotherapy from date of surgery was 21 days [2].

Although there is controversy regarding the optimal regimen for IP therapy, most experts recommend the regimen utilized on the experimental arm of GOG 172 [2]. This consists of six 21-day courses of intravenous paclitaxel (135 mg/m2 over 24 hours on day 1) with IP cisplatin (100 mg/m2 in two liters of warmed normal saline) on day 2 and IP paclitaxel (60 mg/m2) on day 8 [2]

Complications

Patients undergoing IP chemotherapy should be regularly assessed for abdominal pain, catheter-related problems, signs of infection, neurotoxicity, renal toxicity, and myelosuppression. We do not routinely administer growth factor support during the first cycle.

In general, there are three main categories of complications for which IP chemotherapy is discontinued prematurely: abdominal pain with infusions; intolerance to the higher dose cisplatin; and problems related to the access device.

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Neoadjuvant Chemotherapy in Epithelial Ovarian Cancer

(Dr.Ankit Jain, Assistant Professor, Dept. of Medical Oncology, JIPMER)

Ovarian cancer is the leading cause of death from gynecologic cancers in the women both in developing world and western countries. It is estimated that in 2008, 21,650 US women developed ovarian cancer and 15,520 women died of the disease. Approximate 80% of patient with ovarian cancer will present in advanced stages (III or IV) with disease in the upper abdomen and/or outside the abdomen. In most of the Indian registries the incidence of ovarian cancer is on rise. Surgery plays a role at several different time points in the disease course. Most patients are candidates to proceed directly to surgical exploration with planned cytoreductive surgeries at the time ovarian cancer is suspected. The decision to proceed directly to surgery is ultimately a clinical one, particularly in the settings of advanced disease and is based on several factors including distribution of the disease, performance status (PS) and the patient's nutritional state.

If the patient is not a candidate for upfront surgery, or if optimal cytoreduction cannot be achieved, interval surgery (interval cytoreduction) after neoadjuvant chemotherapy (NACT) is a reasonable approach. NACT is a optimum approach in our country as most of the patients present at an advanced stage with poor PS and suboptimal nutritional status.

The advantages of NACT are:

1. Helps in achieving optimal cytoreduction.
2. Less perioperative blood loss.
3. Decreases intensive care unit stay.
4. Less operative time.
5. Improves quality of life (QOL).
6. Decreases morbidities of major surgical resections.

Therefore if patient is not an ideal candidate for upfront optimal cytoreduction, NACT is a reasonable choice. Presently the optimal regimen for NACT in management of advanced ovarian cancer is a combination of paclitaxel and carboplatin. Most promising in support of the equivalency and possible advantages of neoadjuvant chemotherapy is a preliminary report from the European Organization for Research and Treatment of Cancer (EORTC). In this trial, 700 patients with stage IIIC/IV disease were randomly assigned to either initial debulking surgery followed by six cycles of platinum-based chemotherapy or interval debulking surgery preceded and followed by three cycles of platinum-based chemotherapy. With a median follow-up of 4.8 years, median progression-free survival and overall survival were similar for both treatment groups (12 and 30 months, respectively). However, a reduction in complications was seen with the interval debulking surgery as compared to initial surgery group, including a significant reduction in postoperative deaths (2.7 versus 6 percent), grade 3/4 postoperative fever (2 versus 8 percent), grade 3/4 hemorrhage (1 versus 7 percent), and blood clots (0.3 versus 2.4 percent). Despite these findings, multivariate analysis suggested that obtaining optimal debulking surgery regardless of approach was the strongest independent prognostic factor for overall survival.

The recent Cochrane data published in 2009 analyzed all the randomized trials published from Jan 1966 to June 2008 and it concludes that there is no benefits in terms of DFS and OS with Interval cytoreduction but it is an optimum approach if upfront optimal cytoreduction cannot be achieved or initial surgery has been done by less experienced gynecologist.

The timing of interval cytoreduction is not standardized and patient requires a combined evaluation by a medical oncologist and gynec-oncologist after each cycle for both response and treatment related toxicities. Usually 3-4 cycles are required to achieve adequate response prior to interval cytoreduction. More number of cycles should be avoided prior to surgery as this approach increases the number of drug resistance clones.

Suggested Further Readings:

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2. Kang S et al. Does neo-adjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. Annals of Surgical Oncology 2009;16: 2315-2320.

Research Areas in Management of Carcinoma Cervix

(Dr. Pooja Sethi, Senior Resident, Dept. of Radiation Oncology, RCC, JIPMER)

Cervical cancer is the most common cause of cancer related death in women in India. This article reviews some topical areas that are currently under investigation in the treatment of cervical cancer world wide. These include radiosensitizers, technical radiotherapy techniques and biological therapies.

Chemotherapy

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy prior to the use of radical radiotherapy has not been shown to increase overall or disease free survival. The benefit of neoadjuvant chemotherapy prior to surgery is equivocal. Some studies have shown an increased overall survival and others a response rate of 52% but no associated improvement in the surgical pathological findings. However, confounding factors in such studies include the non-randomized use of post-operative radiotherapy. Neoadjuvant chemotherapy is currently not recommended. The EORTC 55994 trial is comparing platinum based neoadjuvant chemotherapy followed by surgery with concomitant chemo-radiotherapy in patients with FIGO IB2, IIA or IIB cervical cancer. NCRI clinical studies group is investigating the use of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer.

Chemotherapy - Concomitant and metastatic settings

Concomitant chemoradiation with single agent platinum has been the standard of care for locally advanced cervical cancer. The addition of chemotherapy provides a 6% overall survival benefit and an 8% increase in 5 year disease free survival. Doublet regimes have been investigated in the treatment of metastatic and recurrent cervical carcinoma. Platinum in combination with paclitaxel, gemcitabine or topotecan has provided the best results. Combination chemotherapy regimens although yet to show an increase in overall survival in comparison with single agent platinum, have shown an increase in progression free survival and response rates. In view of this, platinum and paclitaxel is the current standard regimen for palliative systemic therapy.

New Approaches in Radiotherapy

Image Guided Brachytherapy (IGBT)

Use of intracavitary brachytherapy after external beam radiotherapy enables administration of high and localized radiation dose delivery to the cervix, avoiding organs at risk (OAR) e.g. bowel, bladder and rectum. Inaccurate positioning of applicators may lead to potential overdose to critical organs resulting in long-term complications. With the advent of High Dose Rate brachytherapy, artefact-free CT and MRI compatible applicators and the accessibility of modern imaging techniques, 3D dose prescription is now becoming a possibility.

The benefits of IGBT lie in:

1) Verification of accurate applicator positioning;
2) Accurate definition of normal tissue dosimetry;
3) Conformal dose distribution to tumor volume and OAR;
4) The potential for dose escalation.

Intensity Modulated Radiotherapy (IMRT)

IMRT allows an external beam radiotherapy dose distribution to conform very precisely to the treatment volume. Sparing normal tissues should reduce long-term morbidity. Interfractional assessment of organ motion during treatment delivery is required. As it does the opportunities for dose escalation, particularly areas of nodal disease are likely to be investigated.

Novel Agents

Agents targeting hypoxia

Agents that are activated in a hypoxic environment may target tumor cells. Tirapazamine, a benzotriazine di-N-oxide, is metabolized to free radicals in a hypoxic environment. Free radicals cause DNA double and single stranded breaks leading to cell death. A Phase 3 randomized trial of chemoradiation versus chemoradiation with tirapazamine in stage IB2, IIA, IIB, IIIB, and IVA cervical carcinoma limited to the pelvis is currently being undertaken (GOG 219). Hypoxic cell sensitizers are not currently in routine use.

Epidermal Growth Factor Receptor (EGFR) Inhibitors

High expression of EGFR is one of the main mechanisms by which EGFR signalling is increased in cancer cells. There are two different ways of pharmacologically targeting EGFR: anti-EGFR monoclonal antibodies and tyrosine kinase inhibitors (TKI). Phase 2 results for TKI (Gefitinib and Erlotinib), have been ineffective in recurrent cervical cancer. Preclinical studies of cetuximab, a monoclonal antibody to EGFR, produced significant inhibition in all EGFR-positive cervical cancer cell lines tested (range 37%-58%). The efficacy of single-agent cetuximab in patients with persistent or recurrent cervical cancer is being investigation.

Anti-angiogenesis

The over expression of Vascular endothelial growth factor (VEGF) is associated with poor prognosis. Bevacizumab is a humanized monoclonal antibody that recognizes and blocks VEGF. Bevacizumab in combination with 5FU showed complete or partial response in 34% of the heavily pretreated refractory cervix cancer patients. GOG 240 study is currently recruiting into a phase 3 trial of recurrent, stage IVB or persistent carcinoma of the cervix comparing paclitaxel or topotecan with or without bevacizumab.

Radiation Proctitis: Nonsurgical Management

(Dr. Deepa M. Joseph, Senior Resident, Dept. of Radiation Oncology, RCC, JIPMER)

Introduction:

Pelvic radiotherapy is used in the treatment of a number of malignancies. Treatment outcome is determined not only by control of tumour but also by the incidence of late complications, which may develop in up to 10%, although published reports suggest that this rate may be an underestimate (Komaki1995; Tan1997). A major concern in the treatment of pelvic malignancy is the need to minimise the risk of chronic radiation injury without compromising the possibility of cure. Predisposing factors that may be associated with increased risk of late complications are co-morbid conditions, tumour stage, the radiation prescription, the volume treated, dose distribution, and concurrent therapies (Coia1995).

The term proctitis describes injury to the rectum, which is the site most commonly affected by pelvic radiation. Acute radiation proctitis refers to radition induced injury during radiation or occurring for a short period after radiation. Pathology is an inflammatory process affecting the rectal mucosa, which is by definition self limiting. The usual features are tenesmus, urgency, diarrhoea, and occasionally bleeding. The severity of acute injury is the strongest predictor of a person's predisposition to develop late injury. Late side effects might correlate with acute toxicity, but do not necessarily progress to late phase.

Chronic radiation proctitis can continue from acute injury, or begin after a variable latent period of at least 90 days (median time of eight to twelve months after completion of radiotherapy). The underlying pathology is of submucosal injury with a combination of fibrosis, ischaemia, and subsequent ulceration which can be localised, diffuse or full thickness penetrating the rectal wall. The clinical presentation may have an inflammatory component, producing tenesmus, urgency, diarrhoea or constipation, anal sphincter dysfunction, mucoid or bloody discharge per rectum or frank bleeding with ulceration which may perforate. The psychological impact may be devastating.

The prevalence of chronic radiation proctitis varies from between 5to10% and the severity may range from mild to severe or life threatening. The degree of irregularity of bowel dysfunction, rectal blood loss and pain may be scored according to criteria stated in a number of systems such as LENT-SOMA, RTOG, WHO and the Franco- Italian Glossary (Chassagne1993) where complications are assigned a grade. Severe complications are likely to be associated with persistent bleeding stricture and fistulae. Endoscopic scoring systems use proctoscopy, rigid sigmoidoscopy or flexible sigmoidoscopy. A spectrum of mucosal changes including pallor, erythema, prominent telangiectasia, friability and ulceration may be seen. Tissue biopsy may be inconclusive showing only an inflammatory picture and the diagnosis of late radiation proctitis may be based on the exclusion of coexisting disease and recurrent tumour.

The medical treatment of radiation proctitis is not clearly defined and in the absence of recommendations, management is often unsatisfactory. This is in part, due to difficulties in recognising and establishing the diagnosis and also because a proportion of the biological changes are not reversible. At present there is no 'best' treatment for this clinical scenario and the outcome of both medical and surgical management can be disappointing. Treatment options including low residue or elemental diets, pain control and replacement transfusion. Other therapies are reported to be of variable benefit in controlling symptoms, with the option of surgery if medical management fails or is inappropriate.

Non-surgical treatment options :

- Aminosalicylic acid derivatives: anti-inflammatory agents in this group such as sulfasalazine and mesalazine have been reported to have a role in the management of this condition (Baum 1989). Another agent with anti-inflammatory properties has been WF10 (TCDO – tetrachlorodecaoxide formulated for IV delivery, Oxoferin, Immunokine, Macrokine) (Veerasarn 2006).
- Corticosteroids: steroids either given orally or as enemas are used for their anti-inflammatory properties in alleviating symptoms (Kochhar 1991).
- Sucralfate preparations: Oral and rectal administrations of sucralfate have been described as a method of preventing and controlling intractable post-radiation proctitis (Henriksson 1992; Kneebone 2005; Sasai 1998).
- Short chain fatty acid (SCFA) preparations: these are reported to be used in the form of enemas to optimise the method of delivery of nutrients direct to the colonocyte to accelerate tissue repair.
- Formalin application: reports of local applications or irrigation can reduce and stop bleeding from radiation induced telangiectasia or neovasculature (Roche 1996).
- Thermal coagulation therapy: including Argon laser and endoscopic coagulation therapy may be effective at controlling rectal outlet bleeding (Swaroop 1998).
- Analogues of the naturally occurring superoxide dismutase: inhibit the production of free radicals (the basis of radiation effect), have been used in the treatment of radiation cystitis for oedema and necrosis but also for the fibrotic component which reduces the capacity of the rectum to distend (Marberger 1981).
- HBO: first documented in 1986, can be effective because of its angiogenic effect, increasing vascular density and promoting healing of radiation damaged tissues due to a lack of oxygen (Woo 1997).

- Other agents that has been reported to contribute to the healing of late radiation injury by improving blood flow in compromised tissue is pentoxifylline, although whether there is evidence of this in proctitis will be evaluated (Dion 1990) and antioxidant therapy with vitamin A (Ehrenpreis 2005)

Extreme symptoms may not respond to medical management or are so severe that surgical intervention is the only feasible option. Most surgeons favour a diversion colostomy for a medically intractable proctitis. Others favour a more aggressive approach with resection of the inflamed rectal segment and the colo-anal pull-through anastomosis. Surgery, however, is not without considerable risk, as the tissues may fail to heal because of radiation related changes, and must be carefully considered.

Prevention

Because of complexity of treatment options, it is desirable that preventive measures should be always tried to reduce the incidence of radiation proctitis. The patient should be instructed to maintain a full bladder, which displaces the intestines out of pelvis. Using modern radiation treatment techniques can also avoid the unnecessary exposure of intestines. Appropriate packing to push the rectum and bladder away from the radioactive source also helps in reducing the incidence of radiation proctitis.

Implications for practice and research

If the management of late radiation proctitis is to become evidence based then good quality placebo-controlled studies need to be conducted to support the treatment options recommended. First, the true incidence of the disease is not clear. Therefore, physicians should be aware of this toxicity and elicit symptoms and evaluate the patient thoroughly. Secondly, there is an urgent need to define clearly the diagnostic criteria and a unified grading system by which late radiation proctitis can be categorised. Without such a system, randomized control trials in multicentric setting are difficult. Cases should be enrolled into regional or centralised registers of radiation toxicity. In this way terminology, baseline assessments including co morbidity and the documentation of therapeutic effect could be standardised. Interventions could be randomised and outcome data could be pooled to assess the response to treatment objectively. This approach would provide an evidence base of results of different treatments to develop an integrated care pathway for this difficult condition.

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Management of Radiation Cystitis

(Dr. M.Mangala devi, Senior Resident, Dept. of Radiation Oncology, RCC, JIPMER)

Introduction

Radiation is used with or without chemotherapy to treat malignancies in the pelvis that occur in gynecologic, genitourinary, and gastrointestinal organs. The cells of the urothelium are replenished by undifferentiated basal cells that divide so slowly that their mitotic index cannot be measured.

Acute sequelae during radiation commonly include frequency and dysuria. These symptoms typically occur following more than 20 Gy to the bladder with conventional fractionation. Following completion of radiation, resolution of symptoms is seen in 2–3 weeks.Late radiation complications affecting the bladder have a varied presentation and are affected by the type of tumour treated, its stage, other interventions such as surgery and chemotherapy, comorbid disease and of course technical factors such as the biologically effective dose, tissue tolerance and radiation hotspots in the treated volume.The tolerance doses (TD 5/5) for the whole bladder have been estimated to be 65 Gy. The tolerance increases to 80 Gy, if only two-thirds of the bladder is treated. Long-term sequelae include persistent dysuria, severe pain, contracted bladder, vesicovaginal fistula, and varying degrees of hematuria. Median onset of late complications after radiation is 13– 20 months.

Management

Patients with mild to moderate urinary frequency may be treated symptomatically. Phenazopyridine hydrochloride is frequently used to relieve these symptoms. It acts as an analgesic on the bladder mucosa. Oxybutynin chloride is an antispasmodic that relaxes the bladder smooth muscle and may relieve the symptoms of frequency and urgency. Pharmaceuticals used to increase bladder outlet resistance include ephedrine hydrochloride, pseudoephedrine hydrochloride, and phenylpropanolamine. Treatment for severe radiation cystitis may require hydration, treatment of infection, blood transfusion and bladder irrigation.

Intravesical agents:

- Alum irrigation: Alum works by protein precipitation when the bleeding is mild, alleviating capillary bleeding. In heavy bleeding the precipitant tends to clot in spite of three-way catheters for irrigation, leading to clot retention, distension and more bleeding .
- Formalin instillation: This is performed rarely but under general or regional anaesthesia after vesico-ureteric reflux has been excluded. Formalin is toxic even in very dilute 1% solution and a recognised adverse effect is that reflux may produce a bilateral pyonephrosis with fatal sepsis (Dewan 1993). Therefore use of this agent should

be restricted to the treatment of intractable haemorrhage when the bladder has been diverted to prevent the impact of reflux.

- Placental extract- not previously described in the literature, is known to have an effect on the epithelialisation of venous ulcers when applied topically, and because of its wound-healing properties has been reported in this setting. Growth factors and angiogenic factors have been isolated in the early placenta and for this reason are thought to relate to the healing effect on the mucosa.
- Silver nitrate
- Prostaglandins- have been shown to protect the gastric and jejunoileal mucosa against ulceration by potentially increasing the levels of cAMP and stimulating the active transport of sodium.They are postulated to work in the same way with vesical ulceration by reducing the oedema and inflammatory response.

Systemic Treatment:

- D-glucosamine is a precursor of glycosaminoglycans (GAG). Pentosan polysulphate is a semi-synthetic sulphated polysaccharide that serves as a synthetic GAG and is thought to adhere to the bladder surface supplementing the defective natural GAG layer (Parsons 1986).
- Oestrogens have been noted to have an effect in controlling haemorrhage in late radiation cystitis and it is postulated that this is related to stabilisation of vascular fragility.
- An agent called WF 10 (TCDO, Oxoferin, Immunokine, Macrokine) is a 1:10 dilution of tetrachlorodecaoxide formulated for intravenous delivery. It was developed by Oxo Chemie in Switzerland as an adjunctive therapy to combination antiretroviral and opportunistic infection prophylaxis regimens in AIDS patients. WF 10 specifically targets macrophages. WF 10 has received regulatory approval in Thailand for postradiation cystitis following a trial completed in 1998 in 20 patients who underwent radiation treatment for cervical carcinoma (Srisupundit 1999).
- Other agents include flavoxate which is an antimuscarinic agent used to treat urinary frequency; Newer anti-cholinergic agents include oxybutinin and terodiline, these agents increase bladder capacity by diminishing unstable contractions of the detrusor muscle.

Procedures and radiological interventions:

- Early cystoscopy with diathermy of the bleeding points
- Embolization of the hypogastric arteries
- Urinary diversion
- Cystectomy

Treatments which attempt to reverse the radiation changes

- Analogues of the naturally occurring superoxide dismutase, which inhibits free radical production
- Pentoxyfilline has been reported to contribute to the healing of late radiation injury by improving blood flow through compromised tissue
- Hyperbaric oxygen can be effective because of its angiogenic, increasing vascular density and healing of hypoxic radiation damaged tissues. This requires a number of daily treatments and is clearly not suitable for those who are actively bleeding.

Conclusion

The available follow-up studies performed with various treatment regimens demonstrate that, although all have some effectiveness, no single modality is superior. They also show the recurrent nature of radiation complications of the bladder.

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Role of Adjuvant Radiotherapy in Endometrial Cancer

(Dr. Muzamil Asif, Junior Resident, Dept. of Radiation Oncology, RCC, JIPMER)

Postoperative Radiotherapy is the major modality of adjuvant therapy in endometrial cancer apart from its curative role in medically inoperable patients and palliative role in patients with locoregionally advanced and metastatic endometrial cancer. This article mainly focuses on the role of radiotherapy in the adjuvant setting according to the older FIGO staging as NCCN guidelines have not been updated. Indications, techniques and current and future directions of radiation in this setting are described.

Endometrial Cancer is a complex disease with high cure rates in early stages if managed well. Many well designed studies have been conducted to risk stratify the patient groups and tailor treatment according to the risk group and establish optimum treatment guidelines. According to NCCN, the risk factors to be considered are as follows : High grade (i.e., grade 3 as compared to grade 1 or 2), Greater than 50% depth of myometrial invasion, Tumor extension beyond the uterine fundus (e.g., lower uterine segment, cervix, adnexa, or pelvis) , Involvement of lymphovascular spaces, Large tumor (>2 cm in diameter), and Age >60 yrs.

Low Risk - It includes endometrioid cancers that are confined to the uterus, grade 1 or 2 histology, and with invasion limited to the endometrium (stage IA) or less than one-half of the myometrium (stage IB)

Intermediate Risk – It includes grade 1 or 2 tumors that extend beyond one-half of the myometrium (stage IC), and any grade 3 tumor in which invasion is limited to the endometrium (stage IA) or less than one-half of the myometrium (stage IB).The presence of above mentioned risk factors in otherwise low-risk tumors, designate intermediate-risk rather than low-risk disease.

High Risk - Grade 3 cancers with invasion of more than one-half of the myometrium (stage IC, grade 3), Stage IIA or greater disease, regardless of grade, Papillary serous or clear cell uterine tumors.

Adjuvant Radiotherapy in endometrial cancer:
Stage IA grade 1 and 2 tumors and stage IB tumors without risk factors can be safely observed with adjuvant radiation being recommended in the form of vaginal Brachytherapy. All other Stage I tumors ie, Stage IA Grade 3, Stage IB Grade 3 and Stage I C require adjuvant RT.

Protocol for Stage I Endometrial Cancer

Stage	Risk Factors	Grade 1	Grade 2	Grade 3
Stage I A	Absent	Observe	Observe	Adjuvant RT
	Present	Observe	Observe	Adjuvant RT
Stage I B	Absent	Observe	Adjuvant RT	Adjuvant RT
	Present	Adjuvant RT	Adjuvant RT	Adjuvant RT
Stage I C	Absent	Adjuvant RT	Adjuvant RT	Adjuvant RT
	Present	Adjuvant RT	Adjuvant RT	Adjuvant RT +/- Chemotherapy

All Tumors of Stage II A and greater mandate adjuvant radiotherapy. An exception to this is Stage III A Endometrial Cancer which has been deemed as Stage III A solely on the basis of positive peritoneal washings and no other risk factor. In such patients, Grade 1 and 2 endometrial cancers may be safely observed without the need for adjuvant therapy, provided maximal surgery and complete surgical staging have been done.

Radiation for Endometrial Cancer has been shown definitively to decrease local recurrence rates and may be delivered via Brachytherapy, External Beam RT or a combination of the two. Vaginal Brachytherapy has the advantage of more conformal doses with reduced adverse effects and may be a viable option for early stage cancers where the primary site of recurrence is the vaginal vault. Vaginal Brachytherapy if given alone is delivered using the Linear Vaginal Cylinder Applicators. The Dose Schedules most widely used are 7 Gy x 3 Fractions or 6 Gy x 5 Fractions. When used as a boost after EBRT the dose is usually 5-6 Gy x 2 Fractions. External Beam Radiotherapy when employed must target Gross disease(if any), the external, internal and lower common iliacs, parametrium, upper vagina and presacral nodes. Extended fields when used include the whole common iliac chain and para-aortic nodes. The areas of microscopic disease are treated to a dose of 45 – 50 Gy.

The emerging developments in treatment of Endometrial Cancer have been attempts to replace RT with Chemotherapy in Early Stage Intermediate Risk Tumors as in the GOG 122 trial where Post operative Chemotherpay and RT were shown to be comparable. A closer analysis of the data reveals that even though eventual outcomes were comparable, the rate of local recurrence in the chemotherapy arm was around 35% which was much greater than the RT arm and the comparable outcome may have been a result of Salvage surgery.

In summary, Radiation has a firmly established and continuing role to play in the adjuvant treatment of Endometrial Cancer, other indications notwithstanding and should be a part of any well designed treatment plan for this disease.

Tumour Markers in Gynecological Cancers

(Dr. Aravind, Junior Resident, Dept. of Radiation Oncology, RCC, JIPMER)

Tumor markers are glycoproteins that are usually detected by monoclonal antibodies. Each tumor marker has a variable profile of usefulness for screening, determining diagnosis and prognosis, assessing response to therapy, and monitoring for cancer recurrence. important gynecologic tumor markers are discussed in this article.

Cancer Antigen 125

CA-125 is a mullerian differentiated antigen identified by a monoclonal antibody OC 125. It is expressed by 80% of nonmucinous ovarian tumours including serous, endometroid, & clear cell & undifferentiated ovarian tumours and is also useful as a marker for Endometriosis. It can also be positive in 0.2% of healthy blood donors and 1% of normal healthy women and 5% Benign gynaecological disorder like endometriosis & PID,25% of non gynaecological conditions like cancers of GI tract and breast cancer.High levels of CA-125 is detected also in advanced cases of Adenocarcinoma of cervix, endometrium & fallopian tube.The cut off level of CA-125 is 35 U/ml. A prolonged half-life for CA125, or a less than 7-fold decrease during the early months of treatment, has been shown to predict poor outcome.The most important application of CA125 is in the monitoring of patients with epithelial ovarian cancer. Serial CA125 levels can pre-clinically detect recurrent disease with lead times of 1-17 months (median 3-4 months).Furthermore, longitudinal monitoring with this marker has the potential to detect recurrent disease earlier and more cost-effectively than radiological procedures.

Beta human chorionic gonadotropin

Beta-hCG is expressed in human fetal tissue and cancer cells of various histologic types. In fetus it is selectively produced by syncytiotrophoblast, normal titre is 20 to 30 mIU /ml.Increased levels of beta-hCG occur in patients with choriocarcinoma of the uterus, embryonal carcinomas, polyembryomas, mixed cell tumors, and, less commonly, dysgerminomas.Beta hCG assay is useful for diagnosis, monitoring therapy, and follow-up to ensure that the patient remains in complete gonadotropin remission.Monitoring of the serial beta hCG levels is mandatory during therapy for GTTs to ensure adequate treatment. The 10 to 20% of patients with hydatidiform mole who are not cured by local therapy or do not achieve a spontaneous remission can be identified by a rising or plateaued beta hCG titer on serial determinations after evacuation of a mole. These patients may have persistent trophoblastic disease and therefore require additional therapy.

Alpha-fetoprotein

Alpha-fetoprotein (AFP) is a normal fetal serum protein synthesized by the liver, yolk sac, and gastrointestinal tract. AFP concentration in adult serum is less than 20 ng/Ml. AFP is expressed by most endodermal sinus tumors ovarian embryonal cell carcinoma, immature teratomas, and polyembryomas. Both AFP and beta-hCG play crucial roles in the management of patients with nonseminomatous germ cell tumors.In patients with extragonadal disease or metastasis at the time of diagnosis, highly elevated AFP or beta-hCG values can be used in place of biopsy to establish a diagnosis of nonseminomatous germ cell tumor. AFP values in excess of 10,000 ng/mL or beta-hCG levels above 50,000 mIU/mL at initial diagnosis portend a poor prognosis, with a 5-year survival rate of 50%.

Inhibin

Inhibin is a peptide hormone normally produced by ovarian granulosa cells. Granulosa-cell tumors produce inhibin and its serum levels reflect the the tumor burden. Measurement of inhibin can be used as a marker for primary disease and for tumor surveillance after treatment to assess for residual or recurrent disease.

Estradiol

Estradiol was one of the first markers identified in the serum of patients with granulosa cell tumors. In general, estradiol is not a sensitive marker for the presence of a granulosa cell tumor. Serum estradiol levels postoperatively may be useful for detecting recurrence of an estradiol-secreting tumor.

Human telomerase reverse transcriptase (hTERT)

Human telomerase reverse transcriptase (hTERT) is a novel and newly available biomarker for patients with ovarian and uterine cancers. The hTERT mRNA level has a significant correlation with CA-125 and with histological findings in ovarian cancer. hTERT could be used as an early diagnostic biomarker for cervical cancer in the future.

Müllerian inhibiting substance

Müllerian inhibiting substance (MIS) is produced by granulosa cells in the developing follicles. It has emerged as a potential tumor marker for granulosa cell tumors. The elevated MIS level is highly specific for ovarian granulosa cell tumors.

Carbohydrate antigen 19-9.

Serum carbohydrate antigen 19-9 levels are elevated in up to 35% of patients with endometrial cancer and can be used in a follow-up evaluation of patients with mucinous borderline ovarian tumors. Measurement of serum tumor markers in the follow-up care of these patients may lead to earlier detection of recurrence.

Squamous cell carcinoma antigen

It is a sub-fraction of the glycoprotein TA-4 which can be demonstrated by immunohistochemical methods. Raised levels are seen in SCC of Cervix, Vagina & Vulva,SCC of head, neck, lung, oesophagus and anal canal.

L1 (CAM)

According to Daponte et al, L1 (CAM) immunoreactivity correlates with stage and grade of ovarian cancer. It increases from benign tumors to early carcinomas and to advanced stage carcinomas progressively and significantly. L1 (CAM) expression represents a novel diagnostic marker in serous ovarian neoplasms that shows characteristics of tumor progression. L1 expression is associated with chemotherapy response.

Carcinoembryonic antigen
It is a glycoprotein of mol.wt 200kda. CEA levels are elevated in up to 35% of patients with endometrial cancer,Brenner, endometrioid, clear cell, and serous tumors.

Other markers
Placental Alkaline Phosphatase, normally produced by the placenta.Also expressed by Serous and Endometroid tumours of Ovary as well as by the germ cell tumour, Dysgerminoma.
CA 15-3 is a circulating breast cancer associated antigen identified by two distinct monoclonal antibodies. It is present in a variety of adenocarcinomas of breast, colon, lung, ovary, pancreas.

TATS is a peptide has been found in veins, serum, and cyst fluids of mucinous Ca. It compliments CA125 as clinical monitors for serous Ca. GAT is another peptide used to differentiate ovarian tumour from endometriosis with Ca125.

Conclusion
A large number of other tumour markers have also been found to be associated with gynecological malignancies.However most of them have low & variable specificity.The methods of their detection and estimation are difficult, costly and not widely available.To be of practical use, these problems associated with tumour markers need to be solved.

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Revised FIGO staging (2009) for Carcinoma of the Vulva, Cervix, and Endometrium

(International Journal of Gynecology and Obstetrics 105 (2009) 103–104)

FIGO was the first organization to develop its own classification and staging system in 1958 for female genital cancers. Subsequently, in 1966, the International Union Against Cancer (UICC) published its own staging system, followed by the American Joint Commission on Cancer (AJCC) in 1976. Since then, one of the aims of these 3 organizations has been to review any changes to the different staging systems, and to jointly agree upon them. Cancer of the vulva, cervix uteri, and corpus uteri, were revised in 1988, 1994, and 1988, respectively. Latest amendments for cancer of vulva, cervix and endometrium are published in 2009 (Table 1, 2 &3). Ovarian cancer staging has not been tackled yet.

Carcinoma of the vulva

Stage I - Tumor confined to the vulva
- IA-Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*, no nodal metastasis
- IB- Lesions >2 cm in size or with stromal invasion >1.0 mm*, confined to the vulva or perineum, with negative nodes

Stage II -Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes

Stage III -Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
- IIIA (i) With 1 lymph node metastasis (≥5 mm), or (ii) 1–2 lymph node metastasis(es) (<5 mm)
- IIIB (i) With 2 or more lymph node metastases (≥5 mm), or (ii) 3 or more lymph node metastases (<5 mm)
- IIIC With positive nodes with extracapsular spread

Stage IV-Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
- IVA -Tumor invades any of the following:
  - (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or
  - (ii) fixed or ulcerated inguino-femoral lymph nodes
- IVB - Any distant metastasis including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumor from the epithelialstromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Carcinoma of the cervix uteri

Stage I - The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

IA- Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm

- IA1 Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
- IA2 Measured stromal invasion of ≥3.0 mm and not ≥5.0 mm with an extension of not ≥7.0 mm

IB - Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*

- IB1 Clinically visible lesion ≤4.0 cm in greatest dimension
- IB2 Clinically visible lesion >4.0 cm in greatest dimension

Stage II - Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

IIA - Without parametrial invasion

- IIA1 Clinically visible lesion ≤4.0 cm in greatest dimension
- IIA2 Clinically visible lesion >4 cm in greatest dimension

IIB - With obvious parametrial invasion

Stage III - The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**

IIIA - Tumor involves lower third of the vagina, with no extension to the pelvicwall

IIIB - Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

Stage IV- The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV

IVA - Spread of the growth to adjacent organs

IVB - Spread to distant organs

*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Carcinoma of the Endometrium*

Stage I - Tumor confined to the corpus uteri

IA - No or less than half myometrial invasion

IB - Invasion equal to or more than half of the myometrium

Stage II - Tumor invades cervical stroma, but does not extend beyond the uterus**

Stage III - Local and/or regional spread of the tumor

IIIA - Tumor invades the serosa of the corpus uteri and/or adnexae#

IIIB -Vaginal and/or parametrial involvement#

IIIC - Metastases to pelvic and/or para-aortic lymph nodes#

- IIIC1- Positive pelvic nodes
- IIIC2- Positive para-aortic lymph nodes with or without positive pelvic lymph nodes

Stage IV - Tumor invades bladder and/or bowel mucosa, and/or distant metastases

IVA - Tumor invasion of bladder and/or bowel mucosa

IVB - Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

*Either G1, G2, or G3.

** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

Positive cytology has to be reported separately without changing the stage.

ACOG - Revised Cervical Cancer Screening Guidelines

Obstet Gynecol. November 20, 2009

Newly revised evidence-based guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) - Recommends Less Frequent Screening

Specific ACOG recommendations in the updated guidelines, based on good and consistent scientific evidence **(level A),** are as follows:

- Cervical cancer screening should begin at age 21 years and should be avoided at younger ages, when it may result in unnecessary and harmful workup and treatment in women who are at very low risk for cancer.
- For women aged 21 to 29 years, cervical cytology screening is recommended every 2 years.
- The interval between cervical cytology examinations may be extended to every 3 years for women at least aged 30 years who have had 3 consecutive negative cervical cytology screening test results and who have no history of CIN 2 or CIN 3, HIV infection, immunocompromised state, or DES exposure in utero.
- Acceptable screening techniques are liquid-based and conventional cervical cytology methods.
- Routine cytology testing should be discontinued in women who have had a total hysterectomy for benign conditions and who have no history of high-grade CIN.
- For women older than 30 years, an appropriate screening test is cytology combined with HPV DNA testing. When both these test results are negative in a low-risk woman 30 years or older, rescreening should be performed no sooner than 3 years later.

Specific ACOG recommendations in the updated guidelines, based on limited and inconsistent scientific evidence **(level B),** are as follows:

- Sexually active women younger than 21 years should be counselled and tested for sexually transmitted infections and should be counselled regarding safe sex and contraception. Cervical cytology testing is not necessary, and speculum examination need not be performed in asymptomatic women.
- Cervical cancer screening can be discontinued between the ages of 65 and 70 years in women who have 3 or more consecutive negative cytology test results and no abnormal test results in the past 10 years because cervical cancer develops slowly, and risk factors decrease with age.
- Women previously treated for CIN 2, CIN 3, or cancer remains at risk for persistent or recurrent disease for at least 20 years after treatment and after initial posttreatment surveillance. This group should therefore continue to be screened annually for at least 20 years.
- Even after the period of posttreatment surveillance, screening should continue for women status post hysterectomy with removal of the cervix who have a history of CIN 2 or CIN 3, or in whom a negative history cannot be documented. In this patient group, there are no good data to support or refute discontinuing screening.

Revised ACOG recommendations, based primarily on consensus and expert opinion **(level C),** are as follows:

- Physicians should inform their patients that annual gynecologic examinations may still be appropriate regardless of the frequency of cervical cytology screening, even if cervical screening is not performed at each visit.
- Women who were vaccinated against HPV-16 and HPV-18 should follow the same screening guidelines as nonvaccinated women.

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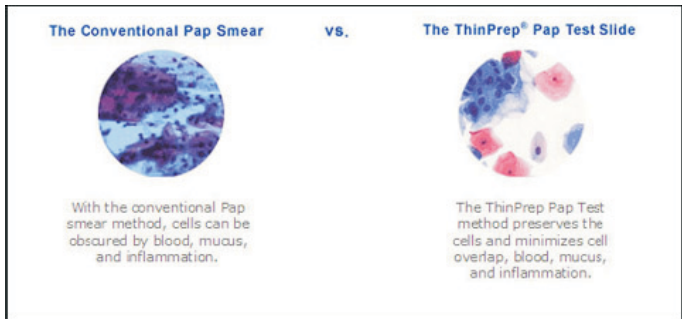
Editors' Picks

HPV Vaccine: Latest Adverse Event Data
Zosia Chustecka
The latest data on adverse events with Gardasil, published in the same issue of the journal, comes from the US Vaccine Adverse Event Reporting System (VAERS). In total, 12,424 adverse events after immunization were reported to in United States between June 2006 and December 2008, during which an estimated 23 million doses had been distributed (with a course of 3 doses per person recommended). This represents a reporting rate of 53.9 reports per 100,000 doses distributed. Of these, 772 reports (6.2% of the total) were described as serious, including 32 reports of death. The authors, headed by Barbara Slade, MD, from the CDC, comment that most of the rates of adverse events after immunization were "not greater than the background rates compared with other vaccines," with the exception of syncope and venous thromboembolic events, which were higher for the HPV vaccine. Other adverse events included local site reactions (reporting rate, 7.5 cases per 100,000 doses distributed), headache (4.1 cases per 100,000 doses distributed), hypersensitivity reactions (3.1 cases per 100,000 doses distributed), urticaria (2.6 cases per 100,000 doses distributed), autoimmune reactions (0.2 cases per 100,000 doses distributed), Guillain-Barré syndrome (0.2 cases per 100,000 doses distributed), anaphylaxis (0.1 cases per 100,000 doses distributed), death (0.1 cases per 100,000 doses distributed), transverse myelitis (0.04 cases per 100,000 doses distributed), pancreatitis (0.04 cases per 100,000 doses distributed), and motor neuron disease (0.009).

Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks.
J Clin Oncol. 2010; 28(2):240-4
Oktay K; Kim JY; Barad D; Babayev SN
Researchers found a significantly increased risk for poor response to ovarian stimulation by using letrozole and gonadotropins for fertility in women who were *BRCA1*-positive, compared with those who were *BRCA1*-negative. Since *BRCA1* is a DNA repair gene and oocytes may not survive if that mechanism is deficient. *BRCA1*-positive women also tended to have lower oocyte numbers. *BRCA1* gene mutations appear to be associated with early depletion of oocyte reserve, supporting the link between breast and ovarian cancer risk and infertility.

Liquid based Pap testing
Since its introduction over 50 years ago, the Pap test has been the single, greatest contributor to the decline in cervical cancer. Liquid-based Pap tests have been shown to improve the detection of cervical cell abnormalities compared to conventional pap testing. Instead of "smearing" the cells onto a slide, the collected cells are placed in a vial of preservative solution. With the conventional Pap smear method, cells can be obscured by blood, mucus, and inflammation. Liquid-based Pap test method preserves the cells and minimizes cell overlap, blood, mucus, and inflammation.



In addition to improved detection of abnormalities, a benefit of Liquid-based Pap tests is the ability to do additional testing. The Thin Prep® Pap test is the only Liquid-based Pap test that has FDA approval to do testing for HPV, Chlamydia and Gonorrhea on the cells collected in the vial.

FDA Approves Blood Test that Helps Detect Ovarian Cancer
Yael Waknine
September 14, 2009 - The US Food and Drug Administration (FDA) has approved a novel blood test (*OVA1*, Vermillion Inc and Quest Diagnostics) to help detect ovarian cancer in adult women with pelvic masses that are known to need surgery.The test consolidates immunoassay results for 5 proteins known to change with ovarian cancer, rating the likelihood of malignancy on a scale of 1 to 10. OVA1 is the first FDA-cleared laboratory test that can indicate the likelihood of ovarian cancer with high sensitivity prior to biopsy or exploratory surgery, even if radiological test results fail to indicate malignancy. Identifying potentially malignant cases before surgery allows involvement of a gynecologic oncologist, which can improve patient outcome. OVA1 should only be used to compliment other diagnostic and clinical procedures; the test is not indicated for screening purposes or to achieve a definite diagnosis of ovarian cancer.

Sore Lips, a Cinderella Adverse Effect of Chemotherapy
Zosia Chustecka
September 22, 2009 (Berlin, Germany)
At the 15th Congress of the European Cancer Organization and the 34th European Society for Medical Oncology Multidisciplinary Congress, show that 69% of patients reported having chapped, sore lips after chemotherapy. Chemotherapy can damage the rapidly dividing basal cells in the vermilion border of the lips, causing dryness, cracking, soreness, bleeding, infections that are fungal in origin, and cold sores from herpes simplex. Anecdotal reports from patients suggest that using a lip balm containing natural products is helpful, but using one containing petrochemicals is not, A lip cream "nature medical," containing bee's wax, shea butter, and organic oil, is now being tested in a randomized trial against a product containing petrochemicals in 200 patients on chemotherapy, who are being monitored for the incidence of chapped lips and cold sores.

7 Clues to Ovarian Cancer
Kathleen Doheny
August 27, 2009 — "Ovarian cancer is not silent, it's noisy,"
Seven symptoms often reported to doctors are associated with

ovarian cancer, according to a study by Hamilton and his colleagues from the U.K., dispelling the idea that the deadly cancer is a "silent killer" with few clues until the advanced stages. Seven symptoms were found associated with ovarian cancer, including: Abdominal distension, Urinary frequency, Abdominal pain, Postmenopausal bleeding, Loss of appetite, Rectal bleeding, Abdominal bloating. Researchers found that three of the ovarian cancer symptoms - abdominal pain, abdominal distension, and urinary frequency -- were reported at least six months before the diagnosis and were significantly associated with ovarian cancer.

HPV Vaccine Remains Highly Protective for as Long as 6.4 Years

Bruce Soloway

In 2001, manufacturer-supported researchers randomized more than 1100 women (age range, 15–25) who were previously uninfected with HPV 16 or 18 to receive three doses of a bivalent HPV-16/18 vaccine or placebo. The investigators reported on extended follow-up of a subset of 776 of these women. After as long as 6.4 years of follow-up, vaccine efficacy was 95% for preventing incident HPV-16/18 infection, 100% for preventing persistent HPV-16/18 infection, 97% for preventing any HPV-16/18–related cervical cytopathology, and 100% for preventing HPV-16/18–related cervical intraepithelial neoplasia (CIN). Total IgG antibodies against HPV-16/18 peaked at 7 months, plateaued at 18 to 24 months, and remained stable thereafter.

Intensity-Modulated Radiotherapy Promising for Cervical Cancer

Clinical Outcomes of Definitive Intensity-Modulated Radiation Therapy with Fluorodeoxyglucose Positron Emission Tomography Simulation in Patients with Locally Advanced Cervical Cancer.

Int J Radiat Oncol Biol Phys. 2009

Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutic S, Mutch DG, Powell MA, Grigsby PW

PURPOSE: This study aimed to evaluate the toxicity and clinical outcomes for cervical cancer patients treated definitively with intensity-modulated radiation therapy (IMRT) compared with non-IMRT treatment. METHODS AND MATERIALS: This prospective cohort study included 452 patients with newly diagnosed cervical cancer treated with curative intent (135 IMRT and 317 non-IMRT). Treatment involved external irradiation and brachytherapy, and 85% of patients received concurrent chemotherapy. All IMRT patients underwent an F-18 fluorodeoxyglucose positron emission tomography (FDG-PET/CT) simulation. A 3-month post-therapy PET was obtained to evaluate treatment response. Toxicity was scored by the Common Terminology Criteria for Adverse Events Version 3.0. RESULTS: The IMRT and non-IMRT groups had similar stage distribution and histology. For all patients, the post-therapy FDG-PET response correlated with overall recurrence risk ($p < 0.0001$) and cause-specific survival ($p < 0.0001$). Post-treatment FDG-PET findings were not significantly different between the IMRT and non-IMRT patients ($p = 0.9774$). The mean follow-up for all patients alive at the time of last follow-up was 52 months (72 months non-IMRT, 22 months IMRT). At last follow-up, 178 patients (39 IMRT, 139 non-IMRT) had developed a recurrence. The difference in recurrence-free survival between the two groups did not reach statistical significance ($p = 0.0738$), although the IMRT group showed better overall and cause-specific survivals ($p < 0.0001$). Of the patients, 62 patients (8 IMRT and 54 non-IMRT) developed Grade 3 or greater bowel or bladder complications, and by cumulative hazard function analysis the risk was significantly less for patients treated with IMRT ($p = 0.0351$). CONCLUSION: Cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy.

EGFR Expression Predicts Poor Treatment Response with Cervical Cancer

Clin Cancer Res 2009

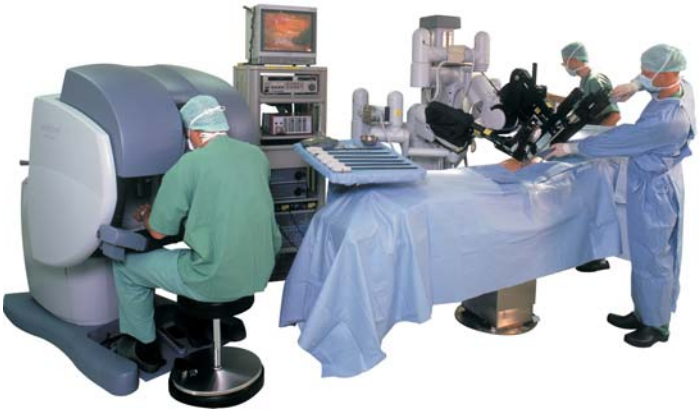
Dr. van der Zee and colleagues measured protein expression of EGFR, activated (phosphorylated) EGFR, PTEN, pAKT, and pERK in relation to response to chemoradiation and survival in 375 women with cervical cancer. Positive staining of tumors for EGFR and activated EGFR was independently related to poor response to chemoradiation. whereas positive staining for PTEN, pAKT, and pERK showed no significant association with treatment response. Five-year disease-specific survival and overall survival rates were lower in EGFR-positive patients (53% and 47%, respectively) than in EGFR-negative patients (63% and 55%, respectively).Three clinical trials are investigating the role of EGFR inhibitors in addition to the standard treatment in locally advanced stage cervical cancer, in which cetuximab, a chimeric human mouse anti-EGFR monoclonal antibody, is added to standard chemoradiation. These trials are phase I and II studies, focusing on tolerability and safety of cetuximab in combination with radiotherapy and cisplatin.

The Use of Minimally Invasive Surgery for Endometrial Cancer: The Role of Robotic Surgery in Gynecology Oncology

Cancer Control. 2009

Marcia M. Humphrey, Sachin M. Apte

The application of minimally invasive surgical techniques, in selected women with endometrial cancer is a safe and effective alternative to laparotomy and appears to provide equivalent disease-free and overall survival rates. Patient benefit is demonstrated by faster recovery, decreased pain, and improved quality of life.Limitations of standard laparoscopy include two-dimensional view, limited instrument dexterity, tremor amplification, and poor ergonomics. The current platform utilizes the da Vinci surgical system (Intuitive Surgical, Sunnyvale, California). This system was approved by the US Food and Drug Administration for gynecologic procedures in 2005. Using this platform, the surgeon is seated a few feet away from the patient with a console controlled by the surgeon's hands and feet. The camera provides a three-dimensional view with up to 10 times magnification. The robotic arms and instruments together provide seven degrees of freedom, replicating that of the surgeon's hand. The role of robotics in the minimally invasive approach to endometrial cancer has yet to be determined definitively and continues to evolve. Prospective studies that compare standard laparoscopy and robotic-assisted laparoscopy are needed to help characterize any benefits offered by this innovative technology. However, with the use of robotics, there is a loss of tactile sense that provides important feedback. The da Vinci Surgical System is bulky, interferes with vaginal access, and could potentially increase operating time with assembly of the equipment. As mature data from GOG LAP2 become available, the feasibility and outcomes will be further clarified.



The da Vinci Surgical System - Surgeon is seated at the console at a short distance from the patient-side cart with the four interactive robotic arms and the vision system. A robotic arm uses instruments that provide seven degrees of freedom.

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial
The Lancet, 2010;375:816-823
RA Nout et al

In this open-label, non-inferiority, randomised trial undertaken in 19 Dutch radiation oncology centres, 427 patients with stage I or IIA endometrial carcinoma with features of high-intermediate risk were randomly assigned by a computer-generated, biased coin minimisation procedure to pelvic EBRT (46 Gy in 23 fractions; n=214) or VBT (21 Gy high-dose rate in three fractions, or 30 Gy low-dose rate; n=213). The primary endpoint was vaginal recurrence. The predefined non-inferiority margin was an absolute difference of 6% in vaginal recurrence. At median follow-up of 45 months (range 18—78), three vaginal recurrences had been diagnosed after VBT and four after EBRT. Estimated 5-year rates of vaginal recurrence were 1·8% for VBT and 1·6% for EBRT. 5-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5·1% for VBT and 2·1%for EBRT. 1·5% versus 0·5% of patients presented with isolated pelvic recurrence, and rates of distant metastases were similar 8·3% *vs* 5·7%. There were no differences in overall or disease-free survival. Rates of acute grade 1—2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12·6% *vs* 53·8%).

Interpretation

VBT is effective in ensuring vaginal control, with fewer gastrointestinal toxic effects than with EBRT. VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis
The Lancet, 2010
Yukiharu Todo

Overall survival was significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group (HR 0·53, 95% CI 0·38—0·76; p=0·0005). This association was also recorded in 407 patients at intermediate or high risk (p=0·0009), but overall survival was not related to lymphadenectomy type in low-risk patients. Multivariate analysis of prognostic factors showed that in patients with intermediate or high risk of recurrence, pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy (0·44, 0·30—0·64; p<0·0001). Analysis of 328 patients with intermediate or high risk who were treated with adjuvant radiotherapy or chemotherapy showed that patient survival improved with pelvic and para-aortic lymphadenectomy (0·48, 0·29—0·83; p=0·0049) and with adjuvant chemotherapy (0·59, 0·37—1·00; p=0·0465) independently of one another.

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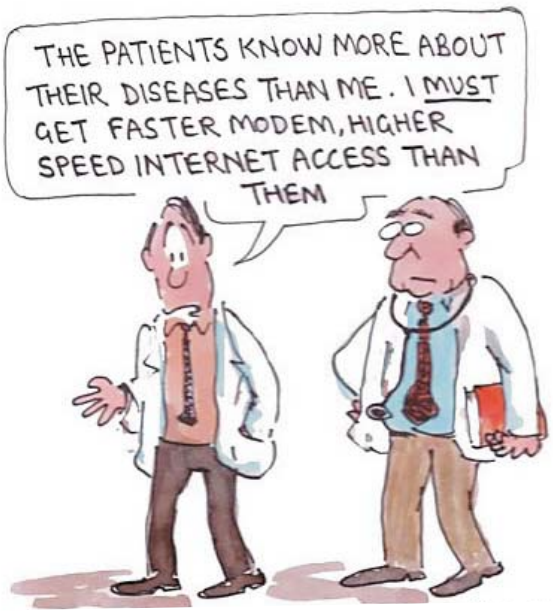
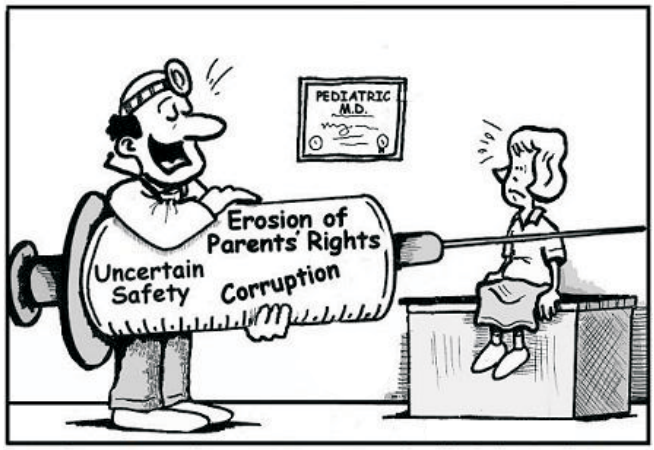
Cancer Statistics 2009, Department of Radiation Oncology, RCC, JIPMER

Malignancy	Male	Female	Total	%
Head and Neck	542	290	832	31.99
Gynaecologic	-	943	943	36.25
Breast	-	292	292	11.23
GIT	61	68	129	4.96
Thorax	39	19	58	2.23
Hematology	41	26	67	2.57
Urology	42	1	43	1.65
CNS	25	24	49	1.88
Thyroid	13	6	19	0.73
Unknown Primary	60	29	89	3.42
Miscellaneous	47	33	80	3.08
Total	870	1731	2601	100





"This new mandatory HPV vaccine shouldn't hurt a bit."


REGIONAL CANCER CENTRE