Chapter 7
Radiation Therapy in Gynecologic Cancer

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Biology of Radiation Therapy

Definitions

- Roentgen = R = unit of exposure: The amount of X-rays or gamma radiation that will produce 1 cm^3 of air at 0 °C.
- 1 Gray = 1 J/kg = 100 cGray = 100 rads.
- Curie (Ci) unit of activity = 3.7×10^{10} disintegrations/s.

Compton Effect

- Principle employed in therapeutic radiation (high energy levels).
  - Incident photon comes into contact with an outer orbiting electron and some of its energy is given to the electron in the form of kinetic energy.
  - This fast electron then breaks out of its orbit and can ionize other atoms of the absorber.
    - Breaking vital chemical bonds, initiating chain of events that translate into radiation changes.

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Photoelectric Effect

- Principle employed at lower energies (commonly diagnostic radiology).
  - Incident photon smashes into a bound electron in the shell of an atom of the absorbing material and all the energy is transferred.
  - An inner orbiting electron is released from orbit after absorbing energy, and the vacancy is filled by and outer electron dropping in to take its place.
  - A new photon of characteristic radiation is produced.

Radiobiology

- How does radiation kill cancer?
  - DNA damage is the primary mechanism by which radiation kills cancer cells [1, 2].
  - Radiation damages DNA by creating:
    - Single- or double-strand DNA breaks.
    - Base damage.
    - Abnormal cross-links between DNA strands.
    - Abnormal cross-links between proteins and DNA.
  - Radiation can damage DNA directly or create free radicals which themselves induce DNA damage.
  - Radiation can also injure cell membranes, which may induce cell death via apoptosis.

Radiosensitivity

- The goal of radiation therapy is to selectively eliminate neoplastic cells while sparing normal tissues [2].
- *Radiosensitivity* refers to how susceptible a cell is to the effects of radiation.
  - Radiosensitivity is characterized by the extent, rapidity, and duration of response [2].
  - Radiosensitivity is determined by how quickly a given cell can repair DNA damage.

- Malignant cells are preferentially destroyed by radiation due to differential DNA repair capabilities.
- Following low doses of radiation (e.g., 1–2 Gy), tumor cells and normal cells sustain sublethal damage to their DNA.
    - Normal cells can repair sublethal damage relatively quickly compared to tumor cells and that is why radiation is typically administered in a fractionated schedule (low doses every day). This schedule gives normal cells a chance for repair while malignant cells accrue mutations.
    - Hypofractionation schedules allow for radiation delivery in relatively larger doses, less than once daily.
- Tumors differ in their radiosensitivity.
    - Some tumors regress with relatively low doses of radiation while others require far greater doses.

Importance of Oxygen

- The more oxygen present, the more sensitive a cell will be to radiation.
    - If oxygen is present, oxygen molecules may attach themselves to damaged DNA, thereby "fixing" the damage.
    - Hypoxic cells are more resistant to injury caused by radiation than non-hypoxic cells.
        - Tirapazamine is an experimental drug that causes DNA damage only in the setting of hypoxia, and may be beneficial in targeting hypoxic regions of the tumor that are less sensitive to radiation.
            - Initial investigations have failed to find a survival benefit associated with tirapazamine in cervical cancer [3].
        - GOG 219 investigated the impact of tirapazamine on PFS and OS in patients with 1B2-4A cervical cancer limited to the pelvis.

- No difference in 3-year PFS or OS between tirapazamine and control arms.
- Increased toxicity with tirapazamine.

Importance of Cycling

- Cycling cells are more susceptible to radiation than non-cycling cells.
- A higher proportion of mitotic cells means that more of the tumor will be susceptible to radiation.
  - Cell position within the cell cycle is also important.
    - Cells in late G2 and mitosis phase are the most sensitive.
    - Paclitaxel is a chemotherapeutic agent that arrests cells in mitosis and thus makes arrested cells more susceptible to radiation damage.

Radiocurability

- *Radiocurability* refers to the ability of a patient to be cured [2].
  - Radiocurability depends on the sensitivity of the tumor, the tolerance of surrounding tissues, and the disease burden.
    - For example, squamous cell carcinoma of the cervix is a relatively radioresistant tumor (requiring doses >70 Gy to obtain a cure); however, it is highly curable because it is accessible to high-dose irradiation as normal surrounding tissues (i.e., the cervix and vagina) can themselves sustain relatively high doses of radiation without undue toxicity.

Therapeutic Ratio

- The *Therapeutic Ratio* is the ratio that quantifies the amount of radiation that induces tumor cell death with the amount that causes normal tissue toxicity.

- Calculated by the toxic dose divided by the therapeutic dose, and the goal of much research in radiation therapy is to maximize the therapeutic ratio, such that the dose required to produce a therapeutic effect is much lower than the dose required to produce a toxic effect.

Radiation Sensitizers

- Radiosensitizers are agents, like paclitaxel, that increase the toxicity of radiation.
- Examples:
  - Chemotherapeutic agents:
    - Cisplatin (inhibits the ability of cells to repair DNA damage), 5-fluorouracil, adriamycin, and gemcitabine.
  - Hypoxic cell sensitizers: improve the response of hypoxic cells to radiation.
    - Misonidazole.
- *Radiation protectors* (radioprotectors) are agents that decrease the toxicity of radiation on normal tissues.
  - Endogenous sulfhydryl compounds and amifostine are examples of radioprotectors.

Inverse Square Law

- The dose of radiation at a given point is inversely proportional to the square of the distance from the source of the radiation ($I = 1/d^2$) [2].
  - The inverse square law explains why the bladder and rectum can be relatively spared from receiving high doses of radiation when radiation is placed directly in the vagina (brachytherapy).
  - The dose rate at 2 cm from the source is one-fourth that at 1 cm.

- The inverse square law dictates why it is important to stand at the door of the room of a brachytherapy patient in order to minimize exposure.

Introduction to Medical Radiation

Overview of Radiation Delivery Modalities: Two Main Types

External Beam Radiation Therapy (EBRT)

- Radiation in the form of electrons, photons, or protons is delivered to body tissues from sources at a distance from the body (e.g., linear accelerators, Figs. 7.1 and 7.2).
  - No radioactive sources within the body.
  - Radiation is delivered without machinery touching the patient directly.
- Specialized forms of external beam radiation therapy.
  - Stereotactic radiotherapy.
    - Uses a standard linear accelerator to deliver high-dose to precise locations in the body.
  - Stereotactic radiosurgery (SRS) delivers radiation to precise locations in the brain.
  - Stereotactic body radiotherapy (SBRT) delivers radiation to precise locations in the body.
  - Proton therapy.
    - Uses a beam of protons to deliver radiation to malignant tissue.
    - Main benefit: improves radiation localization and minimizes exit dose (which can minimize total dose to normal tissues, especially when tumor and normal tissues are juxtaposed).

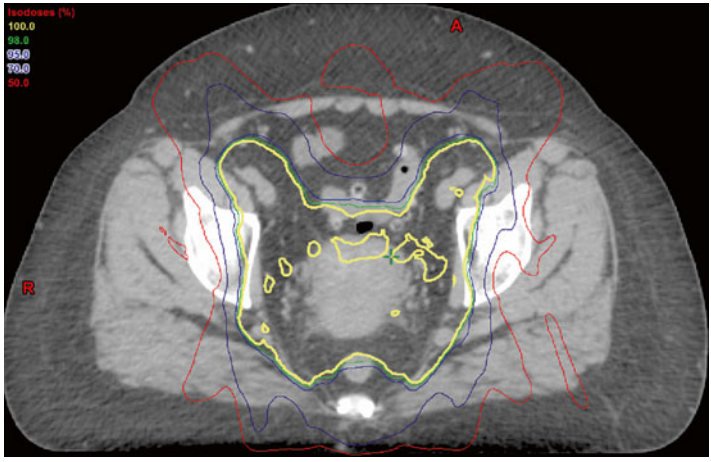

FIG. 7.1. Axial CT view of an image-guided IMRT plan for cervical cancer. Image courtesy of C. Yashar.

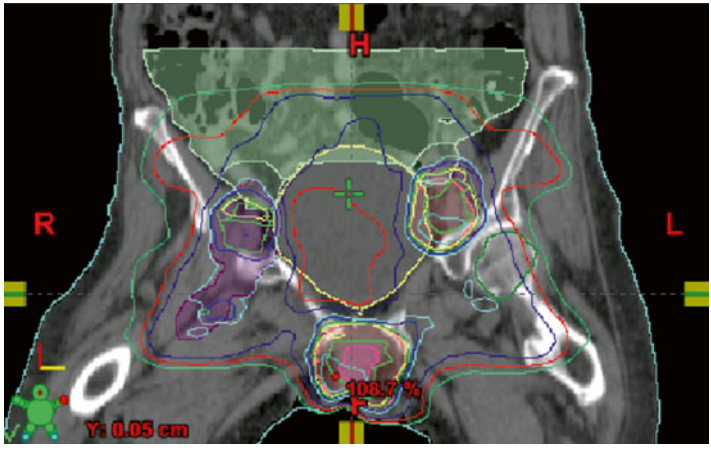

FIG. 7.2. Coronal CT view of an image-guided IMRT plan for vulvar cancer. Image courtesy of C. Yashar.

- Cyber Knife.
  - Radiation is delivered from a robotic arm and targets radiation at any body part from any direction using fiducial markers as guidance
- Gamma Knife.
  - Utilizes cobalt and aims gamma radiation to precise locations in the brain for the treatment of brain tumors with the intent of delivering an ablative dose of radiation in one treatment session.

Local Irradiation (Brachytherapy)

- Radiation emitted from natural isotopes (e.g., iridium, cesium) is predominantly used for interstitial radiation therapy, intracavitary radiation therapy, or brachytherapy [2].
- What is brachytherapy?
  - Radiation is delivered to tissues from sources that are placed inside the body close to the tumor.
  - Intracavitary brachytherapy:
    - Radioactive source is placed directly in a body cavity (e.g., the vagina, Figs. 7.3, 7.4, and 7.5).
  - Interstitial radiation therapy:
    - Radioactive source is placed directly in the tumor bed or body tissue (e.g., the prostate) that isn't a natural cavity.
  - Typically delivered at either a low-dose-rate (LDR) or high-dose-rate (HDR) system.
    - *LDR systems* require hospital admission such that the patient may stay in a shielded room and are less frequently used in the modern era of radiation oncology.
      - LDR systems deliver dose at a rate of around 50–120 cGy/h.

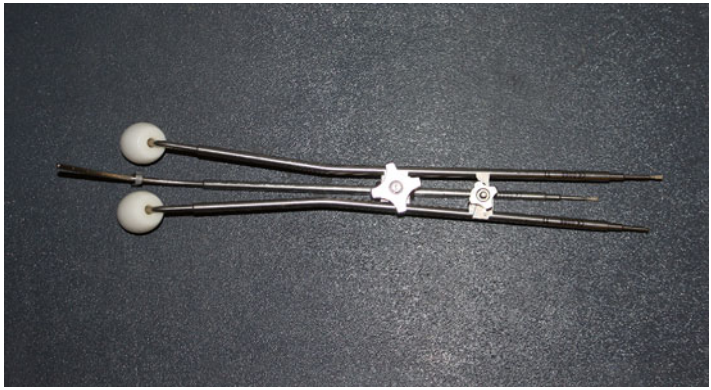

FIG. 7.3. Applicator used for treating cancer of the cervix, endometrium, and vagina. Image courtesy of C. Yashar.

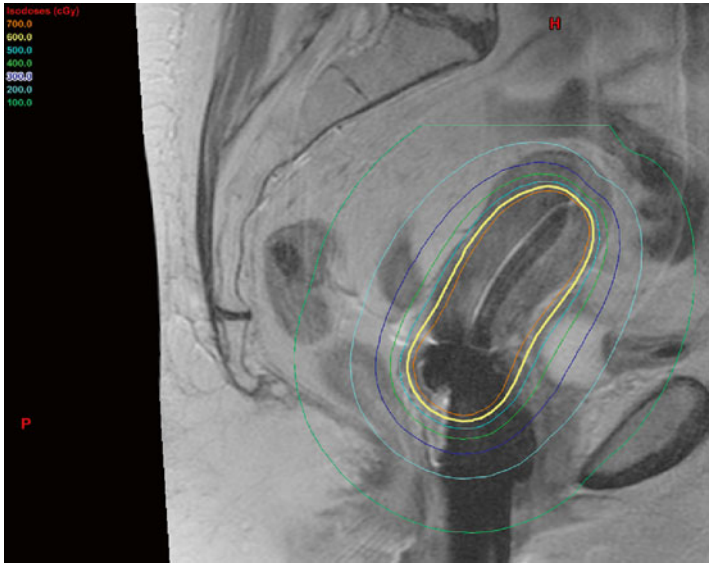

FIG. 7.4. Sagittal MRI display with brachytherapy equipment in place. *Colored lines* represent distribution of dose around the applicator, with dose decreasing as a function of the inverse square law. Image courtesy of C. Yashar.

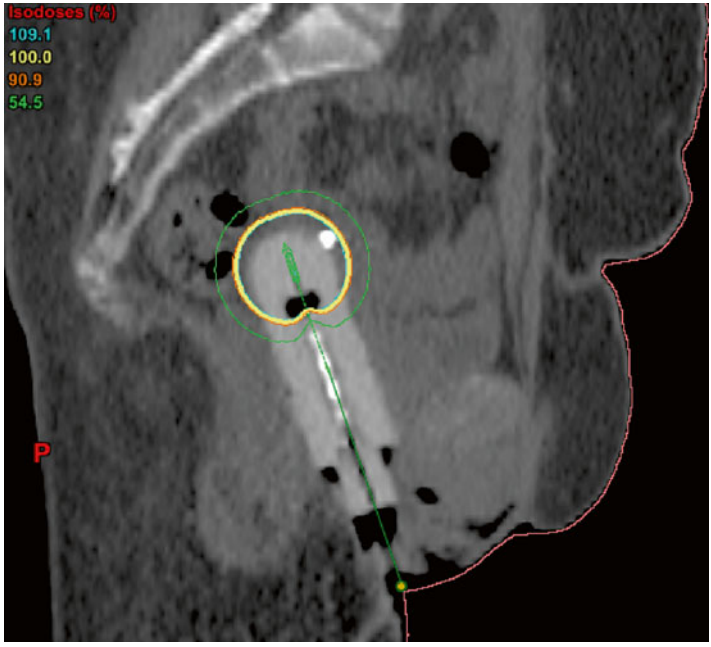

FIG. 7.5. Vaginal cuff brachytherapy. Image courtesy of C. Yashar.

- *HDR systems* are more frequently employed and deliver doses at 100 cGy/min.
- HDR systems are typically employed on an outpatient basis.
- Applicators that can be loaded with radioactive materials (primarily iridium) are used to administer intracavitary radiation.
- Needles that can contain radioactive materials are used to deliver interstitial radiation.
  - Permanent radioactive seeds can be placed in the body. These seeds remain even after decay of the source (Table 7.1) [4, 5].

TABLE 7.1. Radiation dose and organ tolerance [4, 5].

Organ	Tolerance dose (cGy)
Bone marrow	2,000
Spinal cord	5,000
Femoral head	5,000
Stomach	4,500
Bowel	5,000
Rectum	5,000
Ureter	7,500–8,000
Bladder	6,500
Ovary	600–1,000
Uterus	10,000–20,000
Cervix	9,000
Vagina	9,000–10,000
Vulva	2,000–3,000

Radiation Field Margins (for 3D CT-Based Planning) [6]

- Postoperative therapy of cervical cancer and endometrial cancer.
  - Clinical Target Volume (CTV) Definition—identifies target that may contain microscopic spread of disease.
    - Common, external, and internal iliac lymph node regions, and the upper 3.0 cm of vagina and paravaginal soft tissue lateral to the vagina.
      - For patients with cervical cancer (or endometrial cancer with cervical stromal invasion), the CTV should include the presacral lymph node region.
    - Superior border of CTV: begin 7 mm below the L4-L5 interspace (although there is consideration with 2D planning of covering all the common nodes which may join to form the aorta/inferior vena cava more cephalad than the conventional 2D border of L4/L5).
    - Inferior border of CTV: extend to 3.0 cm below the upper extent of the vagina (defined by the vaginal marker) or to 1.0 cm above the inferior extent of the obturator foramen, whichever is lower.
    - Uniform 3D planning target volume expansion: 7 mm.

Radiation Field Margins (for Bony Anatomy-Based Planning)

- Pelvic radiation Stage 1B–4A cervical cancer and endometrial cancer.
  - Superior border: L4-L5 (with 3D therapy, transition to confluence of the common iliac arteries and veins may be practiced, ~L3).
  - Lateral border 1.5 cm beyond lateral margin of bony pelvis.
  - Inferior border mid-point of obturator foramen (allows coverage of upper vagina) or 4 cm below vagina marker, whichever is lower.
  - Posterior border: coverage of at least S3 and with more advanced disease the sacral hollow.
  - Anterior border: Just anterior to symphysis pubis.

Para-aortic Radiation

- Addition of para-aortic radiation to pelvic treatment requires that superior border be moved to body of L1 vertebra, with lateral borders of para-aortic filed encompassing the vertebral processes.
- Anterior border of para-aortic fields is 2 cm anterior to anterior surface of vertebral bodies.
- Posterior border is 2 cm posterior to anterior surface of vertebral bodies.

Inguinal Radiation

- Anterior field
  - Superior border: line 2 cm superior and parallel to inguinal ligament.
  - Lateral border: vertical line parallel to midline at anterior superior ileac spine.
  - Inferior border: 8 cm inferior and parallel to inguinal ligament and 1 cm below most inferior portion of the vulva.

  - Medial border: 2 cm from midline bilaterally.
  - (Above leads to a pair of parallelograms).

- Posterior field.
  - Superior border: mid-SI joint.
  - Lateral border: 2 cm lateral to widest portion of true bony pelvis.
  - Inferior border: mid-point of obturator foramen.

Brachytherapy Landmarks [7]

Point A: 2 cm above external OS and 2 cm lateral to midline (refers to uterus). Represents the parametria.
Point B: 3 cm lateral to point A, or 5 cm lateral to midline (should represent the pelvic sidewall).

The remainder of the chapter provides detail regarding specific radiation protocols used to treat the initial presentation of the most common gynecologic malignancies involving the endometrium, cervix, vagina, and vulva, as well as a brief overview of ovarian cancer, primary peritoneal carcinoma, fallopian tube carcinoma. A general overview of palliative treatment options will be provided at the end of the chapter.

Use of Radiation Therapy in the Most Common Gynecologic Malignancies

Endometrial Cancer

- Most common gynecologic malignancy diagnosed in the USA [8].
- Standard of care: up-front surgery (with consideration of lymph node dissection) serves to stage the cancer.
  - Low risk patients are typically not given a nodal dissection at the time of surgery and are often observed following surgery.
  - *Vaginal brachytherapy*: used for more deeply invasive lesions, higher-grade lesions, older patients, or patients

with lymphovascular space invasion as isolated high risk factor.
- *Pelvic and paraaortic irradiation*: reserved for the highest risk Stage I patients with multiple high risk factors, high risk Stage I patients without a nodal dissection, and advanced stage patients.
- See Table 7.2 for a summary of the key research studies and clinical trials that comprise the basis for the above general treatment recommendations [9, 10, 14–17].

Key Research Studies in the Treatment of Early Stage (Stage I–II) Endometrial Carcinoma

- Aalders et al. (1980)
  - Randomized controlled trial designed to study the benefit of additional pelvic external beam radiation therapy (EBRT) following surgery and vaginal brachytherapy in the treatment of Stage I endometrial carcinoma [9].
  - Five hundred and forty patients with Stage I endometrial carcinoma received a total abdominal hysterectomy and bilateral salpingo-oophorectomy (with no pelvic lymph node dissection) followed by postoperative vaginal cuff brachytherapy. Patients were then randomized to no further treatment versus additional treatment with EBRT to the draining pelvic lymphatics.
  - EBRT significantly reduced the risk of local recurrence (1.9 % vaginal and pelvic recurrence rate in EBRT group vs. 6.9 % recurrence rate in the no additional treatment group, $p < 0.01$).
    - EBRT group non-significantly developed more distant metastases than the no additional treatment group (9.9 % vs. 5.4 %, $0.10 > p > 0.05$) [9].
    - There was no overall survival benefit for additional EBRT observed at 9 years (90 % in the control group vs. 87 % in the EBRT group).

TABLE 7.2. Summary of clinical trials guiding the use of radiation therapy in the management of endometrial cancer [9, 10, 14–17].

Study	FIGO stage (eligible patients)	Control group	Comparison group(s)	Overall survival (OS)	Recurrence risk	Toxicity
Aalders et al. [9]	Surgical Stage I (540)	Surgery plus brachytherapy (BT) alone	Surgery and BT plus EBRT	(1) No OS benefit for additional EBRT (90 % in BT-alone group vs. 87 % in BT + EBRT) (2) Subset analysis: OS benefit for BT + EBRT in Stage IC Grade 3 patients (82 % vs. 72 %)	EBRT decreased risk of pelvic recurrence (1.9 % in EBRT group vs. 6.9 % in brachytherapy alone, $p < 0.01$)	Complications reported include: rectovaginal fistula, urethral stricture (in BT-alone group) and small-bowel obstruction, bladder necrosis (in the BT + EBRT group)
PORTEC-1, Creutzberg et al. [10]	Stage IB (G2–3) or IC (G1–2) (715), specifically no IC3 patients	Surgery alone	Surgery and postoperative EBRT	No survival benefit for additional EBRT (81 %) versus surgery alone (85 %, ns)	Locoregional failures greater in surgery-alone group (14 %) versus surgery + EBRT (4 %, p<0.001)	Treatment-related complications greater in radiotherapy group (25 %) versus surgery-alone group (6 %, $p < 0.001$); mostly grade 1 toxicity

(continued)

TABLE 7.2. (continued)

Study	FIGO stage (eligible patients)	Control group	Comparison group(s)	Overall survival (OS)	Recurrence risk	Toxicity
GOG-99, Keys et al. [14]	Stage IB–II (392)	Surgery alone	Surgery and postoperative EBRT	No overall survival benefit for additional EBRT (92 % in EBRT group vs. 86 % in surgery-alone group, $p = 0.5$)	EBRT reduced risk of recurrence (12 % vs. 3 % in surgery-alone group, $p < 0.01$); Among HIR subset, 26 % in surgery alone group versus 6 % with additional EBRT	Significantly more hematologic, gastrointestinal, genitourinary, and cutaneous toxicities in EBRT group
PORTEC-2, Nout et al. [15]	Stage I–IIA with high-intermediate risk features (427)	Surgery plus EBRT	Surgery plus vaginal brachytherapy	No difference in survival, 85 % versus 80 % (ns)	No difference in vaginal recurrence, locoregional relapse or isolated pelvic recurrences	Acute grade 1–2 toxicity higher in EBRT group (54 % vs. 13 % in BT group, ss)
JGOG-2033, Susumu et al. [16]	Stage IC–IIIC (385)	Surgery plus EBRT	Surgery plus chemotherapy (cyclophosphamide, doxorubicin, and cisplatin)	(1) Low/intermediate risk patients: no survival difference (2) Survival benefit in high-risk patients for chemotherapy (90 % vs. 74 % for EBRT group, $p = 0.006$)	(1) Low/intermediate risk patients: no progression-free survival benefit (PFS) (2) PFS benefit in high-risk patients for chemotherapy (84 % vs. 66 % for EBRT group, $p = 0.024$)	No difference in toxicity between groups (1.6 % of EBRT group had grade 3–4 toxicity vs. 4.7 % of chemotherapy group)

Italy, Maggi et al. [17]	High-risk endometrial, Stage IC G3, II G3, and III (345)	Surgery plus EBRT	Surgery plus chemotherapy (cisplatin, doxorubicin, cyclophosphamide)	No overall survival difference (69 % in EBRT group vs. 66 % in chemotherapy group, ns)	No PFS difference (63 % in EBRT group vs. 63 % in chemotherapy group, ns)	EBRT associated with gastrointestinal and genitourinary side effects; Chemotherapy associated with hematologic, nausea, and vomiting

- *Poor prognostic indicators identified*: age >60 years, FIGO Stage IB (previously termed FIGO Stage IC), histologic Grade 3, and lymphovascular invasion [9].
- A subset analysis revealed that only patients with poorly differentiated (grade 3) tumors, infiltrating more than half of the myometrial thickness, benefit from additional external beam radiation therapy (overall survival 82 % in the EBRT group vs. 72 % in the no additional treatment group) [9].

– The Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial.

- Randomized controlled trial designed to address the benefit of postoperative radiation therapy following initial surgery for endometrial carcinoma [10–13].
- Seven hundred and fifteen patients with Stage IB (grade 2–3) or Stage IC (grade 1–2) received a total abdominal hysterectomy and bilateral salpingo-oophorectomy (with no pelvic lymph node dissection). Patients were then randomized to receive EBRT versus no further therapy.
- Significant reduction in local recurrence with EBRT (5.8 % in the EBRT group vs. 15.5 % in the NAT group at 15 years, $p < 0.001$), but no overall survival benefit [13].
- EBRT was more likely to be associated with adverse events, with up to 26 % of patients in the EBRT arm experiencing toxicity (mostly grade 1–2) compared to 4 % patients in the control arm [11], with side effects from the radiation therapy seen to persist at 15 years post-treatment [13].
- Given the absence of a survival benefit for EBRT and the relatively high rate of toxicity, EBRT is recommended to only be given to patients determined to be at high risk of recurrence.
  - Risk factors: age >60 years, grade 3 lesions, deep myometrial invasion.

- Patients with 2 of these 3 high risk features (high intermediate risk, HIR, patients) were seen to have a 20 % risk of locoregional recurrence without radiation therapy, which decreased to 5 % following EBRT [10].

- Thus, after PORTEC-1, it was felt that there remained an indication for EBRT in HIR patients, but should be avoided in low-intermediate risk patients [13].

– GOG-99 trial

- Conducted to assess the benefit of postoperative radiation therapy versus no additional treatment following surgery for endometrial carcinoma on recurrence-free interval as the primary outcome [14].
- In this study, 392 patients with intermediate or high-intermediate risk were randomized following total abdominal hysterectomy with bilateral salpingo-oophorectomy (with select patients receiving pelvic lymph node dissection) to postoperative radiation therapy versus no additional treatment.
- Significantly lower recurrence rate in the EBRT treated group compared to the group receiving no additional treatment, which was especially pronounced in the high intermediate risk patient subset (6 % in the EBRT group vs. 26 % in the no additional treatment group at 2 years, $p < 0.01$) [14].
- Conclusion: postoperative radiation therapy significantly decreases the risk of recurrence in early stage endometrial carcinoma, but should be limited to patients with high intermediate risk features [14].

– PORTEC-2

- Because most recurrences for limited-stage endometrial carcinoma following surgery occur in the vaginal cuff, PORTEC-2 was designed to compare the efficacy of vaginal brachytherapy with pelvic EBRT for preventing vaginal recurrence following hysterectomy [15].

    - In this study, 427 intermediate or high-risk endometrial carcinoma patients received total abdominal hysterectomy with bilateral saplingooophorectomy (and no lymph node dissection) and were then randomized to receiving either EBRT or vaginal brachytherapy.
    - At 5 years, vaginal brachytherapy is as effective as EBRT for preventing vaginal recurrence.
  - No difference in locoregional-relapse, isolated pelvic recurrence, distant metastases, or overall survival [15].
    - Vaginal brachytherapy was associated with significantly less acute grade 1–2 gastrointestinal toxicity than the EBRT group (13 % vs. 54 %).
    - Conclusion: vaginal brachytherapy should be used in place of EBRT as the standard-of-care adjunctive therapy for patients that fit PORTEC-2 criteria [15].

- *Chemotherapy:* used for patients with more advanced disease, or higher-risk limited stage disease.
- JGOG-2033 trial
  - Conducted to compare postoperative pelvic radiation with chemotherapy for patients with >50 % myometrial invasion (Stage IC–IV) [16].
  - In this trial, 385 patients were randomized following TAH/BSO or radical hysterectomy (with the majority of patients receiving pelvic lymph node dissection) to receive either pelvic radiation therapy (AP/PA field to 45–50 Gy) or 3 courses of cisplatin/doxorubicin/cyclophosphamide.
  - At 5 years, no survival differences between the groups (progression-free or overall) [16].
  - On subset analysis, there was no difference for low or intermediate risk patients.
    - In the high-risk group (defined as patients with Stage IC and age >70 years old, or patients with Stage IC, grade 3 disease, Stage II, or Stage IIIA patients), chemotherapy was associated with an overall survival benefit compared to radiation (89.7 % vs. 73.6 %, $p < 0.01$) [16].

- Maggi et al. (2006)
  - Compared EBRT versus combined platinum-based chemotherapy following surgery for high-risk endometrial carcinoma [17].
  - Three hundred and forty-five patients with high-risk endometrial carcinoma (defined as Stage IC, grade 3, Stage IIC, grade III, with >50 % myometrial invasion, and Stage III patients) were randomized to receiving either EBRT (to 45–50 Gy) or 5 cycles of cisplatin/doxorubicin/cyclophosphamide chemotherapy.
  - At 5 years, there were no differences in overall-survival or progression-free survival between the groups [17].
    - The authors noted that there was a trend toward delayed local relapse with radiation therapy, and a trend for delayed progression to distant metastatic disease with chemotherapy, but these trends were not significant [17].

Key Research Studies in the Treatment of Locally Advanced (Stage III–IV) Endometrial Carcinoma

- For patients with higher-stage endometrial carcinoma, surgery, chemotherapy, and radiation therapy are all vital treatment components.
- Hogberg et al. presented the pooled results from two randomized studies (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) designed to address the benefit of chemotherapy following surgery and radiation therapy for advanced endometrial carcinoma [18].
  - Five hundred and thirty-four patients with high-risk Stage I–III endometrial carcinoma patients received TAH/BSO were randomized to receive radiation therapy alone or sequential radiation therapy and chemotherapy.

  - Additional chemotherapy improves progression-free survival, and there was a trend to improving overall survival [18].

- GOG 184 trial
  - Randomized patients with advanced endometrial carcinoma (Stage III or IV) treated with surgery and tumor-volume directed pelvic irradiation to receive either cisplatin and doxorubicin or cisplatin, doxorubicin, and paclitaxel chemotherapy.
    - No difference in recurrence-free survival between arms.
    - The addition of paclitaxel was associated with increased toxicity [19].

- GOG 122
  - Randomized trial designed to compare whole-abdominal radiation versus chemotherapy in patients with Stage III–IV endometrial carcinoma and no greater than 2 cm of residual disease following hysterectomy [20].
  - Three hundred and ninety-six patients who received a TAH/BSO were then randomized to receive either whole abdominal radiation (AP/PA fields to 30 Gy with 15 Gy boost to lymph nodes) or 8 cycles of doxorubicin and cisplatin chemotherapy.
  - At 5 years, significant improvement in overall survival for the chemotherapy group (55 %) compared to the group receiving abdominal radiation therapy (42 %), however with greater acute toxicity observed in the chemotherapy arm [20].
    - Approximately half of the patients in both arms experienced recurrence; patients in the chemotherapy arm tended to have higher rates of pelvic recurrence, whereas patients in the chemotherapy arm had fewer distant recurrences [20].

  - The whole abdominal radiation dose was relatively low with an outdated administration compared to techniques employed today.

- *Sandwich trials*: administered adjuvant radiation therapy "sandwiched" between courses of chemotherapy.
  - Einstein et al. presented the results from a phase II prospective study designed to assess the tolerability of sequential chemotherapy with radiation therapy for advanced endometrial carcinoma [21]. Following surgery, patients were given a sequence of paclitaxel, radiation therapy, and carboplatin.
    - The treatment was well-tolerated, and the authors reported overall survival of 6.3 years for Stage I/II, 3.0 years for stage III/IV [21].
  - Secord et al. [22] presented the results of a multicenter retrospective analysis of patients with Stage III and IV endometrial carcinoma to assess the whether there was benefit for a particular sequencing of chemotherapy and radiation following surgery.
    - "Sandwich" chemotherapy-radiation-chemotherapy (CRC) was associated with improved survival compared to chemotherapy followed by radiation (CR) and radiation followed by chemotherapy (RC) [22].
- Ongoing trials
  - GOG-0249
    - Designed to assess whether vaginal cuff brachytherapy followed by 3 cycles of chemotherapy (paclitaxel and carboplatin) increases recurrence-free survival compared to EBRT in patients with Stage I–IIA endometrial carcinoma with high-intermediate risk factors.

- PORTEC-3
  - Designed to compare EBRT alone versus concurrent cisplatin-EBRT followed by adjuvant chemotherapy (paclitaxel and carboplatin) in high risk stage I–III patients.
- GOG 0258
  - Addresses the benefit for concurrent cisplatin and tumor-volume directed irradiation followed by carboplatin and paclitaxel versus carboplatin and paclitaxel alone for advanced endometrial carcinoma patients.

Cervical Cancer

- The third most common gynecologic malignancy diagnosed in the USA, following endometrial and ovarian cancer.
- Formerly the most common cause of cancer-related mortality in the USA, however mortality from cervical cancer has decreased dramatically as a result of improved access to Papanicolaou smear screening programs [23].
- Worldwide, however, cervical cancer remains the second most common cause of cancer-related mortality.

Treatment of Microinvasive (Stage IA) Cervical Cancer

- The current primary treatment of Stage IA1 cervical cancer with no lymphovascular space invasion is cervical conization.
- For Stage IA2 disease, or IA1 with lymphovascular space invasion, the treatment is modified or radical hysterectomy with consideration for pelvic lymph node dissection.
- In poor surgical candidates, brachytherapy alone (if stage IA1) or external beam radiation therapy with brachytherapy (stage IA2) are reasonable options [24, 25].

Key Research Studies in the Treatment of Early Stage Non-Bulky (Stage IB1 and IIA <4 cm) Cervical Cancer

- Surgery and radiation are equivalent treatment options for early stage, non-bulky cervical cancer because no trial has shown a survival or disease-free survival advantage for either modality [26, 27].
- However, surgery and radiation therapy differ in their side effect profile.
- Landoni et al. (1997)
  - Randomized 343 patients with Stage IB-IIA cervical cancer to receive radical hysterectomy versus EBRT (to 47 Gy) followed by LDR to a median dose of 76 Gy [26].
  - Patients in the surgical arm who were found to have Stage IIB or greater disease were allowed adjuvant RT, and 63 % of patients in the surgery arm received RT.
  - At 5 years, there was no difference in overall (87 % in the surgery group vs. 90 % in the radiation therapy group) or disease-free survival.
  - For patients with adenocarcinoma histology, there was an overall survival advantage for surgery (70 %) compared to radiation therapy (59 %), as well as a disease-free survival benefit.
  - Surgery was associated with a higher risk of grade 2–3 complications (28 %) compared to radiation therapy (12 %), and patients who had surgery with adjuvant radiation therapy experienced the highest rate of complications [26].
- GOG 71/RTOG 8412
  - Addressed whether surgery plus adjuvant radiation therapy confers benefit beyond radiation therapy alone.
  - Two hundred and fifty-six patients with “bulky” Stage IB cervical cancer (defined as exophytic or “barrel” shaped tumors greater than 4 cm) were randomized to

receive either external beam radiation therapy followed by hysterectomy or external beam radiation therapy alone [27]. Both groups received brachytherapy 1–2 weeks following completion of treatment.

- At 5 years, no difference in overall survival between the groups.
  - But radiation therapy plus hysterectomy had a lower incidence of local relapse (14 %) compared to the radiation therapy alone (27 %).
- There was also a trend towards a progression-free survival benefit with the addition of hysterectomy (62 % vs. 53 %, $p = 0.09$) [27].

- The presence of certain risk factors in Stage IB cervical cancer patients can assist in determining which patients will benefit most from adjuvant radiation therapy [28].
- Delgado et al. (1990)
  - Prospectively evaluated 645 patients with Stage 1 squamous cell carcinoma of the cervix to determine prognostic factors associated with disease-free interval [29].
    - Disease-free interval is strongly associated with depth of tumor invasion, tumor size, and capillary-lymphatic space (or lymphovascular space) invasion.
    - These criteria are the "Sedlis criteria."
      - Patients need postoperative radiation therapy if they have 2 or more of the following factors: 1) size >4 cm, 2) deep stromal invasion (invasion of carcinoma to greater than 1/3 of the stroma), and 3) lymphovascular space invasion.
        - The GOG-0263 is evaluating the role of radiation therapy with or without chemotherapy in patients with Stage I or II cervical cancer (with greater than 2/3 Sedlis criteria) following surgery.

Treatment of Early Stage Bulky (Stage IB2 and IIA >4 cm) and Locally Advanced (Stage IIB–IVA) Cervical Cancer

- Radiation and chemotherapy are indicated for early stage bulky cervical cancer [30].
- For patients with clinically visible disease (at least Stage IB2), or with bulky disease (>4 cm) that invades beyond the uterus but without parametrial invasion (Stage IIA), concurrent chemotherapy and radiation afford a significant survival benefit when compared to radiation therapy alone, with or without surgery [31–36].
  - The combination of surgery and chemoradiation is more toxic than primary chemoradiation, so if there is suspicion that postoperative adjuvant therapy will be needed (if a patient is felt to have a high risk of parametrial invasion, positive margins, or positive nodes on surgery) consideration of primary chemoradiation should be entertained [36].
- Standard of care chemotherapy: cisplatin-based chemotherapy.
  - Two randomized controlled trials have demonstrated a survival benefit for the addition of weekly cisplatin-based chemotherapy given concurrently with radiation therapy [34, 35], and three randomized controlled trials have demonstrated a survival benefit for the addition of cisplatin and 5-fluorauracil given concurrently with radiation therapy [32, 33, 36].
    - Pearcey et al. was the only randomized controlled trial comparing radiation therapy alone with radiation therapy plus weekly cisplatin that did not show a survival benefit for the addition of cisplatin [37]. Other investigators have also published on carboplatin and paclitaxel [38].
    - Combination therapies (with gemcitabine or biologics such as bevacizumab) are currently under investigation. See Table 7.2 for a summary of these trials.

Key Research Studies (See Table 7.3 for More Detail)

- GOG 123
  - Randomized 369 patients with Stage IB2 cervical carcinoma to receive radiation therapy alone or RT plus weekly cisplatin [35].
  - There was an overall and progression-free survival benefit for the addition of weekly cisplatin [35], preserved for a median follow-up of 8 years [31].
- GOG 120
  - Three-arm randomized controlled trial that assigned patients to receive radiation therapy and weekly cisplatin, radiation therapy plus hydroxyurea, or radiation therapy plus cisplatin, FU, and hydroxyurea [34].
  - Similar overall survival and progression-free survival benefits were seen when the two arms containing cisplatin-based chemotherapy were used compared to radiation therapy plus hydroxyurea alone [34].
  - Comparable survival benefits were seen in the GOG 85 trial ([32]; comparing radiation therapy with hydroxyurea with radiation therapy and cisplatin plus fluorouracil), as well as GOG 109 ([36]; comparing radiation therapy alone with radiation therapy and cisplatin plus fluorouracil).
- RTOG 90-01
  - Addressed the distinction between extended-field radiation therapy (with coverage of the para-aortic lymph nodes) versus radiation therapy plus cisplatin and fluorouracil [33].
  - Survival benefit found for the addition of cisplatin/FU chemotherapy.
- NCI Canada study
  - The only randomized controlled trial that did not show a benefit for the addition of cisplatin-based chemotherapy to radiation therapy in the treatment of cervical cancer [37].

TABLE 7.3. Summary of clinical trials guiding the use of radiation therapy, chemotherapy, and surgery in the management of cervical cancer [26, 32–37].

Study	FIGO stage (eligible patients)	Control group	Comparison group(s)	Overall survival (OS)	Progression-free survival (PFS)	Toxicity
Keys et al. [35] GOG 123	IB2 (369)	Radiotherapy	Radiotherapy plus weekly cisplatin	Greater OS in cisplatin + RT group 83 % versus RT alone 74 % ($p = 0.008$)	Greater PFS in cisplatin + RT group 79 % versus RT alone 63 % ($p < 0.001$)	Grade 3 and 4 toxicity greater in radiotherapy plus cisplatin group (21 % vs. 2 %)
Whitney et al. [32] GOG 85/ SWOG 8695 intergroup	IIB-IVA (368)	Radiotherapy plus hydroxyurea (HU)	Radiotherapy plus cisplatin and fluorouracil (FU)	Greater OS in cisplatin/FU group 55 % versus HU group 43 % ($p = 0.018$)	Greater PFS in cisplatin/FU 57 % versus HU group 47 % ($p = 0.033$)	Leukopenia greater with HU (24 % vs. 4 %)
Morris et al. [33] RTOG 90-01	IB2-IVA (386)	Extended-field radiotherapy (with coverage of para-aortic lymph nodes)	Radiotherapy plus cisplatin and FU	Greater OS in RT + cisplatin group 73 % versus RT-alone group 58 % ($p = 0.004$)	Greater PFS in RT + cisplatin/FU group 40 % versus RT alone group 67 % ($p < 0.001$)	Higher rate of reversible hematologic side effects in RT + cisplatin/FU group versus RT alone group

(continued)

TABLE 7.3. (continued)

Study	FIGO stage (eligible patients)	Control group	Comparison group(s)	Overall survival (OS)	Progression-free survival (PFS)	Toxicity
Rose et al. [34] GOG 120	IIB-IVA (526)	Radiotherapy plus hydroxyurea	1. Radiotherapy plus weekly cisplatin 2. Radiotherapy plus cisplatin, FU, HU	Cisplatin 75 % versus cisplatin/FU/HU 75 % versus HU 60 % (relative Risk 0.6 for cisplatin groups)	Cisplatin 67 % versus cisplatin/FU/HU 64 % versus HU 47 % (Relative Risk 0.56 for cisplatin groups)	Grade 3 and 4 toxicity more likely in 3-drug group compared to the other groups
Peters et al. 36] GOG 109/ intergroup 0107/ SWOG 8797/ RTOG 9112	IB or IIA (243)	Radiotherapy	Radiotherapy plus cisplatin and FU	Greater OS in the cisplatin/FU group 81 % versus RT alone group 71 % ($p=0.007$)	Greater PFS in the cisplatin/FU group 80 % versus RT alone group 63 % ($p=0.003$)	Greater grade 3 and 4 toxicity in the RT + cisplatin/FU group
Pearcey et al. [37] NCI Canada	IB-IVA (253)	Radiotherapy	Radiotherapy plus weekly cisplatin	No difference in OS, 62 % in cisplatin + RT versus 58 % in RT alone group ($p>0.05$)	No difference in PFS between groups ($p>0.05$)	Greater decrease in hemoglobin levels in the cisplatin + RT group (30 %) versus RT-alone group (20 %)

Landoni et al. [26]	IB-IIA (343)	Radiotherapy	Surgery (with adjuvant RT delivered for surgical stage pT2b or greater, less than 3 mm safe cervical stroma, cut through or positive nodes)	No difference in OS between groups ($p > 0.05$)	No difference in PFS between groups ($p > 0.05$)	Greater morbidity in surgery group (28 %) versus RT group (12 %), ($p = 0.0004$)
Sedlis et al. [39] GOG 92	IB (277)	Surgery plus adjuvant radiotherapy	Surgery with no further treatment (NFT)	Follow-up too short for survival analysis	Greater PFS in the surgery + RT group 88 % versus surgery alone group 79 % ($p = 0.008$)	Greater grade 3/4 events in surgery + adjuvant RT group (6 %) versus surgery alone (2 %)

- Two hundred and fifty-three patients were randomized to receive radiation therapy alone or radiation therapy plus weekly cisplatin for patients with Stage IB–IVA cervical cancer [37].
- No difference in overall survival or progression-free survival.
- Hypotheses why their study did not show a benefit of cisplatin when five other trials showed a benefit:
  - The GOG 120 [34] and the GOG 85 [32] trials differed from the NCI Canada study because they did not have an RT-alone arm.
  - GOG 85 [32] and GOG 109 [36] trials paired cisplatin with fluorouracil instead of cisplatin alone.
  - The RTOG 90-01 trial [33] had an RT-only arm; however, the radiation therapy delivered was extended-field and modified to cover the para-aortics.
  - In the GOG 85 and GOG 120 trials, the median duration of radiation treatment was 62 and 64 days, respectively, whereas the treatment duration was 51 days in the NCI Canada study.
  - The addition of fluorouracil may have contributed to the survival benefit seen in GOG 85 and RTOG 90-01.
- The GOG 123 [35] trial was the most similar to the NCI Canada study in that the comparison arms were the same in both studies (radiation therapy alone vs. radiation therapy and weekly cisplatin); however, the GOG 123 trial showed that there was a survival advantage to weekly cisplatin whereas the NCIC study failed to find a benefit.
  - In the GOG 123 (Keys et al.) study, patients were limited to bulky stage IB2 cervical cancer, whereas the NCI Canada study included patients with stage IB–IVA. Moreover, all patients in the GOG 123 trial received an adjuvant extrafascial hysterectomy following either preoperative radiation therapy alone or preoperative radiation therapy with cisplatin.

- Current NCCN guidelines recommend treatment with external beam radiation therapy with concurrent cisplatin-based chemotherapy in addition to brachytherapy for treatment of this subset of patients.

Vulvar Cancer

- Carcinoma of the vulva is a rare gynecologic malignancy, comprising less than 3 % of gynecologic cancers [40].
- In women greater than 50 years of age, vulvar cancer is often associated with non-neoplastic epithelial disorders (e.g., chronic inflammation or lichen sclerosis), and does not generally present with cervical neoplasia or condylomas [40].
- In women younger than 50 years, vulvar cancer is often associated with the human papillomavirus (HPV), and generally presents with precursor lesions and condylomata [40].
- The majority of vulvar cancers are diagnosed in the early stages, although older women tend to present with more advanced disease [40].

Treatment of Limited-Stage (Stage I) Vulvar Cancer

- For resectable Stage I vulvar carcinoma, surgery is the primary treatment.
- Radical vulvectomy with bilateral dissection of inguinal groin nodes was the standard of care, but in modern practice, radical local excision is performed with inguinal lymph node dissection based on depth of invasion [40].
- The risk of recurrence is directly related to surgical margins, with >1 cm margin typically associated with the least risk of local recurrence [41].
- Predictors of recurrence following surgery include:
  - Depth of invasion, tumor thickness, infiltrative growth, lymphovascular invasion, increasing keratin, and greater than 10 mitoses on histology [41].

- Adjuvant radiation can be used in the setting of close or positive margins, positive lymph nodes, high-grade lesions and those lesions with lymphovascular space invasion.
- Faul et al. reported results from a retrospective review of 62 patients with either close (<8 mm) or positive margins following surgery [42].
  - Half of the patients received radiation therapy covering the vulva, bilateral groins and lower pelvis, while the other half of patients were observed.
  - The use of postoperative radiation therapy lowered the rate of locoregional recurrence (69 % of the observed group recurred compared to 33 % in the radiation therapy group) [42].

Treatment of Advanced-Stage (Stage II–IV) Vulvar Cancer

- For unresectable, Stage II–IV vulvar carcinoma, the primary treatment is radiation therapy with interstitial or intracavitary brachytherapy [43].
- Chemotherapy can also be used for more advanced cases; commonly used agents include fluorouracil, cisplatin and carboplatin.
- GOG 101
  - Designed to determine the feasibility of preoperative chemoradiation in patients with advanced vulvar cancer [44].
  - Seventy-three patients with clinical Stage III–IV squamous cell carcinoma received a split course (i.e., with a planned treatment break) of concurrent chemotherapy (cisplatin and 5-fluorouracil) and radiation therapy followed by surgical excision of the residual tumor plus bilateral inguinal lymph node dissection.
  - Following chemoradiation, 47 % patients had no visible vulvar cancer, and only 3 % were found to have residual unresectable disease [44].

  - Conclusion: preoperative chemoradiation therapy may decrease the need for total pelvic exenteration in patients with advanced stage vulvar cancer [44].

- GOG 205

  - Designed to improve upon the GOG 101 protocol for utilizing concurrent chemoradiation as the primary treatment of locally advanced vulvar carcinoma [45].
    - The GOG 205 protocol specified weekly cisplatin with radiation therapy (adopting the standard of care for squamous cell carcinoma of the cervix), eliminated the planned treatment break utilized in GOG 101, and delivered a higher total dose to the primary tumor [45].
  - Fifty-eight patients with locally advanced (T3 or T4 tumors not amenable to surgical resection with radical vulvectomy) were given this higher dose of radiation therapy (57.6 Gy) with weekly cisplatin, followed by surgical resection of any residual tumor (or biopsy to confirm no residual tumor) [45].
  - Sixty-four percent of patients achieved a complete clinical response, which was noted to be an improvement from the 47 % cited in the GOG 101 study.
  - Conclusion: based on GOG 101 and GOG 205, primary chemoradiation should be considered as initial treatment for vulvar cancer that would otherwise require pelvic exenteration or partial removal of the closely involved structures (i.e., urethra, vagina, anus, bladder, rectum).

Vaginal Cancer

- Primary vaginal neoplasms are rare, comprising less than 2 % of gynecologic malignancies [46]. If any part of the lesion touches the cervix it is classified as a cervical carcinoma.
- Vaginal squamous cell carcinoma has many of the same risk factors as cervical cancer, and there is a strong

association between the development of vaginal cancer with persistent HPV infection [46].

  - Other risk factors include: infection with HSV or trichomonas, an increasing number of sexual partners, long-term pessary use, smoking, immunosuppression, prior pelvic radiation, and maternal use of diethylstilbestrol.

- Generally, vaginal cancer is preceded by a precursor vaginal intraepithelial neoplasia lesion [46].
- A higher proportion of late-stage disease is seen in Black, Asian Pacific Islander, Hispanic and older women, and a lower 5-year survival rate is seen in these groups [46].

  - Squamous cell carcinoma is the most common histology; however, adenocarcinoma and non-epithelial tumors (e.g., melanoma, sarcoma) are possible and carry a worse prognosis than squamous cell histology.

- Surgery is the standard of care for vaginal carcinoma in situ, and primary radiation therapy (consists of EBRT with a brachytherapy boost) is the standard of care for localized vaginal cancer [47].

  - Brachytherapy can be considered alone for more limited lesions (<2 cm, <0.5 cm thick). Surgical options are generally considered to result in increased morbidity than radiation.

- Most of the literature is retrospective, and there are no randomized controlled trials comparing surgery with radiation therapy.

Retrospective Studies

- Number of retrospective studies have documented outcomes of vaginal cancer treated with primary radiation therapy [48–53].

  - Frank et al. reported outcomes from a retrospective series of 193 patients with Stage I–IV vaginal carcinoma treated with EBRT (40–45 Gy) followed by brachytherapy

(to deliver total of 75–80 Gy) [48]. Disease specific survival was 85 % for Stage I patients, 78 % for Stage II, and 58 % for Stage III–IV patients.

- Most common type of failure was locoregional.
- Conclusion: primary radiation therapy can provide excellent outcomes for patients with vaginal carcinoma [48].

– Mock et al. documented outcomes for using HDR brachytherapy alone or in conjunction with EBRT to treat primary vaginal carcinoma, and report that HDR brachytherapy is effective and tolerable [51].
– Kucera et al. conducted a retrospective series to compare HDR to conventional LDR brachytherapy and found no difference in overall survival with HDR compared to LDR brachytherapy [54].

- Primary radiation therapy is an effective treatment for patients with vaginal carcinoma, especially patients with Stage I disease [53].
- For patients with tumors beyond Stage I, brachytherapy is necessary to enhance locoregional control, and the use of systemic chemotherapy may improve survival in patients with more advanced disease or distant metastases [53].
- Concurrent chemotherapy and radiation therapy can be given in the initial treatment of locally advanced vaginal cancer [55–58].

– Commonly used agents include 5-fluorouracil, cisplatin, mitomycin.
– Samant et al. published results from a Canadian retrospective series that included 12 patients with Stage II–IVA vaginal cancer treated with concurrent weekly cisplatin plus radiation therapy (EBRT plus brachytherapy) [56].

- The overall survival rate after 5 years was 66 %, with 75 % progression-free survival and 92 % locoregional control [56].

  - Dalrymple et al. (2004)
    - Fourteen patients with Stage I–III vaginal carcinoma were treated with primary chemoradiation therapy [57]. Patients received either 5-fluorouracil (5-FU), 5-FU/cisplatin, or mitomycin, and the authors reported 65 % survival after a median follow-up of 8 years [57].

- Thus, primary chemoradiation can be effective for the treatment of vaginal cancer and should be considered especially for more advanced cases.

Ovarian Cancer, Primary Peritoneal, and Fallopian Tube Carcinoma

Ovarian Cancer

- For the majority of ovarian cancer histologies (epithelial, sex-cord stromal, and germ cell) the standard of care is a total abdominal hysterectomy with bilateral salpingo-oophorectomy with staging as the initial treatment.
- For epithelial ovarian cancer, current NCCN guidelines suggest that patients with Stage IA–IB Grade 1 disease be observed, and patients with Stage IA–IB Grade 2 or greater disease receive chemotherapy with a taxane/carboplatin.
- Whole abdomen radiation therapy is no longer recommended in the initial treatment of ovarian cancer, but radiation therapy plays an important role in palliative care.

Primary Peritoneal Carcinoma

- Extra-ovarian primary peritoneal carcinoma is similar to serous ovarian carcinoma in terms of clinical presentation, appearance on histology, and response to chemotherapy [59].
- Primary peritoneal carcinoma accounts for nearly 10 % of cases where the presumed diagnosis is ovarian cancer and

it can arise following bilateral oophorectomy that is performed for reasons of prophylaxis or for removal of benign tumors [59, 60].

  - The histology in most cases is serous, although non-serous tumors can be seen [59, 60].

- Debulking surgery and multi-agent cisplatin-based chemotherapy are the standard treatments [60], and radiation therapy can be employed for palliative indications.

Fallopian Tube Carcinoma

- Primary fallopian tube carcinoma is an extremely aggressive but very rare neoplasm, accounting for less than 2 % of gynecologic malignancies [61].
- Primary fallopian tube carcinoma is treated similarly to epithelial ovarian cancer, with surgery and chemotherapy as cornerstones of treatment [61].
- Klein et al. reported the results of a multicenter retrospective study examining outcomes following postoperative adjuvant radiation or chemotherapy for 95 patients with Stage I–II primary fallopian tube carcinoma [62].

  - The authors reported no difference in overall survival between adjuvant radiation therapy versus chemotherapy [62].

- Radiation therapy can also be used in the palliative setting for cases of advanced primary fallopian tube carcinoma.

Palliative Radiation

- Palliative radiotherapy can be employed to ameliorate pain and bleeding that may arise in the advanced stages of a gynecologic malignancy.
- A variety of regimens have been employed in the palliative setting, ranging from treatments in a single dose, daily treatments or twice-daily fractionation schemes.

- RTOG 7905
  - Phase II study of 48 patients designed to document treatment outcomes with palliative radiotherapy and misonidazole for advanced pelvic malignancy [63].
  - Patients received a single dose of 10 Gy repeated at 4 week intervals for a total of 3 fractions. Approximately 68 % of patients exhibited some response, but there was a high rate of complications (49 % crude late complications rate) [63].
- RTOG 8502
  - Prospective longitudinal study designed to improve upon the palliative fractionation scheme employed in RTOG 7905.
  - Women with advanced gynecologic malignancies received palliative radiation therapy to 44 Gy in 3.7 Gy fractions delivered BID for 2 consecutive days followed by a break before the next set of 4 treatments [64].
  - 6.9 % patients had late grade 3+ complications at 18 months, which represents a significant decrease from the 49 % seen in RTOG 7905, and no one receiving less than 30 Gy had late toxicity [64].

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