EARLY STAGE CERVICAL CANCER

Executive Summary

Cervical Cancer is a pathology with a great impact in developing countries due to the limited economic resources, screening opportunities, health services access, medical treatments and monitoring difficulties. The incidence of cervical cancer is 14 per 100,000 inhabitants and a mortality rate of 6.8 per 100,000 inhabitants; 87% of these deaths occur in developing countries, Africa being the country with the highest incidence.

The available evidence shows that virtually all cases of invasive cervical cancer arise from persistent infection by high risk serotypes of human papilloma virus (HPV). According to the World Health Organization (WHO) there are 3 categories of invasive cervical carcinoma: squamous, adenocarcinoma and other epithelial tumors. The most common histological type is squamous, representing a 70 - 80% of the cases, followed by adenocarcinoma 10-15%.

The staging of invasive cervical cancer is clinical. This is in part due to the increased prevalence of cervical cancer in resource-limited settings, where highly technical imaging studies and other assays may not be readily available. The FIGO (International Federation of Gynecology and Obstetrics) staging is as follows: Stage I tumors are confined to the cervix. Stage II tumors extend beyond of the cervix without involving the pelvic walls; Stage III denotes extension to the pelvic walls, which may cause hydronephrosis, or vaginal lower third invasion of the lower third of the vagina. Stage IV denotes cancer that is distantly metastatic or invades the ladder or rectal mucosa. Some authorities recommend surgical staging of cervical cancer through regional lymphadenectomy, however, this intervention has not been proven to improve survival and is generally not recommended outside the setting of clinical trials.

The stage specific five-year survival rates reported by the Cancer Joint American Committee (CJAC) for 2000-2002 are 60 to 93% to 5 years for early stages of disease (FIGO stages IA, IB1 or IIA1), 16 to 58 %,for locally advanced stages (FIGO stages IB2,IIA2, IIB, IIIA,IIIB or IVA) and) 15% for advanced stages (FIGO stage IVB).

Survival from early stage cervical cancer appears comparable for patients treated either with surgery or with radiotherapy. Most patients with smaller tumors are treated with primary surgery. Acceptable treatment options for early stage cervical cancer include the following:

Stage IA1
- Cervical conization, or total hysterectomy, or cervical brachytherapy (this is often considered in patients at high risk for surgical complications).
Stage IA2
- Total hysterectomy plus pelvic lymphadenectomy.
- Teletherapy plus brachytherapy if there is a high surgical risk.
- Teletherapy plus brachytherapy (70-80 GY to point A), if there is a high surgical risk.

Stage IB1 - IIA1
- Radical hysterectomy + pelvic lymphadenectomy
- External radiation therapy + brachytherapy (80-85 GY to point A), + Concurrent chemotherapy with cisplatin.
- Radical hysterectomy and lymphadenectomy can be done by laparoscopic methods.

Surgical Management:
Patients with stage IA1 or IA2 who have lymphatic or vascular space invasion (LVSI) are treated with radical surgery and lymphadenectomy. Further, preservation of normal appearing ovaries is a reasonable option in patients undergoing surgery for early stage cervical cancer. Where it is available, fertility sparing surgery appears to be a safe and reasonable option for selected patients with early stage cervical cancer.

Patients who undergo surgery for early stage cervical cancer are assigned to low, intermediate or high risk for recurrence according to pathologic criteria:

Intermediate risk (risk of recurrence and death up to 30% after surgery alone):
- Presence of LVSI plus deep one third stromal invasion and tumor of any size
- Presence of LVSI plus middle one third stromal invasion and tumor size $\geq$ 2 cm
- Presence of LVSI plus inner one third stromal invasion and tumor size $\geq$ 5 cm
- No LVSI but deep or middle 1/3 stromal invasion and tumor size $\geq$ 4 cm

High Risk (risk of recurrence and death of up to 50% after surgery alone):
- Positive surgical margins
- Pathologically confirmed involvement of the pelvic lymph nodes
- Microscopic involvement of the parametrium

Public Health Relevance

GLOBOCAN indicates that global cervical cancer prevalence in 2012 was 1,547,000 and labels it as the fourth most common cancer in women (1). There were an estimated 528,000 new incidences in 2012. About 85% (444,300) of all new cases in 2012 occurred in less developed regions, and the remaining 15% (83,000) occurred in more developed regions. Highest-risk regions include Eastern and Middle Africa. Cervical cancer is highly preventable and treatable, if detected in early states. GLOBOCAN estimated that in 2012 there were 266,000 deaths from cervical cancer. 87% of deaths (8.3 with an ASR per 100,000) occurred in less developed regions. While GLOBOCAN does not provide specifics about early stage cervical cancer, the data do suggest that overall cervical cancer disproportionately impacts less developed regions.
Requirements for diagnosis, treatment, and monitoring

**Diagnostics:** The diagnosis of cervical cancer is based on direct tissue biopsy. This can usually be done by vaginal exam in an outpatient setting without anesthesia.

**Histology:** The diagnosis of invasive cervical cancer can be made by a pathologist based on haematoxylin and eosin stains.

**Imaging:** Invasive cervical cancer is a clinically staged disease. Evaluation of the bladder and rectum by use of cystoscopy and proctoscopy is advised when available. IVP is recommended for patients at risk for ureteral obstruction; at many centers CT or MR is now substituted for this evaluation. CT can be useful to evaluate tumor size, correlation with anatomic structures, metastases and nodal involvement. Nuclear magnetic resonance gives high resolution of soft tissues particularly for the cervix, parametrial invasion, bladder or rectal invasion, ureteral obstruction, lymph node enlargement. PET-CT in particular allows for increased sensitivity in assessing lymphatic invasion. Though not part of the clinical staging, evaluation for regional or distant metastases using CT, MR or PET/CT may help guide treatment planning, Routine imaging is not recommended for patients who have completed primary therapy.

**Administration and Care of Patients:** The administration of chemotherapy with a platinum base requires that the patient to have regular access to clinical care and adequate venous access. In developed countries administration is usually done in outpatient centers, although in another environment, Patients can be treated in inpatient facilities. Patients should be encouraged to increase fluid intake from the day before to the treatment. A minimum of 500ml of normal saline should be administered intravenously one hour before cisplatin. Cisplatin doses of 40 mg/m2 should be diluted in normal saline and infused at a rate of 1 mg/min. Due to the risk of dehydration and renal toxicity, IV hydration is highly recommended both pre- and post-chemotherapy. Many physicians administer 500-1000ml or more normal saline intravenously as post-hydration in this setting. Cisplatin is administered the first day of the external radiotherapy, preferably 4 hours before the radiotherapy and repeated weekly for 4-6 cycles of treatment.

**Overview of Regimens**

**Standard Regimens**

Cisplatin 40 mg/m² (maximum dose 70 mg) administered 1 mg/min, 6 Cycles, q week, on Days 1, 8, 15, 22, 29, 36.

**Prescription:** Cisplatin, available in vial of dry powder of 10 and 50 mg.

**Adverse effects:** leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, otoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, ocular toxicity and allergic reactions.
**Postoperative radiotherapy:** Patients with prognostic factors high risk for relapsing
- Pelvic lymph nodes involved.
- Microscopic tumor involvement of the section lines.
- Microscopic tumor involvement, lower than 3 mm to the section line.
- Deep stromal invasion, more than the 50%.
- Lymphatic invasion.
- Vascular invasion.
- Cervical Cancer handled with no surgical oncology.
- Parametrial commitment.

**RADIOTHERAPY:** Radiotherapy planning involves simulation or evaluation of tumor burden with the imaging using the radiotherapy treatment unit or X-ray equipment. Radiation therapy is applied using the four fields technique.

**Anterior and posterior areas:**
- Upper limit: the gap between L4-L5. In patients with histerolinfadenectomía in absence of nodal involvement, the limit may be reduced to L5 - S1.
- Lower limit: the lower edge of the obturator foramina lateral limits: 2 cm outside the bone pelvic wall, according to the parametrial involvement.

**Lateral fields:**
- Anterior limit: middle portion of the pubic symphysis.
- Posterior limit: S2-S3 (rectal half).
- Upper and lower limits: the same limits are preserved of anterioposterior fields.

**Pelvic area with central protection:**
For overprint from 4500 - 5040 cGy, protecting the medium line with a rectangular lead of 4 x 10 cm.

**Teletherapy:** megavoltage energy is used (cobalt or accelerator). White volume: the tumor volume is included along with pelvic nodal disease. Two to four fields are used (antero - posterior and/or laterals). Therapy involves 180 cGy – 200 cGy fractionation for five times a week to complete a cumulative dose of 4400 – 5040 cGy.

**Brachytherapy:** It can be administered by intrauterine catheter, ovoid or intravaginal cylinder and a low or high dose rate can be used. Isotopes used include: 226-Radium, 137-Cesium, and 192-Iridium.
Review of Benefits and Harms

Benefits
Peters 2000/GOG protocol 109: In this study, 268 patients at high risk for recurrence after radical surgery for stage IA2, IB or IIA disease were randomized to receive pelvic radiotherapy or pelvic radiotherapy plus four cycles of chemotherapy with cisplatin and 5-fluorouracil. Twenty-five patients (9%) were considered ineligible; 243 patients were evaluated: 116 in the radiotherapy arm and 127 in the radiotherapy and chemotherapy arm. Patients were enrolled between 1991 and 1996. The average length of follow up was 42 months. Compared to patients treated with RT and chemotherapy, patients treated with RT alone were found to have lower progression free survival at four years (63 vs. 80%), lower overall survival at four years (71 vs. 81%), and decreased grade 3 or 4 toxicity.

Studies of chemo-radiotherapy in the setting of patients at moderate risk for recurrence, such as GOG 263, are ongoing. Outside of the setting of a clinical trial, most of these women are treated with radiotherapy alone.

Harms and Toxicity Considerations

General
Based on GOG 109, treatment of women at high risk for recurrence after surgery for early stage cervical cancer is recommended. Due to the increased toxicity of chemotherapy and a lack of proven benefit, women at intermediate risk for recurrence are treated with radiotherapy alone. In addition, based on trials involving women treated primarily with radiotherapy and chemotherapy for advanced stage disease, treatment with cisplatin alone can be recommended to reduce the toxicity seen with the addition of 5-fluorouracil.

Common
Cisplatin is highly emetogenic, prophylactic antiemetics are necessary to reduce nausea and vomiting in all patients.2 Mild peripheral neuropathy is common with cisplatin. Patients should be followed carefully and dose reduction or discontinuation may be required for moderate or severe symptoms. Ototoxicity is observed with cisplatin and is more common with increasing dose and number of cycles. Audiometry should be considered to monitor patients with toxicity; vestibular defects are less common.

Serious
Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Hypomagnesemia, hypocalcemia and hypokalemia should be followed and deficits repleted. Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity.3
Systematic Reviews


**Background:** Treatment with weekly cisplatin (CDDP) plus radiotherapy (RT) is the standard regimen for stage IB to stage IVA cervical carcinoma (CC). We performed a systematic review and meta-analysis of published studies to evaluate whether CDDP-based doublet therapy improves survival compared to weekly CDDP plus RT in patients with CC. **Materials and Methods:** We conducted a systematic search for randomized and nonrandomized studies in PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Register of Controlled Trials. We then carried out a meta-analysis by using the fixed- or random-effects models. The primary endpoints were overall survival (OS) and progression-free survival (PFS), reported as odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** Four randomized trials and 4 retrospective studies that included a total of 1500 patients matched our selection criteria. Meta-analysis showed that for locally advanced CC, concurrent RT and with CDDP-based doublet chemotherapy significantly improved the OS (OR, 0.65; 95% CI, 0.51-0.81; p=0.0002), PFS (OR, 0.71; 95% CI, 0.55-0.91; p=0.006), and rate of locoregional relapse (OR, 0.64; 95% CI, 0.47-0.89; p=0.008), compared to RT with concurrent weekly CDDP alone. **Conclusions:** In patients with CC, platinum-based doublet chemotherapy plus concurrent RT was associated with improvements in the OS and PFS of 35% and 30% patients, respectively, compared to RT plus weekly CDDP. Therefore, platinum-based combination therapy plus RT should be the preferred treatment over weekly CDDP plus RT for stage IB-IVA CC.


**Background:** Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. A woman's risk of developing cervical cancer by 65 years of age ranges from 0.69% in developed countries to 1.38% in developing countries. Although screening by Pap smear should mean early detection at a curable stage for most women, many still present with advanced or metastatic disease with a worse prognosis. The addition of platinum-based chemotherapy to radiotherapy has improved outcome compared to radiotherapy alone; however, 30% to 50% fail to respond to treatment or develop recurrent disease. There are no standard treatment options for these patients, although platinum-based chemotherapy is frequently used and trials are on-going. **Objectives:** To compare different types and combinations of cytotoxic chemotherapy for the treatment of metastatic/recurrent cervical cancer. **Search Methods:** We searched the Cochrane Gynaecological Cancer Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2012), MEDLINE (1950 to January 2012) and EMBASE (1980 to January 2012). The reference lists from these and those of review articles were also checked. **Selection Criteria:** All randomised controlled trials (RCTs)
involving chemotherapy for metastatic/recurrent cervical cancer. Trials involving radiotherapy, chemoradiotherapy, intra-arterial chemotherapy, biological agents or immunomodulators were excluded.

**Data Collection and Analysis:** Three review authors independently reviewed trials for inclusion and data extraction and assessed risk of bias. **Main Results:** There were no data comparing best supportive care with chemotherapy. Cisplatin-based regimens are the most widely used and therefore we have concentrated on these trials. In terms of response rates some non-platinum regimens are equivalent but toxicity is higher. The most common cisplatin regimen was 50 mg/m² day 1 q21days. Higher doses had similar survivals. There was no direct comparison between single-agent cisplatin and carboplatin. Overall survival (OS) and progression-free survival (PFS) were not adequately reported and quality of life (QoL) outcomes were incompletely documented. Combination regimens were more toxic than single agents, but in the limited reported data this did not appear to adversely affect QoL. No significant difference in response rate by site of recurrence was found, although there was a trend towards improved response when the main site of disease was beyond the previously irradiated pelvis. **Authors’ Conclusions:** Combination cisplatin-based chemotherapy could be a viable option for patients of good performance status with recurrent/metastatic cervical cancer, but further trials that report adequate survival and QoL data are sought. Response rates and improvements in survival are low. Cisplatin-based combinations have significant toxicity. Outcomes are poor and novel cytotoxic/biological agents and optimal scheduling need further investigation. Future trials need to stratify for and perform planned subgroup analysis with respect to previous treatment and site of recurrence.

**Recommendations**

The reviewers recommend the incorporation of early stage cervical cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that cisplatin be added to the core Essential Medicines List.

**Additions proposed for Section 8.2 of the EML**

Cisplatin*

*Carboplatin is currently in the WHO Essential Medicines List for Adults (2013, 18th Edition). Next to Carboplatin in the WHO List is a symbol that states that the listing of the drug indicates “similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is
generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children — see the second EMLc for details. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.” The present proposal calls for the explicit addition of Cisplatin to the EML given its distinct use in the treatment of a number of cancers.
References

Citations


Additional Literature Referenced Throughout*

*Note that the references in the present document need revisions. Please find additional literature below that has been referred to by the authors.


