

# The cervix

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- Often referred to as the “gateway” or entrance to the uterus prone to insults and associated with many diseases.
- Malignant tumors of the cervix are predominantly carcinoma in nature.
  - The literature on the malignant tumors of the cervix is almost synonymous with invasive carcinoma of the cervix.
  - Constitute a scourge and cause reproductive ill health and mortality.
- Sarcomas and secondary tumors of the cervix occur but are rare.

# The cervix

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- Other forms of malignant condition of the cervix arising from the mesenchyme are mainly sarcomas and are not common.
  - They include leiomyosarcomas, endocervical sarcoma, embryonal rhabdomyosarcoma, alveolar soft tissue sarcoma and mullerian adeno-sarcoma
- Metastasis to the cervix may arise as a result of local extension of tumors from the uterus and other adjacent organs such as the bladder and the ovary.
  - choriocarcinomas, lymphomas and leukaemias.

# Cervical Cancer in Nigeria

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- Second commonest malignancy after Ca Breast
- Commonest genital tract malignancy- 62.3-70.5% of gynecological tumours.
  - [Kyari O, Nggada H, Mairiga A. \(2004\)](#), [Uzoigwe SA, Seleye-Fubara D. \(2004\)](#)
- [Uzoigwe SA, Seleye-Fubara D \(2004\)](#).
  - In a 13-year clinico-pathological review of 2,236 malignancies diagnosed at the University of Port Harcourt Teaching Hospital,
  - 302 (13.5%) malignancies of the genital tract.
  - 188 (8.4%) were carcinoma of the cervix constituting 62.3% of female genital malignancies.

# Cervical Cancer- characteristics of patients

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- In various studies spread across the 6 geopolitical regions of the country, characteristics of patients presenting with cervical cancer were reviewed.
- The peak mean age incidence in Nigeria ranges from 43.5 -54.6years.
  - One study reported a cervical malignancy in a 3-year old while the oldest age reported was in an 85-yr old.
    - [Kyari O, Nggada H, Mairiga A.](#) (2004), [Uzoigwe SA, Seleye-Fubara D.](#) (2004)
- The frequency distribution of carcinoma of the cervix appears to have bimodal pattern with a peak age at the fifth and seventh decades of life.
  - [Adeniji KA.](#) (2001)

# Cervical Cancer- characteristics of patients

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Other characteristics include

- A low socio-economic status (defined by employment or lack of employment)
- Limited educational level attained.
- Early coitarche
- Being in a polygamous marriage or a history of multiple sex partners
- Grand multi-parity
  - [Adewuyi SA, Shittu SO, Rafindadi AH.](#) (2008),
  - [Umezulike AC, Tabansi SN, Ewunonu HA, Nwana EJ.](#) (2007),
  - [Olatunji AO, Sule-Odu AO.](#)(2005 )

# Clinical features

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- Vaginal bleeding (51.9-100%)
  - Intermenstrual, post-coital, post-menopausal
- Offensive vaginal discharge ( 25- 79%)
- Pain from nerve involvement on pelvic side wall
- Late presentation
  - Cachxia, anaemia, Backache, Leg pain/oedema, Haematuria

- [Adewuyi SA, Shittu SO, Rafindadi AH. \(2008\)](#), [Umezulike AC, Tabansi SN, Ewunonu HA, Nwana EJ. \(2007\)](#), [Olatunji AO, Sule-Odu AO. \(2005\)](#) , [Ijaiya MA, Aboyeji PA, Buhari MO. \(2004\)](#),

- [Uzoigwe SA, Seleye-Fubara D. \(2004\)](#)

# Clinical features

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- Most present with advanced disease (75-86%).
  - [Umezulike AC, Tabansi SN, Ewunonu HA, Nwana EJ.](#) (2007) [Ijaiya MA, Aboyeji PA, Buhari MO.](#) (2004)
  - [Onwudiegwu U, Bako A, Oyewumi A.](#) (1999)
- As much as 66-71.8% being at least stage 3a.
  - [Adewuyi SA, Shittu SO, Rafindadi AH.](#) ( 2008)
  - [Anorlu RI, Orakwue CO, Oyeneyin L, Abudu OO.](#)( 2004)
- The histological diagnosis in 70-97% cases were described as squamous cell carcinoma.
- The next common being adenocarcinoma.
  - [Umezulike AC, Tabansi SN, Ewunonu HA, Nwana EJ.](#) (2007)
  - [Olatunji AO, Sule-Odu AO.](#) ( 2005)
  - [Onwudiegwu U, Bako A, Oyewumi A.](#) (1999)

## Omoniyi-Esan OG , Fasubaa OB, Adelusola KA, Ojo OS (2004)

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- Over a 10 year period
- 422 cervical surgical biopsies.
- 192 were malignant tumors i.e. 45.5%
- 190(98.9%) were carcinoma of the cervix.  
There were only 2 cases of sarcoma  
(leiomyosarcomas, endocervical stromal  
sarcoma)

# Omoniyi-Esan OG , Fasubaa OB, Adelusola KA, Ojo OS (2004)

- Sq. cell carcinoma constituted the predominant histological type (85.4%)
  - Non – keratinizing large cell squamous cell carcinoma was the predominant histological variant.
- Only 2 cases of sarcoma (leiomyosarcomas, endocervical stromal sarcoma)

Tumour types	Freq.	% total
Sq. CC	164	85.4
Adeno carcinoma	16	8.3
Adenosquamous	7	3.6
Metastatic	3	1.6
Sarcoma	2	1.0
Total	192	99.9

# Clinical features

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- Anorlu RI, Orakwue CO, Oyeneyin L, Abudu OO. (2004)
- Investigated the reason for late presentation of 127 patients seen over a 1-year period
- 60.7% of the patients first went to private hospitals.
  - interval between onset of symptoms and seeking healthcare was 6.10 +/- 9.31 months;
  - time elapsing between seeking healthcare and referral to a tertiary hospital was 9.35 +/- 12.9 months.
- **CONCLUSION:** Patients' delay in seeking healthcare and care providers' delay in referring patients to a tertiary hospital contributed to the late presentation.

# Management options

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- Olatunji AO, Sule-Odu AO. ( 2005)
- 56 histologically diagnosed cancer of the cervix (1991-2000).
  - 96.4%- squamous cell carcinoma
  - most (78.6%) presented in the advanced stages.
  - Majority (80.4) were referred for radiotherapy ( LUTH , UCH)
  - Only 5.4% of cases were treated by radical hysterectomy.

# Management options

- Campbell OB, Arowojolu AO, Akinlade BI, Adenipekun A, Babarinsa IA.(2000)
- retrospective study of 500 patients with advanced cervical cancer (FIGO Stages IIB, III and IVA). between 1988 and 1992.
- Mainstay of treatment- External pelvic radiation therapy plus intracavitary radioactive caesium brachytherapy.

	Complete response to therapy	local tumour control
IIB	68%	65%,
3	57%	54%
IVa	41.2%	41%.

# Management options

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- Campbell OB, Arowojolu AO, Akinlade BI, Adenipekun A, Babarinsa IA.(2000)
- The cumulative rates of survival at 5 years- 41.5%.
- The cumulative rates for disease-free survival at 5 years was 25.5%.
- Conclusion
- Radiotherapy as the sole treatment modality yielded poor results.
- An urgent need to evolve a new treatment policy.

# Management options

- Campbell OB, Akinlade IB, Arowojolu A, Babarinsa IA, Agwimah RI, Adewole IF.
- 408 with histologically confirmed carcinoma of the uterine cervix.
- 1988- 1992
- Randomized to hypofractionated radiotherapy or conventional fractionated radiotherapy
- Concluded
- Admin., of hypofractionated radiotherapy with the aim of maximizing the use of the limited radiotherapy facilities available will result in high post treatment morbidity.

5-yr survival	Hypofractionated radioT	conventional
I	91.3%	92.8 %
II	67.2 %	69.2 %
II	40.2 %	42.5 %
IV	18.0 %	19.6 %
Early radiation effects	Similar	Similar
Marked late adverse radiation effects	More	Less

## CHALLENGES - STAGING OF ADVANCED CERVICAL CANCER

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- Assessing the size of the primary tumour and the extent of spread is an important step before deciding on a management plan.
- This information can be obtained by
  - Clinical (FIGO) staging,
  - surgical staging (laparotomy or laparoscopy)
  - and imaging (MRI, PET and CT scans].

# CHALLENGES - STAGING OF ADVANCED CERVICAL CANCER

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- Clinical staging: examination under anaesthesia
- Inability to clinically delineate the extent of the disease accurately.
- The FIGO staging system, remains inappropriate to this end.
  - (EUA)25% inaccuracy in stage I and 50% inaccuracy in stage II.
- Reflected in 5-year survival rates reported from around the world.
  - stage I ( 52 to 90%) ,stage II ( 38 to 68%), stage III (22 to 61%), and stage IV(0 to 10%).

# STAGING OF ADVANCED CERVICAL CANCER

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- Surgical staging
- disease mapping e.g. staging laparotomy in the hope of tailoring subsequent radiotherapy- Transperitoneal, Retroperitoneal,
- Laparoscopic lymph node dissection- more accurate than either, less morbid.
- Patients with loco-regionally advanced cervical cancer that are surgically staged have a better outcome than those who are not.
  - Nevertheless the surgical staging introduces significant cost and morbidity.

# STAGING OF ADVANCED CERVICAL CANCER-

## Magnetic resonance imaging

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- Clinical estimation of tumour diameter is a poor correlate for the actual tumour volume.
  - CT scans- lack of distinction between tumour and normal tissue.
- MRI of the uterus can distinguish
  - uterus from the surrounding soft tissues.
  - the transitional zone separating the corpus uteri and cervix.
  - between gross cervical tumour and surrounding normal tissue.
  - Extent of cervical tumour in MRI images and subsequent whole mount histopathological sections showed a good approximation.
  - used to determine tumour volume in cervical cancer patients.
- Craniocaudal diameter can also be detected through MRI.- has prognostic significance.

# STAGING OF ADVANCED CERVICAL CANCER- Positron emission tomography

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- Staging pretherapeutic lymphadenectomy
  - The only means of accurately diagnosing nodal disease in inoperable cervical cancer.
  - Assoc. considerable morbidity.
  - Selective diagnostic lymphadenectomy- shown to improve survival in patients treated by radical radiotherapy.
  - The information about nodal disease is incorporated in defining the upper level of the radiotherapy field and areas requiring an additional radiotherapy boost.
- Now possible to detect lymph node metastases non-surgically using PET.

# Introduction- CA CX in pregnancy

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- Approximately 30% of women with cervical cancer are in their reproductive Years
- 3% of cervical cancers are diagnosed during pregnancy.
- pregnant women have a two- to three-fold higher probability of being diagnosed in an operable stage.
- Diagnostic and therapeutic management difficult
  - because two people are involved.

# Invasive cervical cancer during pregnancy

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- Both maternal and fetal considerations determine management decisions- dependent upon
  - gestational age at diagnosis, stage of disease, lesion size, the patient's desire for the pregnancy and the patient's desire for future fertility.
- Accurate staging by radiographic imaging
- Necessary- take the pregnant state into consideration.
  - The radiation effect on fetal life seems to be dose dependent
  - whereas the adverse effects of radiation are directly related to GA (the earlier the gestation, the more detrimental the expected effect).

# Invasive cervical cancer during pregnancy

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- imaging tests for staging purposes should be limited to those associated with the lowest exposure to ionizing radiation.
- Avoid when possible- X rays, isotope Scans, CT.
- Abdominal and pelvic ultrasound and MRI are indicated during pregnancy.
  - Ultrasonography- to evaluate liver and urogenital involvement.
  - MRI- to evaluate genito-urinary system involvement.
  - has excellent tissue contrast. can be used to calculate tumor volume and assess spread to adjacent organs.
  - Lymph node metastasis might also be detected

# Invasive cervical cancer during pregnancy

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- MRI- Not recommended during the first trimester
- a chest X ray with abdominal shielding for evaluation if pulmonary metastatic disease is warranted.
  - The radiation dose to the fetus from a maternal chest radiograph is 0.0000007 Gy

# Management of ICC before 12 weeks of gestation

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- In young, healthy women with early-stage, surgical treatment is preferred
  - offer immediate treatment,
  - Avoids radiation-associated vaginal strictures, diarrhoea and malabsorption syndromes,
  - preserves ovarian function
  - and allows the surgeon to explore the pelvis and abdomen thoroughly for possible metastatic disease.
- Radiation treatment is mainly used for patients who are unsuitable for surgical management.

# Management of ICC before 12 weeks of gestation

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- Advanced disease (FIGO stages IIB, III and IV) may inhibit conception, uncommonly diagnosed during pregnancy.
- In those rare advanced cases, the treatment of the mother is regarded as of prime importance and chemoradiotherapy is advised- Cisplatin-based.
- Alternatively, neo-adjuvant chemotherapy (NACT) followed by surgery.

# Management of ICC after 1<sup>ST</sup> trimester and non-viable fetus

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- FIGO stages IA2, IB and IIA-
- Before 20 weeks,
- possible treatments are
  - a radical hysterectomy with the fetus in situ
  - or radiation therapy. External-beam and then intracavitary brachytherapy after spontaneous abortion occurs.
- After 20 weeks of gestation,
  - Fetus should be evacuated before radical Caesarean hysterectomy.
  - prudent to evacuate the fetus before radiation treatment because of the higher rate of failure of spontaneous abortion.

# Management of ICC after 1<sup>ST</sup> trimester and non-viable fetus

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- In cases of locally advanced disease, the treatment of choice is cisplatin-based chemoradiotherapy or NACT followed by surgery.
- Planned treatment delay (6-12weeks)- if expectant mother refuses to sacrifice her pregnancy, the use of NACT might be considered in cases of locally advanced cervical carcinoma in an effort to allow time to reach fetal viability by disease regression or stabilization of disease.

# The rationale, benefits and risks of chemotherapy during pregnancy.

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- chemotherapeutic agents in pregnancy poses a significant clinical dilemma for patient and physician.
- In pregnancy, both maternal and fetal tissue may be affected.
- For the mother it depends on the agent, timing and dose: spontaneous abortion and sterility.

# The rationale, benefits and risks of chemotherapy during pregnancy.

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- Theoretically, all chemotherapeutic agents are teratogenic.
- Effect on the fetus depends:
  - on the choice of agents, timing, length and dose of exposure, and the pharmacokinetics of the drug.
  - High lipid solubility, low molecular weight, and loose binding to plasma proteins favour placental transfer of drugs.

# The rationale, benefits and risks of chemotherapy during pregnancy.

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- The rate of chemotherapy-associated fetal malformations depends on
  - the gestational age, agents used and dosage.
- During the first trimester,
  - Estimated risk ~ 7.5-17% (single agent) ~ to 25% (combination chemotherapy)
- During the second and third trimesters
  - risk of birth defects are similar to those of the general population (1–3%).

# The rationale, benefits and risks of chemotherapy during pregnancy.

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- Use of chemotherapy during the first trimester increases
  - the risk of spontaneous abortion, stillbirth,
  - major malformations, teratogenesis, mutations
  - carcinogenesis and organ toxicity (general hepatobiliary and endocrine effects,
  - gonadal dysfunction and infertility,
  - bone marrow suppression with associated susceptibility to infections,
  - bleeding and anaemic complications), and direct effects of the tumour sometimes confound the risks of fetal loss.

# The rationale, benefits and risks of chemotherapy during pregnancy.

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- Chemotherapy during the second and third trimesters
- Organogenesis is complete by the 13th week of pregnancy, except for the brain and gonads.
- Therefore, the main fetal effects relate to
  - intra-uterine growth restriction, fetal death in utero,
  - prematurity and low birth weight (due to both lower gestational age and substantial intrauterine growth retardation).
  - Furthermore, haematopoietic suppression, infertility, retarded development, carcinogenesis and second-generation teratogenesis have been observed.

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- Since the brain develops throughout pregnancy, neurodevelopment and cognitive capacities of children exposed to chemotherapy in utero is an important study area.

# Chemotherapy in pregnancy- Cis- platin.

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- In cervical cancer, the most effective cytotoxic drugs investigated
- Cisplatin
  - placental transfer increases as the placenta matures, potentially resulting in toxic effects in more developed fetuses.
  - Despite these concerns, reports of normal births have been documented.
  - some reports of malformations following exposure in the 2<sup>nd</sup>/3<sup>rd</sup> trimesters :
    - moderate bilateral hearing loss, alopecia, cerebral atrophy, ventriculomegaly in one case.

# Chemotherapy in pregnancy- Paclitaxel.

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- Paclitaxel has a unique antineoplastic mode of action.
- four cases of use in human pregnancy without apparent fetal effects. normal psychophysical development.

## Summary- chemotherapy in pregnancy

- Data on long-term outcome after use of chemotherapy in pregnancy are sparse.
- anomalies induced may not become manifest until the progeny is older.
- use of chemotherapy in the 2<sup>nd</sup>/ 3<sup>rd</sup> trimesters is relatively safe.

# Management of ICC in the case of a viable fetus

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- When fetal maturity is achieved, or if the fetus is mature at the time of diagnosis,
- Immediate delivery, followed by definitive treatment of the mother.
  - if necessary after steroid therapy for achieving fetal lung maturity.
- recommended treatment
- classical Caesarean delivery followed by radical hysterectomy.
  - no more hazardous compared with the non-pregnant state.
- In advanced stages, whole pelvic radiation immediately post partum, followed by intracavitary irradiation.

# Mode of delivery.

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- For higher stages- Mode of delivery more controversial.
- Caesarean section preferred.
- Complications of vaginal delivery through a cervix with ICC.
  - dissemination of disease into lymphovascular channels, haemorrhage, sepsis, obstructed labour and cervical laceration.
  - implantation of malignant cells in the episiotomy site.
- Caesarean section not completely safe either.
  - several reports of abdominal scar recurrences after radical hysterectomy.

# PROGNOSIS

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- Better than the non-pregnant population due to high proportion of early-stage disease.
- However, after stratifying for stage, no differences between the pregnant and the non-pregnant group with regard to
  - tumour characteristics, the course of disease, survival analyses and complication rates of the treatment.

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