Cervical Cancer
Clinical Review and Update
Gynaecologic Oncology Tumour Group, NCIS-NUHS

Cervical cancer is the major cause of gynaecologic cancer deaths worldwide, with almost half a million new cases diagnosed each year. In Singapore, about 200 women are diagnosed with cervical cancer each year. This review will provide a quick update on cervical cancer for the busy general practitioner.

Epidemiology
The reported incidence rates of cervical cancer in developing countries are much higher than those in developed countries. In Singapore, the incidence rate has consistently declined over the last four decades; the age-standardised rate was 18.1 per 100,000 between 1968 and 1972, compared to 8.5 per 100,000 between 2004 and 2008. It now ranks as the 7th commonest cancer amongst Singapore women and the 3rd commonest gynaecologic cancer after uterine and ovarian cancers [Table 1]. The peak incidence in Singapore appears to be between 55 and 70 years of age. Indian women have a substantially lower risk (30%) compared to Chinese [Table 2]. During the period 2004-2008, 388 women died from cervical cancer, and this constituted 4% of all cancer deaths in women.

Prevention
Almost 100% of cases of cervical cancer have been attributed to oncogenic Human Papilloma Virus (HPV) infection, of which types 16 and 18 account for up to 70% of all cervical cancers. Oncogenic HPV is also implicated in the development of other cancers, including neoplasms of the vulva, vagina, anus, penis, as well as of the head and neck. HPV types 6 and 11, though non-oncogenic, account for 90% of genital warts. Currently, two vaccines are available in Singapore: Gardasil® and Cervarix®. Gardasil® is licensed for use in girls and women aged nine to 26 years, whereas Cervarix® is licensed for girls and women aged 10 to 25 years. The efficacy for both

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No</th>
<th>%</th>
<th>CR (95% CI)**</th>
<th>ASR (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>7,160</td>
<td>29.2</td>
<td>80.5 (78.7-82.4)</td>
<td>59.5 (58.1-60.8)</td>
</tr>
<tr>
<td>2</td>
<td>Colo-rectum</td>
<td>3,579</td>
<td>14.6</td>
<td>40.3 (38.9-41.6)</td>
<td>29.3 (28.4-30.3)</td>
</tr>
<tr>
<td>3</td>
<td>Lung</td>
<td>1,948</td>
<td>8.0</td>
<td>21.9 (20.9-22.9)</td>
<td>16.0 (15.3-16.7)</td>
</tr>
<tr>
<td>4</td>
<td>Corpus uteri</td>
<td>1,434</td>
<td>5.9</td>
<td>16.1 (15.3-17.0)</td>
<td>12.2 (11.5-12.8)</td>
</tr>
<tr>
<td>5</td>
<td>Ovary</td>
<td>1,403</td>
<td>5.7</td>
<td>15.8 (15.0-16.6)</td>
<td>12.3 (11.7-13.0)</td>
</tr>
<tr>
<td>6</td>
<td>Lymphoid neoplasms</td>
<td>1,012</td>
<td>4.1</td>
<td>11.4 (10.7-12.1)</td>
<td>10.0 (9.4-10.7)</td>
</tr>
<tr>
<td>7</td>
<td>Cervix uteri</td>
<td>1,001</td>
<td>4.1</td>
<td>11.6 (10.6-12.0)</td>
<td>8.5 (7.9-9.0)</td>
</tr>
<tr>
<td>8</td>
<td>Skin (Incl. Melanoma)</td>
<td>941</td>
<td>3.8</td>
<td>10.6 (9.9-11.3)</td>
<td>7.5 (7.1-8.0)</td>
</tr>
<tr>
<td>9</td>
<td>Stomach</td>
<td>932</td>
<td>3.8</td>
<td>10.5 (9.8-11.2)</td>
<td>7.4 (7.0-7.9)</td>
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<tr>
<td>10</td>
<td>Thyroid</td>
<td>702</td>
<td>2.9</td>
<td>7.9 (7.3-8.5)</td>
<td>6.2 (5.7-6.7)</td>
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<tr>
<td></td>
<td>Others</td>
<td>4,385</td>
<td>17.3</td>
<td>4,385</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Sites</td>
<td>24,498</td>
<td>100.0</td>
<td>275.6 (272.1-279.0)</td>
<td>206.7 (204.1-209.4)</td>
</tr>
</tbody>
</table>

*CR, Crude rate per 100,000 per year
** ASR, Age-standardised rate per 100,000 per year. ASR derived by the direct method using the "World Population".
vaccines has been demonstrated in large Phase III randomised controlled trials involving healthy young women. The vaccines are highly efficacious against HPV 16/18-related pre-cancerous lesions. However, long-term efficacy is still being evaluated. Both vaccines are generally safe and well tolerated and no serious adverse events have been documented. Local side effects such as pain, swelling, itching and redness at the site of injection are common.

Guidelines on the clinical use of HPV vaccines in Singapore have been recently published through a joint statement of the Society for Colposcopy and Cervical Pathology of Singapore (SCCPS), Obstetrical and Gynaecological Society of Singapore (OGSS) and the College of Obstetricians and Gynaecologists, Singapore (COGS). The key recommendations are as follows:

HPV vaccination is recommended for girls and women aged between nine and 26 years. For maximal benefit, the vaccine should be given before the onset of sexual activity, as it does not protect against pre-existing HPV infections. However, sexually active women can be vaccinated. However, as women who are sexually active are at risk of HPV infection, these women should be advised that the vaccine may be less effective compared to women who have had no previous HPV exposure at the time of vaccination. If infected by one HPV type, vaccination confers protection against other HPV types for which the patient has not been exposed to. Testing for HPV DNA is not necessary prior to vaccination.

The HPV vaccine is not a substitute for cervical cancer screening. It must be emphasised that women aged 25 years and above, who are sexually active or who have ever had sex, must continue with pap smear screening once every three years, regardless of their HPV vaccination history.

Women with current HPV infection, current cervical intraepithelial neoplasia (CIN) or previously-treated CIN can be given the HPV vaccine. However, these women must be informed that the HPV vaccine is not therapeutic for existing infection or CIN, and that the benefits of the vaccination may be limited to the prevention of future HPV infection.

Vaccination can be given to women who are immunocompromised e.g., those who are on steroids or have HIV infection. However, these women should be informed that their immune response to the vaccine may be lower compared to immunocompetent women.

HPV vaccine is not recommended for use in pregnancy. Women who become pregnant before completing the vaccination schedule should defer the subsequent doses until the pregnancy is completed. There is no need to restart the entire vaccination schedule but there should not be a delay of more than 12 months between the 2nd and 3rd dose. Lactating women can be vaccinated. The HPV vaccine is an inactivated vaccine which does not contain a whole virion, hence it does not affect the safety of breastfeeding for mothers or infants. Males can be vaccinated on request. Early data from a phase III double blind randomised study involving males aged 16 to 26 years show that the Gardasil® vaccine can protect men against genital warts. The possibility that this vaccine also protects men from penile pre-cancers or HPV-related cancers, like anal and penile cancers, is still being evaluated.

Surgery

Early stage cervical cancers may be treated by radical hysterectomy and pelvic lymphadenectomy, or by primary pelvic radiotherapy, with equal survival outcome. Locally advanced cervical cancer is treated with pelvic radiotherapy and concurrent chemotherapy.

The development of laparoscopic equipment in recent years has made minimally invasive surgery feasible in the surgical management of cervical cancer. Compared to open surgery, it is associated with decreased blood loss, analgesic requirements, and reduced length of hospital stay, as well as with improved cosmesis and faster return to normal function. Radiation or chemotherapy can also be initiated earlier after surgery.

However, the technical drawbacks of conventional laparoscopic instruments, such as its limited range of motion and poor surgeon ergonomics, have limited its adoption in complex procedures due to the long learning curve. The advent of robotic-assisted laparoscopy appears to overcome these limitations with its seven degrees of intra-abdominal instrument articulation [Figure 1], three-dimensional vision, motion...
The da Vinci® Surgical System (Intuitive Surgical, Sunnyvale CA) is the robotic surgical system that has been approved by the FDA for gynaecologic and other surgical procedures. Due to its advantages and shorter learning curve, robotic surgery is increasingly being adopted for radical hysterectomy, radical parametrectomy, radical trachelectomy, pre-radiation nodal dissection and even in pelvic exenteration for cervical cancer. Preliminary experience suggests a similar short-term oncological outcome in patients undergoing robot-assisted radical hysterectomy. A prospective multi-institutional randomised trial comparing open versus laparoscopic or robot-assisted radical hysterectomy for early-stage cervical cancer is presently underway to establish if the robotic surgical platform should be the standard approach in the surgical management of patients with early stage cervical cancer.

**Radiotherapy**

In locally advanced cervical cancer, pelvic radiation is delivered via external beam radiation to the whole pelvis, followed by brachytherapy which delivers a high dose of radiation to the central part of the tumour, sparing the nearby vital organs like the bladder and rectum due to a rapid fall off in radiation dose circumferentially. Such a good therapeutic ratio is not practically achievable even with the most sophisticated external beam radiotherapy alone such as IMRT, Tomotherapy or Cyberknife.

In large tumours extending to the parametrium or pelvic side wall, the challenge is in the delivery of a sufficiently high dose of radiation without compromising the nearby organs at risk. Conventionally, CT imaging has been used in radiation planning for brachytherapy, which is delivered using conventional metal tubes and ovoids.

Today, state-of-the-art radiation planning for brachytherapy utilises MRI, which remains the gold standard for soft tissue imaging. MRI has a significant advantage over CT in soft tissue delineation of the cervical tumour and uterus with clear demarcation of bladder and rectum in normal and pathological states [**Figure 2**]. The conventional metallic Fletcher applicators are replaced with the new Vienna Ring applicator [**Figure 3**] which is MRI-compliant and optimises the dosimetry to bulky tumours during intracavitary and interstitial radiation.
Along with the hardware innovation, new computerised software assists in planning radiotherapy to enable accurate dosimetry calculation in three dimensions and improve actual dose delivery to the tumour and normal organ at risk to prevent long-term radiotherapy damage. The volume-based calculation gives a better estimation in three dimensions rather than a two dimensional point-based calculation. In the best centres, this new innovation in brachytherapy has advanced the disease control rates of bulky cervical cancers from 67% to 90%.²

Chemotherapy
The majority of cervical cancers seen are locally advanced at presentation. The value of adding cisplatin or cisplatin-based chemotherapy to radiation for the treatment of locally advanced cervical cancer is strongly supported by randomised studies and meta-analyses. In 2000, the National Cancer Institute issued a Clinical Alert advising that concurrent chemotherapy be incorporated into the treatment programme of women with cervical cancer scheduled to receive definitive pelvic radiotherapy. The adoption of this new standard has improved overall survival and decreased the recurrence rate by 50%. However, the prognosis is very poor for patients who do relapse, as therapy in this setting is palliative in nature. Effective cytotoxic treatment options for advanced cervical cancer are exceedingly limited. Recent results from the GOG (Gynecologic Oncology Group)-204 study demonstrated that cisplatin-doublets with paclitaxel, vinorelbine, gemcitabine or topotecan only produce similar median survival rates of less than a year, with different toxicity patterns.³

In recent years, significant improvements in our understanding of the altered molecular events in tumour cells have led to the discovery of new targets and agents for clinical testing. The role of targeted therapies both in locally advanced and advanced disease is promising, but still at an investigational stage. Two monoclonal antibodies, cetuximab, which targets epidermal growth factor receptor (EGFR), and bevacizumab, which target the vascular endothelial growth factor (VEGF) signaling pathway, are being evaluated as monotherapy and in combination with other agents and/ or radiotherapy for the treatment of cervical cancer. In addition, VEGF receptor tyrosine kinase inhibitors, such as sorafenib and pazopanib, are being studied in phase I/II clinical trials. It is imperative that novel regimens continue to be evaluated for the treatment of advanced cervical cancer.

Due to its advantages and shorter learning curve, robotic surgery is increasingly being adopted for radical hysterectomy, radical parametrectomy, radical tracheectomy, pre-radiation nodal dissection and even in pelvic exenteration for cervical cancer.

References

A/Prof Jeffrey Low completed his subspecialty fellowship in Gynaecologic Oncology in 1999. He presently leads the Gynaecologic Oncology Tumour Group (GOTG) at the National University Cancer Institute, Singapore (NCIS). The GOTG is a multidisciplinary group of clinicians, nurses, scientists and allied healthcare professionals committed to the prevention, treatment, management and wellbeing of women with gynaecologic cancers. A/Prof Low is also Head and Senior Consultant of the Division of Gynaecologic Oncology in the Department of Obstetrics & Gynaecology (O&G) at the National University Hospital. His special interests are in cancer surgery, robotic surgery and ovarian cancer research.

Dr Choo Bok Ai graduated from the University of Aberdeen in UK and obtained his postgraduate internal medicine qualification (MRCP) from the Royal College of Physician of London in 2002. He completed his clinical oncology specialist training in 2007 and currently a Fellow of the Royal College of Radiologist UK. Dr Choo currently practises as a Consultant in Radiation Oncology at the National University Cancer Institute, Singapore (NCIS). His interests include IMRT and advanced image guided brachytherapy in breast and gynaecological cancers.

Dr Lim Yi Wan graduated from the University of Cambridge, England and obtained her postgraduate qualification (MRCP) from the Royal College of Physicians (UK) in 2001. She completed her advanced specialty training in Medical Oncology in 2007. Dr Lim currently practices as a consultant medical oncologist at the Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS). Her main interest is in gynaecologic oncology.