

Cervical Cancer In HIV Seropositive Patients

¹Adewuyi, SA; ²Shittu, SO; ³Rafindadi, AH

¹Radiotherapy and Oncology Center, ²Department of Obstetrics & Gynaecology,

³Department of Pathology, Ahmadu Bello University Teaching Hospital, Zaria

Correspondence: Dr. S. A. Adewuyi, Clinical & Radiation Oncologist Radiotherapy and Oncology Center, A. B. U. Teaching Hospital, Shika Zaria, P. M. B. 06 E-mail: sadewuyi2003@yahoo.com

ABSTRACT

Cervical cancer is the commonest gynaecologic malignancy in this environment (anecdotal) and this may be related with the sociocultural lifestyle of the people. Now with the HIV pandemic there is a change in the pattern of presentation of this disease.

The 3 case reports highlight the pattern of cervical cancer in patients who are HIV seropositive and presented at a very young age with locally advanced and metastatic disease. There were distant metastases at unusual sites and tumour was poorly differentiated carcinoma. The disease was very aggressive with short duration of symptoms and poor response to conventional treatment modality. The natural history of cervical cancer appears to be different in HIV positive patients.

Key words: Pattern of presentation, cervical cancer, HIV seropositive

INTRODUCTION

Cervical cancer is the second most common malignancy in women worldwide, second only to breast cancer and it remains a leading cause of cancer-related death for women in developing countries.¹ The incidence of invasive cervical cancer has declined steadily in developed countries over the past few decades. However, it continues to rise in many developing countries.²

Apart from the well known association of cervical cancer with Human papilloma virus (HPV), cervical cancer has been associated with Human Immunodeficiency virus (HIV), and it is classified as Acquired immunodeficiency syndrome (AIDS) defining disease since 1993 (CDC).³ The World Health Organization (WHO) estimated two thirds of the 40 million people in the world with Human Immunodeficiency Virus (HIV) lives in Africa.³ We are yet to see if the HIV pandemic will have any effect on the epidemiological trend, natural history of cervical cancer, response to standard

treatment and overall survival. We describe below our recent experience with 3 cervical cancer patients with HIV infection.

CASE REPORT 1

A 30 year old para³⁺³ woman presented with 8 months history of post-coital bleeding and mass in her vagina; 4 months afterwards, she developed discharge per vagina, suprapubic pain, swelling of her left lower limb, and pain in the left hip joint. There was also associated dysuria, and feeling of incomplete voiding, but no haematuria and urinary incontinence. There were no any other systemic symptoms. She married twice with only 1st child alive. Her 2nd and 3rd children died at age of 8 and 9 months respectively. Cause of death not known but attributed to weaning process. First marriage was at the age of 13 years and lasted for 4 years which yielded the only surviving child. The 2nd marriage was after 3 years of divorcing the first husband. Both husbands have many wives and also had multiple sexual partners. She is the second wife of her current husband who is a police man. There was no history of sexually transmitted diseases in the past. Her last childbirth was 14 years ago. She attained menarche at age of 13 yrs, with regular menstruation (K₁₃ 4/28) cycle, but no dysmenorrhoea. She was referred from a sister teaching hospital as a case of advanced cervical cancer with involvement of posterior bladder wall. Histopathology of the incisional biopsy revealed poorly differentiated carcinoma.

On examination, she was not pale, anicteric, or dehydrated. She had shotty peripheral lymphadenopathy affecting the inguinal regions and mild left lower limb lymphoedema. Her Karnofsky performance status was KPS 80. Digital vagina examination revealed a normal external genitalia with foul smelling, creamy discharge per vagina. There was no evidence of urinary incontinence. There was an exophytic growth,

circumferential on the cervix measuring about 6cm in diameter, obliterating both parametria and extending to the pelvic side wall on the left. The proximal two-third of the vagina especially anteriorly was involved. There was significant contact bleeding and positive cervical excitation tenderness. Rectal examination revealed no pathology. There was no abnormality detected on examination of the other systems. An impression of locally advanced cervical cancer was made. Joint consultation between the gynaecologists and radiation oncologist was done and the patient was scheduled for investigations and to have external beam radiation therapy to be followed by chemotherapy.

The significant findings were CD4 counts of 0520 cells/ul, Seroreactive to HIV-1 with positive confirmatory test. IVU shows a pelvic mass with secondary mass effect on the left ureter, and abdomino-pelvic ultrasound revealed a bulky cervical mass with infiltration of the lower aspect of the urinary bladder. Her staging was therefore FIGO Stage IVA.

She had external beam radiation therapy, 5400 cGy in 27 fractions over 5.5 weeks by parallel-opposed pelvic beams (200 cGy/day, MPD). Due to her HIV status, she could not receive brachytherapy and as such she was given a boost dose of 1400 cGy in 7 fractions over 2 weeks with reduced field size after a break of 6 weeks from the first treatment.

After external beam radiation therapy, there was excellent response. There was no clinical evidence of locoregional disease, no fistula or lymphoedema. She absconded from clinic for about 4 months only to present with multiple lumps in the left supraclavicular region, left chest wall (overlying the 9th, 10th ribs posteriorly and the 3rd and 4th rib anteriorly) above the left breast. The lumps measured 8cm x 7cm, 8cm x 5cm and 5cm x 5cm respectively. Abdominal ultrasound scan revealed paraaortic lymphadenopathy and secondaries in the liver and multiple intraabdominal masses. However, there was no local relapse of her disease.

Prognosis of the disease was explained to the patient and she was advised to resume the HAART drugs and to receive chemotherapy subject to normal CD4 counts. Her husband was advised to do HIV screening but he declined. The patient opted for traditional herbal medication and died of progressive disease after 2 months.

CASE REPORT 2

A 32 year old para⁴⁺¹ woman presented with 12 months history of post-coital bleeding, 10 months history of intermenstrual bleeding and 1 month history of lower abdominal pain and vaginal discharge and 2 weeks history of unprovoked PV bleeding necessitating blood transfusion. There were no other systemic symptoms. She had received at least 8 pints of blood transfusion since onset of illness. She married only once at the age of 17 years but had her first coitus at 16 years of age. She had 4 deliveries but 3 are alive and that the 3rd delivery died as a result of breech delivery. Her first childbirth was at age of 17 years. She attained menarche at age of 16 yrs, with regular menstruation (K₁₆ 4/28) cycle, and no dysmenorrhoea. There was no history of recurrent vaginal discharge or STDs in the past. She denied any history of multiple sexual partners. She was the only wife of her husband who is a teacher. She was referred from a sister teaching hospital as a case of advanced cervical cancer. Histopathology of the incisional biopsy revealed poorly differentiated carcinoma.

On examination, she was not pale or icteric and her Karnofsky performance status was KPS 60. Detailed digital vaginal examination could not be done due to obvious profuse bleeding in clots per vagina necessitating immediate haemostatic irradiation.

There was a solitary lump in the axillary tail of the right breast measuring 5cm x 5 cm in the soft tissue, attached to the underlying ribs, not mobile and tender. Abdominal examination revealed a mobile suprapubic mass of about 8 - 10 weeks gestational size, arising from the pelvis which was tender. There was no abnormality detected on examination of the other systems.

An impression of metastatic cervical cancer (FIGO Stage IVB) was made. She had 1200 cGy in 4 fractions over 4 days as haemostatic dose which stopped the profuse vaginal bleeding. Post haemostatic dose revealed a residual growth on the cervix with involvement of the parametria and extension to the pelvic side walls especially on the right. She had further investigations prior to treatments.

The significant findings were Seroreactive to HIV-1 with positive confirmatory test, pelvic ultrasound revealed a large solid cervical mass measuring 8.6cm x 6.7cm without involvement of surrounding organs, fine needle aspiration biopsy of the right axillary lump result confirmed metastasis, and chest x-ray showed a soft tissue mass on the lateral wall of the chest on the right with erosion of the underlying ribs.

She had additional external beam radiation therapy, 4000 cGy in 20 fractions over 4 weeks by parallel-opposed pelvic beams (200 cGy/day MPD) and was scheduled to receive palliative radiotherapy to the right chest wall, 3000cGy in 10 fractions over 2 weeks. Due to her HIV status, she could not receive brachytherapy. Prognosis of the disease was explained to the patient and she was advised to resume the HAART drugs and her husband was also advised to do HIV screening.

Six weeks after external beam radiation therapy, there was excellent response, with no evidence of locoregional disease and no fistula or lymphoedema. She was then evaluated for possible chemotherapy administration but she began to deteriorate clinically with worsening performance status. She was unfit for further treatment and was therefore referred to parent gynaecologist for palliative care and HAART administration. She was confirmed death 8 weeks afterwards.

CASE REPORT 3

A 30 year old para⁵⁺¹ woman presented with 12 months history of unprovoked vaginal bleeding, dragging sensation in the vagina and protrusion of a mass from the vagina on micturition. There was occasional vaginal discharge. There was associated lower abdominal pain, lower abdominal mass and low back ache. There was no history of leg swelling and no systemic symptoms apart from loss of appetite and weight loss. She was transfused with 5 pints of blood prior to presentation in our center. She married twice with 5 children alive. Her first marriage was at the age of 15 years when she had her first coitus. She had 2 children for the first husband and 3 children for the current husband. Both husbands have polygamous families with multiple sexual partners. There was no history of sexually transmitted diseases in the past. She attained menarche at age of 13 yrs, with regular menstruation (K₁₃ 4/28) cycle, no dysmenorrhoea. She was referred from a Federal Medical Center as a case of locally advanced cervical cancer. Examination under anaesthesia by the referring gynaecologist revealed a bulky haemorrhagic friable mass in the vagina down to the vestibule with an anterior and posterior lip separated by a slit, continuous with a bulky uterus (about 12/52). There was extension to the pelvic side walls.

Histopathology of the incisional biopsy revealed Squamous cell carcinoma (large cell keratinizing), poorly differentiated. She was clinically staged FIGO IIIB.

On examination, she was pale, lethargic, anicteric, and acyanosed, with multiple discrete inguinal lymphadenopathies. She had no lymphoedema and Karnofsky performance status was KPS 60.

Digital vaginal examination revealed obvious profuse bleeding per vagina in fresh clots and as such, detailed digital examination was suspended to avoid provoking torrential haemorrhage. The abdomen was scaphoid with obvious asymmetry and tenderness in the suprapubic region. There was a suprapubic mass of about 16/52 in size. Rectal examination revealed no pathology. There was no abnormality detected on examination of the other systems. She had a tender, fluctuant mass in the left gluteal region (injection abscess) which was drained.

An impression of locally advanced cervical cancer (FIGO Stage IIIB) was made. She was scheduled for investigation and to have external beam radiation therapy to be followed by chemotherapy. The significant findings were low PCV (27%), Seroreactive to HIV-1 antibodies with positive confirmatory test, ultrasound revealed hour glass appearance of the uterus due to bulky cervix. The bulky cervix contained an echogenic mass measuring 6.7 cm in its AP diameter. There was fluid collection in the pouch of Douglas. The husband's HIV result was negative.

After correcting the anaemia, she had external beam radiation therapy, 5400 cGy in 27 fractions over 5.5 weeks by parallel-opposed pelvic beams (200cGy/day, MPD). Due to her HIV status, she could not receive brachytherapy. Six weeks after external beam radiation therapy, there was excellent response, with no evidence of locoregional disease, no fistula and no lymphoedema. She was placed on antiretroviral drugs which she could not get placement. At the first 3-monthly follow up, she has developed full blown Acquired Immunodeficiency Syndrome (AIDS) with marked weight loss, chronic diarrhoea, oral thrush and persistent low grade fever. Prognosis of her disease and clinical condition was explained to the patient and her husband. She died after few weeks.

Table 1: Pattern of presentation of carcinoma of the cervix in 3 HIV positive patients

Case No.	Age(yrs)	Stage	Histology	HIV Subtype	Site of metastasis	Duration of symptoms	Overall survival
1	30	IVB	Poorly Differentiated Squamous cell carcinoma	HIV-1	Liver, Soft Tissues, para-aortic Lymph node Supraclavicular Mass	8 months	16 months
2	32	IVB	Poorly Differentiated Sqia, pis cell carcomp,a	HIV-1	Bone, Soft tissues	12 months	18 months
3	30	IIIB	Poorly Differentiated SCC	HIV-1	Nil	12 months	19 months

Table 2: Treatment modalities according to stage of disease for carcinoma of the Cervix

Stage	Treatment Modality
Stage O	Cryotherapy, laser ablation, and loop excision. Hysterectomy (for those with other gynaecologic indications)
Stage IA IB1	Radical hysterectomy of brachytherapy
Stage IB2-IIA	Combination of external beam radiotherapy and brachytherapy Or radical hysterectomy with bilateral lymphadenectomy
Stage IIB-IVA	External beam radiation therapy, brachytherapy and adjuvant Chemotherapy (single agent or combination regimen)
Stage IVB	Chemotherapy (single agent or combination regimen) Palliative radiotherapy (external beam radiation therapy, with or without brachytherapy)
Stage IVB	Chemotherapy (single agent or combination regimen) Palliative radiotherapy (external beam radiation therapy, with or without brachytherapy)

Discussion

With an improved prognosis for patients with HIV infection as a result of advances in supportive care and antiretroviral therapy, the neoplastic complications of HIV infection is expected to increase. It is also clear that durable remissions will translate into long-term survival in patients whose HIV load can be suppressed to very low or undetectable levels. The resultant effect is the possibility of HIV-infected patients developing HIV-related malignancies such as Kaposi sarcoma, lymphoma, cervical cancer, and anal cancers.⁴ The virus is transmitted sexually, parenterally, and vertically although worldwide, heterosexual transmission is the most common.⁵ Highly Active Anti Retroviral Therapy (HAART) is generally recommended for all patients with acute HIV infection or within the first 6 months after seroconversion. In addition, for all patients with full blown AIDS or when there is low CD4 count, it is expected that this therapy will decrease viral load to the lowest level, sustain viral load suppression for as long as possible, prevent immunological decline and the clinical progression, prolong survival and improve quality of life and prevent vertical transmission.⁶

Although cervical cancer has been recognized by the Centers for Disease Control as an AIDS-defining illness, an excess of cervical cancer attributable to HIV remains to be conclusively demonstrated. However, some evidence suggests that HIV-infected women with cervical cancer are more likely to have advanced disease at presentation (Table 1) and to have a higher recurrence rate than non-HIV-infected women. Furthermore, cervical intraepithelial neoplasia occurs more frequently in women with HIV infection.⁷ Cervical cancer is the commonest gynaecologic malignancy in developing countries¹ and the associated risk factors include sex at a young age (before age of 17 years), multiple sexual partners (including polygamy, divorce and remarriage, and promiscuity), smoking, multiparity, and history of sexually transmitted diseases especially human papilloma viruses (HPV) and Human immunodeficiency virus (HIV), immunosuppression, and oral contraceptive use.^{8, 9} In this environment, due to the sociocultural lifestyle, religion and poverty, a lot of the women are exposed to these risk factors.

The incidence and mortality from invasive carcinoma of the cervix has decreased dramatically in the developed world since the American Cancer Society recommended

the use of the Papanicolaou test (Pap smear) for cervical cancer screening in the mid 1940s. In women screened routinely, the most common finding is an abnormal Pap smear result. In this environment, the reverse is the case because the women rarely do Pap smear and as a result, late presentation with advanced disease is the norm.

Early invasive cancers may be asymptomatic, although some women will notice postcoital, intermenstrual, or postmenopausal spotting. Other symptoms may include malodorous vaginal discharge, dyspareunia, or cramping pelvic pain from uterine contractions caused by the accumulation of blood and uterine deciduas in menstruating patients with occlusion of the endocervical canal. Chronic blood loss may result in symptomatic anaemia in some patients. Major haemorrhage is unusual except in locally advanced disease. Pelvic pain, lower extremity swelling, or problems with micturition or defecation indicate advanced regional disease and portend an ominous prognosis. In this environment where late presentation is the norm, urinary or faecal incontinence due to a local tumor eroding into the bowel or bladder may be the symptom that drives patients to the hospital. Metastatic disease involving supraclavicular nodes, bones, or lungs can be the cause of presenting symptoms, but rarely in the absence of pelvic symptoms. Constitutional symptoms, including anorexia, dyspepsia, and weight loss, are often seen in patients with very advanced disease.¹⁰

The findings on physical examination in patients with early-stage cervical cancer can be relatively normal. As the disease progresses, the cervix may become abnormal in appearance, with gross erosion, ulcer, or mass. An exophytic or ulcerative lesion may be obvious on clinical examination, but an endocervical lesion may have a normal-appearing ectocervical mucosa with a firm, enlarged cervix. These abnormalities can extend to the vagina. Rectal examination may reveal an external mass or gross blood from tumor erosion. Bimanual examination findings may reveal pelvic metastasis in advanced disease.

The diagnostic workup includes a Pap smear in every patient suspected to have a diagnosis of cervical cancer. The patient should be referred to a gynaecologist for colposcopy, direct biopsies, and endocervical curettage. For details of other investigation see table 2.

The staging for cervical cancer is clinical and not surgical staging and also CT scan and MRI are complementary investigations.⁸ The most common histologic type of cervical cancer is predominantly of epithelial origin, with squamous cell carcinoma as the major group (85%). The remainder are usually adenocarcinoma (endocervical or mucinous). More rare epithelial subtypes exist, including adenosquamous, glassy-cell, adenoid cystic, adenoid basal, small cell, carcinoid, melanoma, lymphoma and undifferentiated.¹¹

The treatment of cervical cancer depends mainly on the stage of the disease, size of tumour, histology and patients choice and in addition in this environment, the performance status and financial standing of the patient. The management frequently requires a multidisciplinary approach involving a gynaecologic oncologist, radiation oncologist, and medical oncologist.

The treatment of choice for carcinoma in situ (stage 0) is local ablative measures such as cryosurgery, laser ablation, and loop excision. Hysterectomy should be reserved for patients with other gynaecologic indications to justify the procedure. This group of patients require lifelong surveillance.¹²

The standard treatment for stages IA-IB1 is surgery or brachytherapy and it is potentially curative. For microinvasive disease (stage IA) the procedure is total hysterectomy. Selected patients with stage IA1 disease but no lymphovascular space invasion who desire to maintain fertility may have a therapeutic conization with close follow-up, including cytology, colposcopy, and endocervical curettage. Patients with medical comorbidities who are not surgical candidates can be successfully treated with brachytherapy. For stage IB1, the surgical procedure of choice is a radical hysterectomy with resection of the parametria and pelvic lymph node dissection. Para-aortic lymph nodes should be examined and sampled if suggestive of metastatic disease. If parametrial extension or regional nodal metastasis is identified intraoperatively, many gynaecologic oncologists abort the hysterectomy and proceed to adjuvant pelvic radiotherapy. The outcome for surgery and radiotherapy is similar.^{13,14}

For patients with stage IB2 and IIA disease, treatment options are either combined external beam radiation with brachytherapy or radical hysterectomy with bilateral pelvic lymphadenectomy. Radical hysterectomy

with bilateral pelvic lymphadenectomy is associated with severe morbidity and mortality and mostly done in developed countries where complications can be managed effectively. In this environment, this group of patients are managed as locally advanced disease (stage IIB-IVA) because of risk of nodal metastasis. Most retrospective studies have shown equivalent survival rates for both procedures, although such studies usually are flawed due to patient selection bias and other compounding factors.^{15,16}

For locally advanced cervical carcinoma (stages IIB, III, and IVA), radiation therapy traditionally has been the treatment of choice. Those patients with stage IVA disease may require surgical intervention such as colostomy and or nephrostomy so as to tolerate radiation therapy and minimize radiation toxicity. Treatment begins with a course of external beam radiation to reduce tumor mass, stop bleeding, and give a better geometry to enable subsequent intracavitary application. Intracavitary brachytherapy is delivered using afterloading applicators that are placed in the uterine cavity and vagina. This may be performed in the form of either high dose rate (HDR) or low dose rate (LDR) applications using iridium-192 and caesium-137 respectively. The total combined external beam and brachytherapy dose to point A usually is 75-80 Gy.¹⁶⁻¹⁸ In addition, adjuvant chemotherapy using single or combination chemotherapy improves the therapeutic outcome.¹⁶

The treatment for disseminated cervical cancer (stage IVB) is primarily palliative in nature because cure is remote. Chemotherapy with single agents such as cisplatin or ifosfamide results in response rates of approximately 20%.¹⁶ Combination regimens have higher response rates and can prolong disease-free survival. However, toxicity is increased and no survival advantage is gained. In addition, the duration of response usually is short.¹⁹ Palliative radiation is used on individual basis to control bleeding, pelvic pain, or urinary or partial large bowel obstructions from pelvic disease. Similarly, bone metastasis and supraclavicular masses can be palliated.²⁰ Invasive procedures such as nephrostomy or diverting colostomy sometimes are performed in this group of patients to improve their quality of life if there are associated fistulae. Special effort should be made to ensure comprehensive palliative care, including adequate pain control for these patients.

The above treatment protocol is meant for all patients with carcinoma of the cervix irrespective of their retroviral status. The management of patients with cervical cancer with HIV infection pose a lot of problems which may have contributed to the treatment outcome. Brachytherapy is the most important treatment factor in the control of local disease and the resultant prognosis for stages IB-IVA. This treatment modality eludes patient with HIV infection in this environment because the applicators being used are not disposable, they are recycled. Until disposable applicators are available for each patient, treatment outcome is bound to remain very poor.

In summary, for early invasive cancer, surgery is the treatment of choice. In more advanced cases, radiation therapy (external beam radiotherapy and/or brachytherapy) combined with chemotherapy is the current standard of care. In patients with disseminated disease, chemotherapy or radiation provides symptom palliation.

Prognosis of cervical cancer depends on disease stage. In general, the 5-year survival rate for stage I disease is higher than 90%, for stage II is 60-80%, for stage III is approximately 50%, and for stage IV disease is less than 30%.²¹ The overall survival in these cases presented was very poor, far from the expected. There are a lot of question yet to be answered. Pap smear is rarely done in this environment, and now with the HIV pandemics, will the incidence increase in this environment? What is the best way to manage this group of patient? What is the role of HAART in the treatment? There is an ongoing prospective multidisciplinary study to answer some of these questions.

Conclusion

With the presence of HIV infection (HIV-1) in patients with carcinoma of the cervix, the pattern of presentation of cervical cancer seems to be evolving to presentation at younger age, locally advanced and metastatic disease, shorter duration of symptoms, poor differentiation of tumour with metastasis to unusual sites.

References

1. National Institutes of Health Consensus Development Conference Statement: Cervical Cancer, April 13, 1996. *J Natl Cancer Inst Monogr* 1996; 21:vii.
2. Eddy DM: Screening for cervical cancer. *Ann Intern Med* 1990 Aug 1; 113(3): 214-26.
3. UNAIDS/WHO: AIDS epidemic update 2002.
4. Dal Maso L, Serraino D, Franceschi S: Epidemiology of AIDS-related tumours in developed and developing countries. *Eur J Cancer* 2001; 37: 1188-1201.
5. Sepkowitz KA: AIDS: The first 20 years. *N Engl J Med* 2001; 344:1764-1772.
6. Dybul M, Fauci AS, Bartlett JG, et al: Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. *Ann Intern Med* 2002; 137:381-433.
7. Gates AE, Kaplan LD: AIDS malignancies in the era of highly active antiretroviral therapy. *Oncology (Huntingt)* 2002; 16:441-451.
8. Perez CA. Uterine cervix. In: Perez CA, Brady LW, eds. *Principles and practice of radiation oncology*, 3rd ed. Philadelphia: Lippincott Raven Publishers, 1998:1733-1834.
9. Benedet JL, Odicino F, Maisonneuve P, et al: Carcinoma of the cervix uteri. *J Epidemiol Biostat* 2001; 6(1): 7-43.
10. Russel HA, Seiden VM, Duska RL, et al. Cancers of the Cervix, Vagina, and Vulva. In: Abeloff MD, Armitage OJ, Niederhuber JE, Kastan BM, McKenna GW, eds. *Clinical Oncology*, 3rd ed. Elsevier Churchill Livingstone Publishers, 2005: 2217-2272.
11. Robert ME, Fu YS. Squamous cell carcinoma of the uterine cervix: a review with emphasis on prognostic factors and unusual variants. *Semin Diagn Pathol* 1990; 7:173.
12. Creasman WT, Hinshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. *Obstet Gynecol* 1984; 63:145.
13. Orr JW Jr: Cervical cancer. *Surg Oncol Clin N Am* 1998 Apr; 7(2): 299-316.
14. Roy M, Plante M, Renaud MC, Tetu B: Vaginal radical hysterectomy versus abdominal radical hysterectomy in the treatment of early-stage cervical cancer. *Gynecol Oncol* 1996 Sep; 62(3): 336-9.
15. Landoni F, Maneo A, Colombo A, et al: Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 1997 Aug 23; 350(9077): 535-40.
16. Peters W: Cisplatin and 5-fluorouracil plus radiation therapy are superior to radiation therapy as adjunctive therapy in high-risk early-stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy. Report of a Phase III Intergroup study. 1999.

17. Rose PG, Bundy BN, Watkins EB, et al: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999 Apr; 15; 340(15): 1144-53
18. Whitney CW, Sause W, Bundy BN, et al: Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999 May; 17(5): 1339-48.
19. Thigpen JT, Vance R, Punecky L: Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. *Semin Oncol* 1995 Apr; 22(2 Suppl 3): 16-24
20. Spanos WJ, Perez CA, Marcus S, et al. Effect of rest interval on tumour and normal tissue response: a report of phase III study of accelerated split course palliative radiation for advanced pelvic malignancies (RTOG-8502). *Int J Radiat Oncol Biol Phys* 1993; 25:399.
21. Perez CA, Grigsby PW, Nene SM, et al. Effect of tumour size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* 1992; 69:2796.
22. American Joint Committee on Cancer: *AJCC Cancer Staging Manual*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1997.