Rama Med J 2009; 32: 106-110

บทบรรณาธิการ

What is New about Cervical Cancer during Last Decade?

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Cervical cancer is the second most common female cancer worldwide. In Thailand, it also ranks the second most common cancer in female while the most common cancer is breast cancer. This is the national statistic reported in 2010 with the age-standardized incident rate 18.1 per 100,000 women year[1]. There are approximate 500,000 new cases from all over the world each year. Around twenty-seven thousand cases died from the disease. Seventy percent of cervical cancer cases occur in developing countries. Although cervical cancer is a preventable disease, investigators still work hard to find the solution to eliminate it. Cervical cancer treatment has been studied; there are still many aspects of treatment modalities that are on developmental process. This article will focus in the changing views about cervical cancer and some of the update issues during past 10 years.

Prevention

In the year 1983, Professor Harald Zur Hausen identified Human Papilloma Virus (HPV) 16 DNA in cervical cancer tumors by Southern blot hybridization. This was followed by discovery of HPV18 a year later, thus identifying the culprits responsible for ~75% of human cervical cancer. This made a big change in knowledge of etiology and strategies in cervical cancer prevention. In 2006, the US FDA approved the quadrivalent HPV vaccine for the 9-26 years old women. Now there are quadrivalent HPV vaccine and bivalent HPV vaccine available in the market with at least 70 percent coverage in prevention of high risk HPV. Not only the vaccination, but also health education in cessation of smoking and avoiding risks of HPV infection such as having sexual intercourse form very young age and having multiple sexual partners play role in primary cervical cancer prevention.

Because of the long latency in preinvasive disease, the screening for cervical cancer has been proven in effectiveness in cervical cancer reduction. Papanicolaou's smear was first reported for screening cervical cancer since 1943 by Georgios Papanikolaou. Although the specificity is almost 95%, the sensitivity of this test is only 50-60 percent. There are two types for cytologic screening now, the conventional smear and the liquid-base smear. The later smear has been proven in increasing the detection rate of cervical cancer or high grade intraepithelial lesion. Now HPV

DNA testing for high risk HPV type is available in the clinical use for the primary screening purpose. With approved by US FDA in 2003, the hybrid capture II method (DigeneR HPV Test) is more accepted than the PCR method for increase sensitivity and specificity of cervical cancer screening with Pap's smear and for one of the options in management of ASCUS result Pap's smear. The treatment options for cervical cytologic abnormalities' patients have been clarified and stated as a guideline in 2007. The American Society of Colposcopy and Cervical Pathology (ASCCP) guideline 2007 for management of preinvasive disease of cervix is simplified and more conservative than the previous one. The screening program for detection of preinvasive disease and prompt treatment of its abnormal result yield good results in secondary prevention of cervical cancer.

In the low resource setting, Visual Inspection of Acetic acid or VIA is a simplified novel screening tool for cervical cancer screening. It aims for increase the screening coverage. This model handles by well-trained nurses. In one VIA setting requires only a report form or registers to record the results, an examination table that enables the woman to position herself so that the examiners can insert a speculum and view the cervix, adequate light source (halogen torch or flashlight), an instrument tray, cotton swabs, a vaginal speculum that can be locked open, leaving the examiner's hands free to adjust the light and swab the cervix, new examination gloves or high-level disinfected surgical gloves and 3% to 5% acetic acid (white table vinegar) solution. When the abnormal lesions (which are not suspected cancer) are seen, cryotherapy has been use for treatment option on the same visit. If cervical cancer was suspected, that patient was refer to the province hospital for further treatment. In 2010, there are 26 provinces in Thailand running the VIA screening program. The coverage population is increased from 10 to 30 percent.

For tertiary prevention, there are many advanced cervical cancer treatment modalities for better outcomes and lower morbidity.

Novel treatment options

Pretreatment evaluation

In developed countries, not only the imaging tools such as computerized tomography scan (CT scan) or Magnetic Resonance Image (MRI) but also the surgical staging such as laparoscopic surgery which are the investigational tools have been purposed as pretreatment evaluation in the disease extension. In 2006, the gynecologic oncology unit, obstetrics and gynecology department and the radiation oncology unit, radiology department of Ramathibodi Hospital stated an update guideline in cervical cancer treatment. The guideline recommends the CT scan instead of the intravenous pyelography as a tool for pretreatment evaluation for cervical cancer treatment. Although it does not include in the clinical staging tools for cervical cancer by the international federation of gynecologists and obstetricians (FIGO), the result of CT scan does help in the treatment plan.

Surgery

The ideal treatment for an early carcinoma of cervix (FIGO stage IA to IB1) is surgery alone. This therapy is effective, rapid, low morbidity and preserves ovarian function. To reduce the morbidity from pelvic nerve injury, the nerve-sparing radical hysterectomy was effectively demonstrated in small sized tumor. The women who desire for fertility function, radical trachelectomy reported the new fertility-sparing technique for cervical cancer treatment. The laparoscopic radical hysterectomy is appealing because it may lead to less blood loss, improved cosmetic results, shorter duration of hospitalization and faster recovery. In some hospital, laparoscopic robotically assisted radical hysterectomy is an optional treatment for the early stage cervical cancer patients.

Radiation therapy

Radiation therapy (RT) has been the cornerstone of treatment for cervical cancer since its inception as a treatment modality. Treatment consists of external beam radiation followed by intracavitary sources. The effectiveness of radiation for cervical cancer is due, to a large degree, to the ability of radiation oncologists to deliver high doses of radiation to the tumor and minimal doses to surrounding normal tissues based on the unique anatomy of the genital tract. The radiation therapy fails to achieve tumor control in 20 to 65% of patients with advanced or locally advanced cervical cancer.

Concomitant use of chemotherapy and radiation has been studied extensively by the Gynecologic Oncology Group (GOG) and results of five randomized studies have been reported[2,3]. The concept of chemoradiation encompasses the benefits of systemic chemotherapy with the benefits of regional radiation therapy. Additionally, the use of chemotherapy to sensitize cells to radiation therapy has been shown to improve local-regional control. The results of these trials showed statistically significant improvement in progression-free survival and overall survival. These new results have changed the way cervical cancer is treated in many medical centers.

Southwest Oncology Group (SWOG) Protocol 8797/Gynecologic Oncology Group (GOG) Protocol 109 addressed the role of adjuvant RT and chemotherapy (CT) after radical hysterectomy and lymphadenectomy[4]. This study evaluated women, found to have positive pelvic lymph nodes and/or microscopic involvement of the parametrium and/or positive surgical margins, who were randomly allocated to receive either pelvic RT alone or RT in combination with CT (intravenous bolus cisplatin 70 mg/m^2 and a 96-hour infusion of fluorouracil 1,000 mg/m^2 every three weeks for four cycles). The results of this clinical trial demonstrated that progression-free survival and overall survival were significantly improved with the addition of CT (hazard ratio 2.01, P=0.003 and 1.96, P=0.007, respectively). Cisplatin administered weekly for six weeks at a dose of 40 mg/m^2 (maximum of 70 mg) has become standard when radiation is administered to women with large or locally advanced tumors (stage IB2 - IVA) when surgery is not feasible.

Chemotherapy

• Neoadjuvant chemotherapy

In a recent Cochrane meta-analysis evaluating neoadjuvant chemotherapy plus surgery versus surgery alone, progression-free survival was significantly improved with neoadjuvant chemotherapy. However, there was no overall survival benefit (HR=0.85, 95% confidence interval=0.67 to 1.07, p=0.17) (5). Similarly, a meta-analysis evaluating individual patient data comparing neoadjuvant chemotherapy before RT compared to RT alone from 18 trials showed that survival may be jeopardized unless a quick, dose-dense chemotherapy schedule is used[6].

• Chemotherapy for advanced disease

There is still no optimal chemotherapy regimen in treatment of advanced stage or persistent or recurrent cervical cancer. Most of the regimens used in recent clinical practice are ongoing trials. The standard regimen has been systemic cisplatin at 50 mg/m^2 administered every 3 weeks. This regimen has yielded response rates in the range of 18 to 21% with a median survival of 8 to 9 months. Adding paclitaxel, doubling the cisplatin dose, or adding ifosfamide all have been shown by the GOG to increase response rates but not to a degree that results in prolongation of survival. The combination of paclitaxel and cisplatin was generally felt to be the most active regimen of these 3 choices increasing the response rate to 37% as well as prolonging the progression-free survival[7]. However, because of the lack of a clear survival advantage, increased neuropathy, increased cytopenia and associated

alopecia, this combination can not be routinely recommended.

Recently, the GOG reported a randomized phase III Trial of cisplatin versus cisplatin plus topotecan in the treatment of stage IVB, recurrent or persistent carcinoma of the cervix. This study was the first to show that adding a second drug to the standard regimen of single agent cisplatin 50 mg/m^2 administered every 3 weeks resulted in a highly significant prolongation of survival (9.4 versus 6.5 months, p=0.017)[8]. In addition, this combination was found to be well tolerated and not associated with a decrease in quality of life[9].

Other cisplatin containing doublets have shown promising activity in phase II trials. Significant activity of carboplatin containing regimens have been reported, however, it is generally recognized that these regimens are inferior to cisplatin containing regimens based on prior GOG studies. Cisplatin containing doublets are the standard of care in the setting of recurrent cervical cancer. Cisplatin doublets with gemcitabine and vinorelbine are currently being compared to topotecan within the GOG (Protocol 204)[10]. This four arm study also includes a paclitaxel containing doublet.

In summary, surgery is ideal for young healthy women with small lesions. Occasionally, radiation, usually with chemotherapy, is recommended if high risk factors are discovered intra-operatively. Larger tumors are treated without surgery using a combination of radiation (external and internal therapy) and weekly cisplatin chemotherapy. Finally, for those with recurrent, metastatic or widespread lesions (stage IVB) participation in the four arm GOG protocol 204 is recommended.

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