Chapter 2
Cervical Cancer

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Anatomy

- Cervix (Latin for "neck") = neck of the uterus.
  - Average 2–4 cm in length and the point where the cervix joins the uterus is called the isthmus.
  - The intravaginal portion of the cervix is called the exocervix and is covered with stratified squamous epithelium identical to the lining of the vagina.
  - The stroma of the cervix consists of stratified muscle and connective tissue.
  - Blood supply to the cervix:
    - Via the broad ligament and parametrium which support the cervix laterally.

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R.N. Eskander and R.E. Bristow (eds.), *Gynecologic Oncology: A Pocketbook*, DOI 10.1007/978-1-4939-1976-5_2,

Epidemiology

- Worldwide cervical cancer remains the second most common cancer of women with a mortality rate of 52 % [1].
  - 86 % of cervical cancers are diagnosed in the developing world [1].
  - Global incidence and mortality depend on presence of screening and vaccination programs. These interventions have led to a 75 % decrease in incidence and mortality of cervical cancer in the past 50 years in developed countries [2].
- There will be 12,360 new cases of cervical cancer and 4,020 cervical cancer related deaths in the USA in 2014 [3].
- In the USA, cervical cancer is the third most common gynecologic malignancy (after uterine and ovarian cancer) and the 12th most common cancer of women.
  - The mortality from cervical cancer in the USA has declined from 15/100,000 in 1945 to 3.4/100,000 in 1991.
- Cervical cancer is the only malignancy for which the causative agent is known.
- The etiologic agent resulting in cervical cancer has been identified as a sexually transmitted oncogenic virus, human papillomavirus (HPV).
  - HPV is a circular, double-stranded DNA virus when in its' infectious state. Viral DNA integration into host DNA leads to a malignant phenotype. Once integrated, HPV E6 codes for a protein that degrades p53 and HPV E7 codes for a protein that complexes with pRB releasing transcription factor E2F causing the cell to be immortal (Table 2.1). Low risk strains of HPV (types 6 and 11) cause genital warts whereas high risk strains (types 16, 18, 31, 45, and less commonly 33, 35, 39, 51, 54, 55, 56, 58, 59 66, and 68), if integrated into host DNA, cause cervical dysplasia and cervical carcinoma (Fig. 2.1) [4].

TABLE 2.1. HPV genome.

E1	E2	E4	E5	E6	E7	L1	L2
ATPase	Regulator of E6 and E7	Disrupts cytokeratin matrix for release of virions	Potentiation of membrane bound EGF receptors	Bind and inactivate p53	Bind pRB leading to E2F activity	Major capsid (conserved)	Minor capsid (variable)

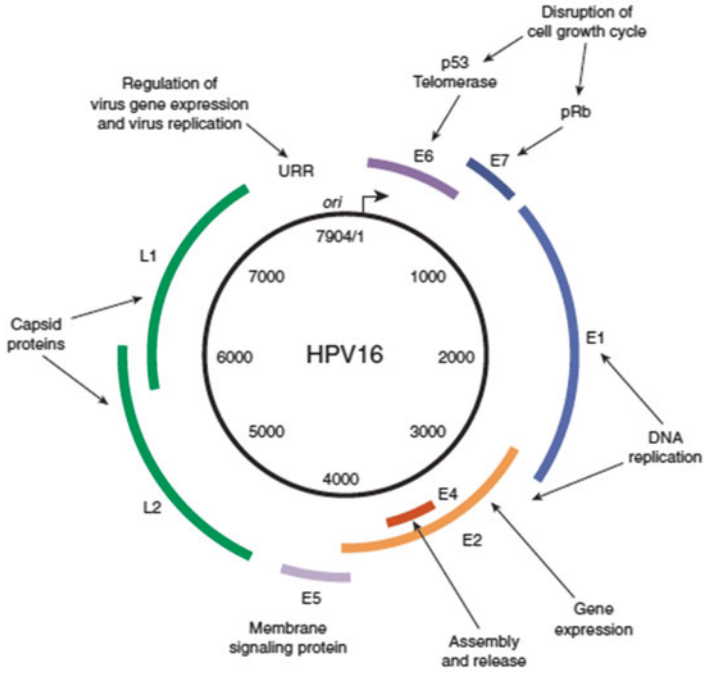

FIG. 2.1. Human papillomavirus genome [4]. Reprinted from Clinical Gynecologic Oncology, 7th Edition, Di Saia PJ, Creasman WT. Chapter 3 Invasive Cervical Cancer, Monk BJ, Tewari KS, Copyright 2007, with permission from Elsevier. Clinical gynecologic oncology by Di Saia PJ, Creasman WT. Reproduced with permission of Elsevier Mosby in the format reuse in a book/textbook via Copyright Clearance Center.

- HPV is detectable in over 95 % of squamous cell carcinomas and 30–40 % of adenocarcinomas.
- High-risk strains cause a mutation of cells in the squamocolumnar junction leading to cervical dysplasia and cancer.
- Incidence of progression without treatment:
  - CIN1 (16 %), CIN2 (30 %), CIN3 (70 %).
  - CIN3 → invasive disease: 0–20 years.

- Risk factors:
  - Lower socioeconomic status.
  - Multiple sexual partners, early age of first intercourse, promiscuous partners, co-infection with other sexually transmitted diseases.
  - Tobacco use.
  - Immunocompromised conditions (HIV or pharmacologic).
- The greatest risk for developing cervical cancer is infrequent or no prior screening.
  - In many South American, African, and Asian countries, cervical cancer is the leading cause of cancer related death in women.

Prevention

- Abstinence prevents HPV related cervical carcinomas, but the large majority of women are sexually active and therefore at risk for exposure to HPV infection.
- Two US Food and Drug Administration (FDA)-approved vaccines indicated to prevent cervical cancer (Table 2.2).
  - Quadravalent Vaccine: GARDASIL.
    - FDA approved in 2006.
    - In 2007 the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II reported results from a randomized, double-blind trial of 12,167 women aged 15–26 years who received Gardasil or placebo. For 3-year follow-up, vaccine efficacy for preventing dysplasia or invasive disease was 98 % in the per-protocol population (44 % for the intention-to-treat population).
    - FUTURE I was a phase III, randomized, double-blind, placebo-controlled trial involving 5,455 women aged 16–24 years. Vaccine efficacy for preventing anogenital warts as well as dysplasia or invasive disease associated with HPV types 16 or 18 was 100 %.

Table 2.2. HPV directed vaccines.

	Gardasil	Cervarix
HPV types	6,11, 16, 18	16, 18
Dose schedule	0.5 mL IM 0, 2, 6 months	0.5 mL IM 0, 1–2, 6 months
Indications	Cervical cancer, CIN, AIS, Vulvar cancer, VIN, Vaginal cancer, VAIN, Anogenital warts	Cervical cancer, CIN, AIS
Population approved	Males and females aged 9–26 years	Females aged 9–25 years
Advisory Committee on Immunization Practices (ACIP) recommendations	Females aged 11 and 12 years with catch-up vaccination for females aged 13–26 years. Permissive for boys aged 9–26 years	
Technology used	Yeast	Insect cell substrate
Adjuvant	Amorphous hydroxyphosphate sulfate (Merck and Co., Inc)	Aluminum hydroxide + 3 = deacetylated monophosphoryl lipid A (MPL, Coixa/GSK)

- In a double-blind, randomized trial of 3,817 women aged 24–45 years, GARDASIL efficacy against infection related to HPV-6, -11, -16, and -18 was 90.5 %.
- Merck is currently comparing the efficacy of GARDASIL to a nanovalent HPV vaccine.

– Bivalent Vaccine: CERVARIX.

- Phase II, randomized, double-blind, controlled trial known as Papilloma TRIal against Cancer In young Adults (PATRICIA) published in 2009. In this study, 18,644 women aged 15–25 years received placebo or were vaccinated with CERVARIX.
- Vaccine efficacy against HPV-16 and -18 CIN II–IIII was 92.9 %.
- Evidence of cross-protection efficacy.
- There has not been a direct head-to-head efficacy trial between GARDASIL and CERVARIX.

Diagnosis

- *First* symptom of early cervical cancer: frequently thin, clear or blood-tinged vaginal discharge usually unrecognized by the patient.
- *Classic* symptom: intermittent, painless metrorrhagia or postcoital spotting, although this is not the most common symptom.
- With progression, bleeding becomes heavier, more frequent, and ultimately continuous. Usually if this bleeding occurs in a postmenopausal woman, it leads to earlier medical attention.
- Late stage disease involves spread into the parametria or the pelvic sidewalls and causes *flank or leg pain*, which is usually a sign of involvement of the ureters or sciatic nerve. Bladder or rectal invasion frequently leads to *hematuria*, *rectal bleeding*, and possibly vesicovaginal or rectovaginal *fistula*. Lymphedema may be a sign of late stage or recurrent disease due to venous blockage from extensive sidewall disease.
- Gross clinical appearance.
  - Most common: exophytic, large, friable polypoid lesion arising from the ectocervix (Fig. 2.2). These lesions may arise within the endocervcial canal creating a barrel-shaped lesion.
    - Lesions within the endocervical canal are more commonly adenocarcinomas, which arise in the endocervical mucous-producing gland cells. Because of the origin within the cervix, the lesion may be present for longer time before it is clinically evident.
  - Firm cervix with little visible ulceration or mass.
  - An ulcerative tumor that erodes through the cervix.

Screening

- Prevention, screening, and early treatment are imperative.
- Cervical dysplasia and cancer is slow to progress, able to be diagnosed early with current screening modalities, and almost always cured when diagnosed early.

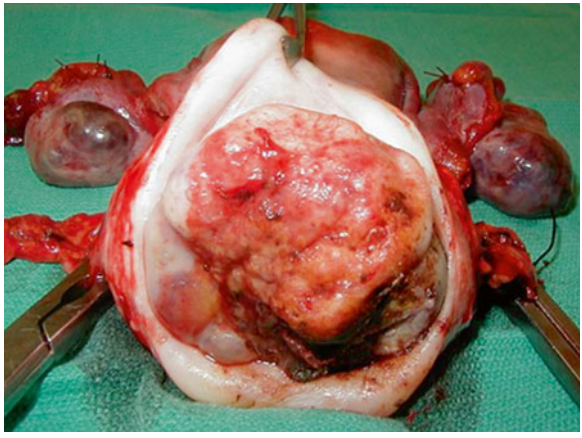

FIG. 2.2. Gross image of invasive cervical carcinoma (Image provided courtesy of Dr. Krishnansu S. Tewari).

- Late diagnosis most frequently results in incurable disease and death.
- Cytology, using the Papanicolaou (Pap) smear, and colposcopy are both valuable screening tools.
- Cervical cancer screening guidelines according to American Society for Colposcopy and Cervical Pathology (ASCCP) (Table 2.3).
- Abnormal pap smears may require further workup with colposcopy with possible need for biopsy.
- Colposcopy involves use of 5 % acetic acid applied to the cervix and inspection with a colposcope that magnifies the cervix and allows for visualization with color filters.
  - A satisfactory colposcopy requires that the entire squamocolumnar junction (SCJ) be visualized.
  - Concerning findings for which biopsy should be obtained:
    - Acetowhite changes.
    - Irregular contour.
    - Atypical vessels.
    - Coarse mosaicism or punctation.
    - Large multiquadrant lesions.

TABLE 2.3. ASCCP cervical cancer screening guidelines.

Population	Screening recommendation
<21 years	No screening
21–29 years	Cytology every 3 years without HPV testing
30–65 years	Cytology and HPV co-testing every 5 years
>65 years	No screening if negative adequate prior screening (as long as no prior history of CIN or cervical cancer)
After hysterectomy	No screening (as long as cervix removed and no prior history of CIN or cervical cancer)
After HPV vaccination	Same as unvaccinated women

TABLE 2.4. Rates of pelvic and para aortic lymph node metastases by stage [4].

Stage	Rate of pelvic lymph node metastases (%)	Rate of para aortic lymph node metastases (%)
I	15	6
II	29	17
III	47	30

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- An endocervical curettage (ECC) should be done as long as the patient is not pregnant.
- Cervical dysplasia or early invasive cervical cancer (Stage IA1) can be treated with loop electrosurgical excision procedure (LEEP) or cold knife cone (CKC).
- ASCCP guidelines (www.asccp.org) should be used to triage abnormal cytology and histology.

Pathology (Refer to Table 2.4) [4]

- There are *four main routes of spread* of cervical carcinoma:
  - Direct spread into the vaginal mucosa.
  - Spread into the myometrium, particularly with lesions originating in the endocervix.

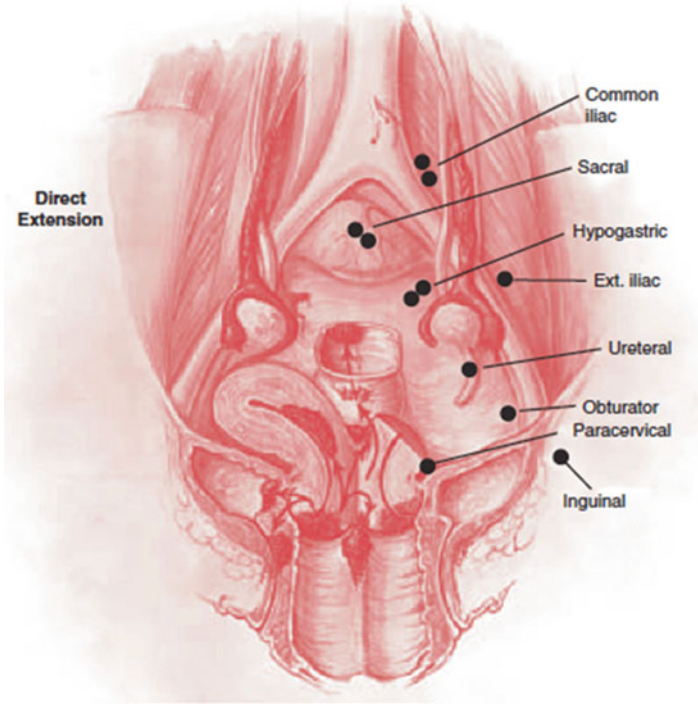

Fig. 2.3. Patterns of lymphatic spread in cervical carcinoma [4]. Reprinted from Clinical Gynecologic Oncology, 7th Edition, Di Saia PJ, Creasman WT. Chapter 3 Invasive Cervical Cancer, Monk BJ, Tewari KS, Copyright 2007, with permission from Elsevier. Clinical gynecologic oncology by Di Saia PJ, Creasman WT. Reproduced with permission of Elsevier Mosby in the format reuse in a book/textbook via Copyright Clearance Center.

- Spread into the paracervical and parametrial lymphatics and then further (primarily: obturator, hypogastric, external iliac, and sacral nodes and secondarily: common iliac, inguinal, and para-aortic nodes) (Fig. 2.3) [4].
- Direct extension into adjacent structures (parametria, bladder, bowel).

TABLE 2.5. Five-year survival according to stage and mode of treatment [5].

Stage	Surgery only (%)	Radiation only (%)	Surgery + radiation (%)
Ib1	94.5	80.1	83.6
Ib2	91.4	73.7	76.7
IIa	72.6	64.5	76.2
IIb	73.0	64.2	64.3

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- Adenocarcinomas arise from the endocervical mucous-producing glands and, because they originate within the endocervical canal, it takes longer until these tumors are clinically evident. This growth pattern results in the classic barrel-shaped cervix.
- No difference in survival between cervical adenocarcinomas and squamous carcinomas after correction for stage (see Tables 2.5 and 2.6 [5]).
  - 1998 FIGO Annual Report of over 10,000 squamous cell carcinomas and 1,138 adenocarcinomas noted no difference in survival in Stage I cancers.

Staging

- Cervical cancer is clinically staged based on (Table 2.7):
- Exam.
- CKC or LEEP.
- Imaging—CXR, IVP, CT urogram, Barium enema.
- Cystoscopy.
- Proctosigmoidoscopy.

PET/CT Staging

- In 2005 the Centers for Medicare and Medicaid Services approved coverage for FDG-PET for staging newly diagnosed and locally advanced cervical cancers and screening for cervical cancer recurrence.

Table 2.6. Histologic types of cervical cancer.

Pathology	Prevalence
Nonglandular	
Squamous cell	65–85 %
Verrucous	Rare
Sarcomatoid	Rare
Glandular	
Endocervical	10–25 %
Endometrioid	Rare
Clear cell	Rare
Mucinous	Rare
Serous	Rare
Adenoid cystic	Rare
Villoglandular	Rare
Other, mixed epithelial tumors	
Adenosquamous	5 %
Glassy cell	Rare
Small cell	Rare
Nonepithelial tumors	Rare
Carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, germ cell tumors, melanoma, lymphoma, neuroendocrine	

Table 2.7. Cervical cancer staging according to the International Federation of Gynecology and Obstetrics (FIGO) revised in 2009.

FIGO Stage	Description
0	Carcinoma in situ
Ia1	Invasion of stroma <3 mm in depth and ≤7 mm in width
Ia2	Invasion of stroma >3 mm and ≤5 mm in depth and ≤7 mm in width
Ib1	Clinical lesions greater than Stage Ia but no greater than 4 cm
Ib2	Clinical lesions confined to the cervix that are greater than 4 cm
IIa	Involvement of the upper 2/3 vagina
IIb	Involvement of the parametria without sidewall involvement
IIIa	Extension to lower 1/3 vagina
IIIb	Extension to pelvic sidewall or hydronephrosis or non-functional kidney
IVa	Extension to bladder or rectum
IVB	Distant metastasis or disease beyond the pelvis

- Sensitivity of PET in detecting pelvic nodal metastases in patients with untreated cervical cancer = 80 %, sensitivity of CT = 48 % [6].
- A 2007 meta-analysis of 41 studies concluded that PET/CT had the highest sensitivity (82 %) and specificity (95 %) for detection of positive nodes compared to CT (50 and 92 %) and MRI (56 and 91 %). PET positive nodes have been found to be a prognostic biomarker predicting treatment response, pelvic recurrence risk, and survival [6].

Genetics

- There is no known genetic basis for cervical cancer.

Indication for and Modes of Treatment (Surgery/Chemotherapy/Radiation Therapy)

- During the past several decades, staging definitions and treatment recommendations for cervical cancer have changed significantly (Table 2.8).
- First radical hysterectomy was performed by Dr. Joe V. Meigs at Harvard University in 1944.
- Morbidity: 1–5 %.
- There are five traditional classes of radical hysterectomy as described by Piver and Rutledge (Table 2.9).
- Understanding of the eight pelvic spaces is critical in the completion of a radical hysterectomy (Fig. 2.4) [4].
- Pelvic lymph node dissection boundaries:
  - Lateral—genitofemoral nerve.
  - Medial—superior vesical artery.
  - Distal—Deep circumflex iliac vein.
  - Proximal—2 cm above bifurcation of common iliac artery.
  - Inferior—Obturator nerve.
- In the hands of an experienced surgeon, complication rates are less than 5 % (Table 2.10).

Table 2.8. Treatment of cervical cancer by stage.

Stage	Standard treatment	Fertility preserving treatment
IA1, –LVSI	Extrafascial hysterectomy	Cervical cone biopsy
IA1, +LVSI	Extrafascial hysterectomy, +/– pelvic lymph node dissection	Cervical cone biopsy and laparoscopic pelvic lymph node dissection
IA2, occult IB1	Modified radical hysterectomy with pelvic lymph node dissection, +/– adjuvant therapy	Radical trachalectomy with pelvic lymph node dissection
IB1, IB2, IIA	Radical hysterectomy with pelvic lymph node dissection, +/– adjuvant therapy	Radical trachalectomy with pelvic lymph node dissection only if IB1 $\leq$2 cm, and *not* small cell histology
IB2–IVA	Chemoradiation with HDR brachytherapy +/– pretreatment laparoscopic pelvic lymph node dissection	Radical hysterectomy with lymph node dissection and adjuvant therapy only if IB2–IIA
Isolated central pelvic recurrence	If prior radiation then proceed with pelvic exenteration with urinary diversion	If no prior radiation then proceed with chemoradiation
IVB, persistent, or non-central recurrence	Cisplatin and paclitaxel and bevacizumab +/– palliative radiotherapy for bleeding or bone metastases	Cisplatin and paclitaxel and bevacizumab +/– palliative radiotherapy for bleeding or bone metastases

Table 2.9. Piver and Rutledge classification of radical hysterectomy.

Class	Description	Indication
I	Extrafascial hysterectomy	CIN, early stromal invasion
II	Removal of medial half of the cardinal and uterosacral ligaments, upper 1/3 vagina	
III	Removal of entire cardinal and uterosacral ligaments, upper 1/3 vagina	Stage Ib and IIa
IV	Removal of all the periureteral tissue, superior vesical artery, ¾ vagina	Anteriorly occurring central recurrences
V	Removal of portions of the distal ureter and bladder	Central recurrent cancer, or primary disease involving portions of the distal ureter or bladder

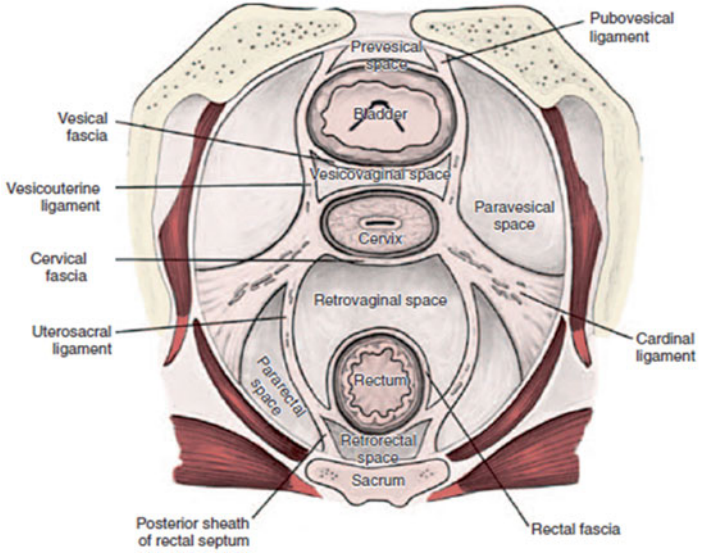

FIG. 2.4. Cross section of the pelvis to illustrate the 8 pelvic spaces [4]. Reprinted from Clinical Gynecologic Oncology, 7th Edition, Di Saia PJ, Creasman WT. Chapter 3 Invasive Cervical Cancer, Monk BJ, Tewari KS, Copyright 2007, with permission from Elsevier. Clinical gynecologic oncology by Di Saia PJ, Creasman WT. Reproduced with permission of Elsevier Mosby in the format reuse in a book/textbook via Copyright Clearance Center.

TABLE 2.10. Complications of radical hysterectomy.

Severe bladder atony	4 %
Lymphocyst requiring drainage	3 %
Ureterovaginal fistula	2 %
Thrombophlebitis	2 %
Ureterovaginal fistula	2 %
Vesicovaginal fistula	1 %
Bowel obstruction requiring surgery	1 %
Pulmonary embolus	1 %

Robotic-Assisted Surgery for the Management of Cervical Cancer

- Robotic-assisted surgery using the da Vinci surgical system is gaining momentum as the primary surgical approach to treat cervical cancer.
- Advantages:
  - 3D and magnified visualization.
  - Improved ergonomics.
  - Articulated instruments that mimic the human wrist.
  - Enhanced dexterity.
  - Tremor reduction.
  - Camera stability.
  - Steep learning curve.
- Disadvantages:
  - Increased operating time.
  - Increased cost.
  - Prolonged steep Trendelenberg.
  - Potential instrument malfunction.
- Evaluation of oncologic outcomes and cost–benefit analysis of the robotic approach is ongoing.

Ovarian Transposition

- The incidence of premature ovarian failure after pelvic radiation without ovarian transposition is high (nearly certain ovarian failure after 8 Gy single dose or 10 Gy fractionated dose).
- Ovarian transposition is an intraoperative procedure in which the infundibulopelvic ligament is mobilized and bilateral ovaries are sutured ("transposed") to the paracolic gutters. The new location of the ovaries is generally marked with staples in order to be visible on imaging and assist with postoperative radiation planning.
- Ovarian failure after transposition and pelvic radiation decreases but is still 28–50 %. If radiation is not required, risk of ovarian failure from transposition alone is 5 % [6].

Indications for Postoperative Adjuvant Therapy

- Recommendation for postoperative adjuvant pelvic radiation with or without radio sensitizing chemotherapy following radical hysterectomy is based on pathologic risk factors.
- High-intermediate risk factors (GOG 92):
  - Tumor diameter (>4 cm).
  - Depth of stromal invasion (>1/3).
  - Presence of lymphovascular space invasion.
- High-risk factors:
  - Positive margins.
  - Positive parametria.
  - Positive lymph nodes.
- A simple hysterectomy performed for a cervical cancer greater than Stage IA1 is considered a "cut through" hysterectomy and is not adequate therapy. Prognosis in this setting is poor and probability of curative radiotherapy is greatly decreased [6].

Clinical Trials Supporting Current Treatment Algorithms

Locally Advanced Cervical Cancer

- Five pivotal trials support the use of chemoradiation in locally advanced cervical cancer (Table 2.11) [7–11]:
- Radiation alone fails to control cervical cancer in 35–90 % of women with locally advanced disease [6].
- Concurrent radio sensitizing chemotherapy improves local control and often eradicates distant metastases.
- The rationale for radiosensitizing chemotherapy is based on the discovery that tumor radio sensitivity is enhanced through the formation of DNA–platinum adducts. Additionally, the addition of chemotherapy helps prevent the repair of sublethal damage in cancer tissue preferentially.

Table 2.11. Five pivotal trials supporting chemoradiation in locally advanced cervical cancer [7–11].

Trial	Eligibility	Arms	OS (months)	PFS (months)	Conclusion
GOG 109 [7]	IA2–IIA	• Adjuvant pelvic RT	71	63	Benefit of radio sensitizing cisplatin
		• Adjuvant pelvic RT + cisplatin 70 mg/m^2	81	80	
GOG 123 [8]	IB2	• Pre-op pelvic RT + cisplatin 40 mg/m^2/week	86	80	
		• Pre-op pelvic RT	72	64	
RTOG 9001 [9]	IB–IVA	• Pelvic RT + cisplatin 75 mg/m^2 + 5-FU 4 g/m^2/96 h (3 cycles)	73	67	Benefit of radiosensitizing cisplatin
		• Pelvic RT + extended field RT	58	40	
GOG 85 [10]	IIB–IVA	• Pelvic RT + cisplatin 50 mg/m^2 + 5-FU 4 g/m^2/96 h (2 cycles)	65	60	Cisplatin + 5-FU superior to hydroxyurea
		• Pelvic RT + hydroxyurea 3 g/m^2 (2×/week)	50	48	
GOG 120 [11]	IIB–IVA	• Pelvic RT + cisplatin 40 mg/m^2/week	60	60	Both cisplatin arms superior to hydroxyurea alone
		• Pelvic RT + cisplatin 50 mg/m^2 + 5-FU 4 g/m^2/96 h + hydroxyurea 2 g/m^2	58	60	
		• Pelvic RT + hydroxyurea 3 g/m^2 (2×/week)	34	45	

Table 2.12. Single agents evaluated in the treatment of advanced stage, persistent or recurrent cervical cancer categorized by trial outcome [12–23].

Positive signal[a]	Negative signal[b]
Thigpen et al. [12]: cisplatin	McGuire et al. [13]: carboplatin; iproplatin
Sutton et al. [14]: ifosfamide	Fracasso et al. [15]: oxaliplatin
Schilder et al. [16]: gemcitabine	Thigpen et al. [17]: Mitomycin-C
Bookman et al. [18]: topotecan	Look et al. [19]: irinotecan
Curtin et al. [20]: paclitaxel	Garcia [21]: docetaxel
McGuire et al. [22]: paclitaxel	
Muggia et al. [23]: vinorelbine	

[a]Agents included in subsequent combination trials given response rates
[b]Agents abandoned as single agent therapeutic options due to limited response and/or unacceptable toxicity

- The most common regimen is weekly cisplatin 40 mg/m^2 (maximum dose of 70 mg/week) given during radiation treatment.

Metastatic Cervical Cancer: Combination Cytotoxic Regimens

- In 1981 single agent cisplatin established as the chemotherapy backbone for the treatment of metastatic/advanced stage cervical cancer.
- Numerous single agent trials evaluating various agents subsequently conducted with mixed signals (Table 2.12) [12–23].
- Despite rigorous investigation, cisplatin remained the historical standard treatment.
- Ultimately, various combination regimens were studied to improve oncologic outcomes in this vulnerable population.
- Not curative, but progression free survival has improved with systemic chemotherapy (see Table 2.13) [24–28].
- Following publication of GOG 110 and GOG 149 it became evident that improvement in RR and PFS did not translate into improvements in OS.
- Thus, the importance of evaluating QOL on treatment emerged and subsequent trials tracked QOL, patient reported outcomes.

TABLE 2.13. Combination regimens tested in phase III studies for the treatment of advanced Stage (IVB), recurrent or persistent cervical cancer [24–28].

Trial	Regimen	RR (%)	OS (months)	PFS (months)
GOG 110 [24]	Cisplatin 50 mg/m^2	17.8	8	3.2
	Cisplatin 50 mg/m^2 + DBD 180 mg/m^2	21.1	7.3	3.3
	Cisplatin 50 mg/m^2 + Ifosfamide 5 g/m^2 + mesna	31.1	8.3	4.6
GOG 149 [25]	Cisplatin 50 mg/m^2 + Ifosfamide 5 g/m^2	32	8.5	4.6
	Cisplatin 50 mg/m^2 + Ifosfamide 5 g/m^2 + Bleomycin 30 units	31.2	8.4	5.1
GOG 169 [26]	Cisplatin 50 mg/m^2	19	8.8	2.8
	Cisplatin 50 mg/m^2 + Paclitaxel 135 mg/m^2	36	9.7	4.8
GOG 179 [27]	Cisplatin 50 mg/m^2	13	6.5	2.9
	Cisplatin 50 mg/m^2 + Topotecan 0.75 mg/m^2 d1–3	26	9.4	4.6
	MVAC	NA	NA	NA
GOG 204 [28]	Cisplatin 50 mg/m^2 + Paclitaxel 135 mg/m^2	29.1	12.9	5.8
	Cisplatin 50 mg/m^2 + Topotecan 0.75 mg/m^2 d1–3	23.4	10.3	4.7
	Cisplatin 50 mg/m^2 + Gemcitabine 1,000 mg/m^2	22.3	10.3	4.6
	Cisplatin 50 mg/m^2 + Vinorelbine 30 mg/m^2	25.9	10	4.0

DBD dibromodulcitol, *RR* response rate, *OS* overall survival, *PFS* progression free survival, *d* day, *MVAC* methotrexate 30 mg/m^2 days 1, 15, and 22, vinblastine 3 mg/m^2 days 2, 15, and 22, doxorubicin 30 mg/m^2 day 2, and cisplatin 70 mg/m^2 day 2 given every 4 weeks, *NA* not applicable as study arm closed early

- *GOG 169* showed a near doubling of the RR with combination cisplatin + paclitaxel, without deterioration in QOL and this became the standard chemotherapeutic approach moving forward.
- *GOG 179* subsequently established cisplatin + topotecan as superior to cisplatin alone, and was the first trial in this disease setting to show an improvement in OS resulting in FDA approval of the regimen.

  - OS advantage criticized, given what was described as a relative underperformance of the cisplatin control arm of GOG 179, in comparison to GOG 110 and GOG 169.
  - This was attributed to increased use of radiosensitizing cisplatin, and "re-treatment" with platinum in patients enrolled and treated on GOG 179.
    - GOG 169: 31 % received prior radiosensitizing cisplatin.
    - GOG 179: 58 % received prior radiosensitizing cisplatin.

- *GOG 204* then developed and opened in May 2003 comparing four chemotherapy doublets.
  - 70 % received prior cisplatin containing chemoradiation.
  - Cisplatin + Paclitaxel regimen stood out with highest RR, and longest PFS and OS (despite lack of significance).
  - Response rate to combination cisplatin + paclitaxel attenuated in GOG 204 when compared to GOG 169, and once again attributed to increased prior cisplatin exposure in the patients enrolled on GOG 204 (i.e., these patients may have a degree of platinum resistance from prior platinum exposure).

- In an effort to mitigate nephrotoxicity and shorten chemotherapy infusion, JGOG conducted a non-inferiority phase 3 trial of cisplatin + paclitaxel versus carboplatin + paclitaxel.
  - Median OS and PFS nearly identical between study arms (HR 1.04; 95 % CI 0.8–1.35).
  - In a secondary analysis of 117 patients not receiving prior platinum therapy the cisplatin + paclitaxel regimen appeared superior to carboplatin + paclitaxel.
    - Median OS 23.2 versus 13 months (HR 1.57; 95 % CI 1.06–2.32).

- Unfortunately, despite the above, limited gains made in OS.

- Moore et al. attempted to help identify patients a priori who were unlikely to respond to cytotoxic therapy (*Moore criteria*).
  - Identified 5 factors independently prognostic of poor response: African-American, PS > 0, pelvic disease, prior radiosensitizer, and time interval from diagnosis to first recurrence <1 year.
  - Patients with 4–5 risk factors had a RR of only 13 %, and median PFS and OS of 2.8 and 5.5 months, respectively.

Exploration of Non-platinum Doublets

- With early closure of GOG 204, the cervical cancer committee was tasked with development of a replacement phase 3 protocol.
- *GOG 240* was designed as a 4 arm trial, with cisplatin + paclitaxel (with or without bevacizumab) being compared with topotecan + paclitaxel (with or without bevacizumab) [29] (Table 2.13) [24–28].
  - Four hundred and fifty-two patients accrued onto study. Notably the majority of patients on each backbone had a PS of 0, and 75 % of the entire cohort had previously received platinum (even between arms).
  - Topotecan + paclitaxel was not shown to be superior or inferior to cisplatin + paclitaxel (HR 1.20; 95 % CI 0.82–1.76).
  - Importantly, the investigators showed a significant improvement in OS in the bevacizumab containing arms relative to non-bevacizumab controls (17 months vs. 13.3 months, respectively; HR 0.71; 95 % CI 0.54–0.95; $p = 0.0035$).
  - Analogous improvements in PFS were identified (8.2 months bevacizumab containing arm and 5.9 months in control arm (HR 0.67; 95 % CI 0.54–0.82; $p = 0.0002$).
  - Exploratory sub-analysis indicated the beneficial effects of bevacizumab in patients with prior platinum

Table 2.14. GOG 240 Schema and regimens [29].

Trial	Eligibility	Arms	Conclusion
GOG 240	Metastatic, recurrent, or persistent SCC, AS, or adenocarcinoma	• Paclitaxel 135 mg/m^2 over 24 h or 175 mg/m^2 over 3 h • Cisplatin 50 mg/m^2 on day 1 or 2 • Paclitaxel 135 mg/m^2 over 24 h or 175 mg/m^2 over 3 h • Cisplatin 50 mg/m^2 on day 1 or 2 • Bevacizumab 15 mg/kg • Paclitaxel 175 mg/m^2 • Topotecan 0.75 mg/m^2 • Paclitaxel 175 mg/m^2 • Topotecan 0.75 mg/m^2 • Bevacizumab 15 mg/kg	Patients who received Bevacizumab had 3.7 month improvement in OS

exposure, recurrent or persistent disease, and squamous histology. Importantly, the benefits of bevacizumab persisted in patients with recurrent disease in a previously irradiated field, which was hypothesized to be relatively hypoxic.

– These findings represent the first time a targeted anti-angiogenic agent has shown an improvement in OS in patients with gynecologic cancer.

- Current new standard of care is based on results from GOG 240 recommending cisplatin, paclitaxel, and bevacizumab (see Table 2.14.) [29].
- Toxicity of bevacizumab on GOG 240.
  - Within the bevacizumab-containing arms, there was an increase in grade ≥3 GI and GU fistula ($n=5$), as well as grade ≥2 hypertension, grade ≥4 neutropenia and grade ≥3 thrombocytopenia. This did not translate into a significant deterioration in HRQOL (FACT-Cx TOI).
  - The most common adverse events included HTN and proteinuria. Rare but serious adverse events included thromboembolic disease and GI/GU fistulas.

Beyond Angiogenesis in Cervical Cancer

- To date, the largest study exploring non-bevacizumab anti-angiogenic agents in the treatment of cervical cancer was reported in August 2010.
  - Monk et al. studied pazopanib and lapatinib as single agents and in combination in patients with Stage IVB persistent/recurrent cervical carcinoma not amenable to curative therapy and at least one prior regimen in the metastatic setting [30]. The primary end point was progression-free survival (PFS), and secondary end points were overall survival (OS), response rate (RR), and safety.
    - One hundred and fifty-two were randomly assigned to the monotherapy arms: pazopanib ($n=74$) or lapatinib ($n=78$). Importantly, the futility boundary was crossed at the planned interim analysis for combination therapy compared with lapatinib therapy, and the combination arm was terminated.
    - Pazopanib improved PFS (HR 0.66; 90 % CI, 0.48–0.91; $p=0.013$) and OS (HR 0.67; 90 % CI, 0.46–0.99; $p=0.045$). Median OS was 50.7 weeks and 39.1 weeks and RRs were 9 and 5 % for pazopanib and lapatinib, respectively. The only grade 3 AE > 10 % was diarrhea (11 % pazopanib and 13 % lapatinib). Grade 4 AEs were 9 % (lapatinib) and 12 % (pazopanib).
    - The results of this phase 2 study confirmed the activity of anti angiogenic agents in advanced and recurrent cervical cancer and demonstrated the benefit of pazopanib based on the prolonged PFS and favorable toxicity profile.
- Sunitinib, an analogous, oral multi-TKI, exerts its antiangiogenic effects via inhibition of VEGFR-1, -2, and -3, PDGF α and β, and related receptor tyrosine kinases [31].
  - A phase 2 clinical trial was developed investigating the efficacy and safety of sunitinib in patients with unresectable, locally advanced or metastatic cervical carcinoma [32].

- A total of 19 subjects were enrolled on this multicenter phase II study. Unfortunately, there were no documented objective responses on therapy, with significant morbidity (fistula rate of 26 %).
- Median time to progression was reported as 3.5 months. Given lack of signal, it was determined that sunitinib has insufficient activity as a single agent in cervical cancer to warrant further investigation.

Anti-vascular Strategies in the Treatment of Cervical Cancer

- Interest into the study of *vascular disrupting agents* (VDAs) emerged in an effort to circumvent acquired resistance to traditional antiangiogenic therapies.
- VDAs result in a rapid and selective shutdown of tumor vasculature via destruction of endothelial cells [33].
- One of the best-studied agents within this class is combretastatin A-4 phosphate (CA4P), a synthetic, phosphorylated prodrug of the natural product combretastatin A-4 (CA4) [34]. It functions by binding β–tubulin subunits, preventing microtubule formation resulting in cytoskeletal changes within endothelial cells [35]. The anti-vascular effects of CA4P have been demonstrated in both in vitro and in vivo models, and appear to be the result of endothelial damage, leading to increased vascular resistance, reduced tumor blood flow, and central tumor necrosis [34, 35].
- The most extensively studied VDA in the treatment of cervical cancer is the investigational anticancer drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA) [36].
  - In a phase 1 trial exploring DMXAA in the treatment of several solid tumors, DMXAA (22 mg/kg by intravenous infusion over 20 min) resulted in a partial response in one patient with metastatic cervical squamous carcinoma. Given the clinical and preclinical data, six separate VDA have been synthesized and are in various stages of phase 1 and 2 clinical trials exploring their efficacy in patients with solid tumors [37].

Pelvic Exenteration for Centrally Recurrent Cancers

- Total pelvic exenteration can be offered to certain patients with central pelvic recurrence after prior pelvic radiation with or without prior radical hysterectomy.
- Contraindications:
  - Lymphatic metastases.
  - Extension of disease to the pelvic sidewalls.
  - Distant metastases.
- Patients must be carefully selected, as they must be highly motivated to manage multiple ostomies and potential postoperative complications.
- Total pelvic exenteration removes the bladder, uterus, vagina, and rectum and requires extensive reconstruction including urinary conduid (continent or non-continent), low rectal anastomosis or frequently end colostomy, and potential vaginoplasty with split thickness skin graft or myocutaneous flaps. The salvage rate is 60–70 % with a 2 % mortality from the procedure.

Neoadjuvant Chemotherapy

- In certain situations, neoadjuvant chemotherapy is beneficial prior to surgery for cervical cancer. The chemotherapy used is often based on the "Buenos Aires Protocol":
  - Cisplatin 50 mg/m^2 day 1.
  - Vincristine 1 mg/m^2 day 1.
  - Bleomycin 5 mg/m^2 days 1–3 (3 cycles at 10 day intervals).

Cervical Cancer in Pregnancy

- Stage for stage, pregnancy does not worsen survival. Diagnosis is however often delayed during pregnancy.
- Recent studies suggest that there is no decrease in survival with treatment delay during pregnancy.
- Cesarean delivery is often recommended for invasive lesions due to friability of the tumor although vaginal delivery does not worsen prognosis.

- Consideration may be given for neoadjuvant chemotherapy during pregnancy, followed by surgical resection at the time of delivery.
- Ultimately, a multidisciplinary approach involving gynecologic oncology, maternal fetal medicine and neonatology is recommended in the management of these uncommon cases.

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http://www.springer.com/978-1-4939-1975-8

Gynecologic Oncology
A Pocketbook
Eskander, R.; Bristow, R.E. (Eds.)
2015, XIII, 427 p. 28 illus., 23 illus. in color., Softcover
ISBN: 978-1-4939-1975-8