Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Koehler C, Gottschalk E, Chiantera V, Marnitz S, Hasenbein K, Schneider A. From laparoscopic assisted radical vaginal hysterectomy to vaginal assisted laparoscopic radical hysterectomy. *BJOG.* 2012;119(2):254-262.	Review/Other-Tx	N/A	To describe the technique and results of laparoscopic assisted radical vaginal hysterectomy and the transition to vaginal assisted laparoscopic radical hysterectomy.	Vaginal assisted laparoscopic radical hysterectomy is an oncologically valid alternative to abdominal radical hysterectomy, laparoscopic assisted radical vaginal hysterectomy, total laparoscopic, and robotic in patients with cervical cancer <IB2. It offers low blood loss and few intraoperative complications.	4
2. Clark JG. A more radical method of performing hysterectomy for cancer of the uterus, *Bull. Johns Hopkins Hosp*. 6 (1895).120-124.	Review/Other-Tx	20 cases	Historical article: based on autopsy series showing that 15/20 patients with cervical cancer had disease past limits of resection, developed and performed first 2 cases of what is now recognized as radical abdominal hysterectomy for cervical cancer.	No long-term follow-up. Operative notes describe wide excision of broad ligament, ligation of uterine artery at origin, resection of upper vagina.	4
3. Wertheim E. A discussion on the diagnosis and treatment of cancer of the uterus. *British Medical Journal.* 1905;2:689-704.	Review/Other-Tx	>270	Historical article: presented an update of his extensive operative series at 73rd annual meeting of British Medical Association. Emphasized importance of resecting pelvic lymph nodes.	18% operative mortality. 60%–70% DFS at 4–5 years. 28% positive lymph nodes (associated with more advanced tumors), 30% enlarged but negative lymph nodes. By 1922 he had performed over 1,500 operations.	4
4. Okabayaski H. Radical abdominal hysterectomy for cancer of the cervix uteri. *Surg Gynecol Obstet.* 1921;33:335-341.	Review/Other-Tx	N/A	Historical article: described alternative approach to the radical abdominal hysterectomy: 1) more extensive resection of cardinal ligament; 2) complete resection vesicouterine ligament; 3) posterior procedures (isolation of rectum, resection of uterosacral and cardinal ligaments) performed first.	No patient outcomes in this description of an operative technique developed by his teacher, Professor Takayama, who had operated on an average of 200 cases of uterine cancer per year. Only palpably enlarged lymph nodes were removed.	4
5. Schauta F. Die operation des gebaermutterkrebs mittel des Schuchardtschen paravaginalschnittes. *Motasschr Geburtschiffe Gynaekol.* 1902;15:133-152.	Review/Other-Tx	N/A	Historical article: popularized the vaginal approach to radical hysterectomy.	The advantage of this approach was the markedly lower operative mortality. By 1920 he had performed over 850 radical vaginal operations. Difficult to compare outcomes with other sources because many patients had uterine and not cervical cancer.	4
6. Liu W, Meigs JV. Radical hysterectomy and pelvic lymphadenectomy; a review of 473 cases including 244 for primary invasive carcinoma of the cervix. *Am J Obstet Gynecol.* 1955;69(1):1-32.	Review/Other-Tx	473 cases	To analyze clinical aspects of patients with cancer of the uterus or vagina who had radical hysterectomy and to review the result of surgical treatment for cervical cancer.	Low operative mortality in series (1.7%). One operative death among 244 operations for primary cancer of the cervix. Value of radical hysterectomy with pelvic lymphadenectomy for carcinoma of corpus is yet to be determined.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol.* 1974;44(2):265-272.	Review/Other-Tx	114 extended abdominal hysterectomies	To describe 5 classes of extended hysterectomies used in treating women with cervical cancer.	56% of the women in the Class II operations group had no complications as compared to 20% for Class III and 0% for Class IV and V hysterectomies. Proper use of radical hysterectomy and pelvic lymphadenectomy for women with cervical cancer is debatable.	4
8. Querleu D, Morrow CP. Classification of radical hysterectomy. *Gynecol Oncol.* 2009;115(2):314-315; author reply 315-316.	Review/Other-Tx	N/A	Comment on a letter published in Gynecologic Oncology 2009; 113: 397-398 by Batist Trimbos. Trimbos proposes a classification of radical hysterectomy based on the combination of different letters (L, V, C and D) and numbers, each describing a specific extent of excision of cervical ligaments in the lateral, ventral, caudal, and dorsal direction, respectively.	New categorization of radical hysterectomy is needed. Prof. Trimbos' proposal is not an improvement as a classification, as it is not adaptable to general use. Authors agree that referring to a TNM model recalls that every operative report should precisely describe the extent of excision in all directions.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. Plante M, Gregoire J, Renaud MC, Roy M. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. *Gynecol Oncol.* 2011;121(2):290-297.	Observational-Tx	125 vaginal radical trachelectomies	To review vaginal radical trachelectomies to assess the oncologic, fertility and obstetrical outcomes.	During the study period, 140 vaginal radical trachelectomies were planned and 125 were performed. The median age of the patients was 31 and 75% were nulliparous. The majority of the lesions were stage IA2 (21%) or IB1 (69%) and 41% were grade 1. In terms of histology, 56% were squamous and 37% were adenocarcinomas. Vascular space invasion was present in 29% of cases, and 88.5% of the lesions measured ≤2cm. The mean follow-up was 93months (range: 4–225 months). There were 6 recurrences (4.8%) and 2 deaths (1.6%) following vaginal radical trachelectomies. The actuarial 5-year recurrence-free survival was 95.8% [95% CI: 0.90–0.98], whereas it was 79% [95% CI: 0.49–0.93] in the group where the vaginal radical trachelectomies was abandoned (P=0.001). Higher tumor grade, LVSI and size >2 cm appeared to be predictive of the risk of abandoning vaginal radical trachelectomies (P=0.001, P=0.025 and P=0.03, respectively). Tumor size >2 cm was statistically significantly associated with a higher risk of recurrence (P=0.001). In terms of obstetrical outcome, 58 women conceived a total of 106 pregnancies. The first and second trimester miscarriage rates were 20% and 3%, respectively, and 77 (73%) of the pregnancies reached the third trimester, of which 58 (75%) delivered at term. Overall, 15 (13.5%) patients experienced fertility problems, 40% of which were due to cervical factor. 12 (80%) were able to conceive, the majority with assisted reproductive technologies.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Cibula D, Pinkavova I, Dusek L, et al. Local control after tailored surgical treatment of early cervical cancer. *Int J Gynecol Cancer.* 2011;21(4):690-698.	Observational-Tx	192 patients who had undergone radical hysterectomy (n = 171), radical parametrectomy (n = 12), or radical trachelectomy (n = 9)	To analyze oncological outcome and prognostic parameters in patients with early stages cervical cancer after tailored and well-standardized surgical treatment with an adequate follow-up.	Event-free and overall 5-year survivals probabilities reached 92.7% (CI, 89.5%–95.9%) and 94.1% (CI, 90.9%–97.3%). There was only 1 isolated pelvic recurrence found of the total of 10 recurrences. Adjuvant RT was given to only 22% of patients. The most significant independent prognostic parameters in stage IB tumors were lymph node status, histological type, and tumor volume, whereas in stage II, the parameters included histological type and tumor volume, the latter being inversely related to the prognosis.	2
11. Suprasert P, Charoenkwan K, Khunamornpong S. Pelvic node removal and disease-free survival in cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy. *Int J Gynaecol Obstet.* 2012;116(1):43-46.	Observational-Tx	826 patients	To examine the relationship between the number of pelvic nodes removed and 5-year DFS in early-stage cervical cancer patients who underwent radical hysterectomy and pelvic lymphadenectomy.	5-year DFS was not significantly different among the 4 groups. When patients with and without nodal involvement were considered separately, the 5-year DFS in all groups was not significantly different. At multivariate analysis, the number of pelvic nodes removed was not an independent prognostic factor.	2
12. Du XL, Sheng XG, Jiang T, et al. Sentinel lymph node biopsy as guidance for radical trachelectomy in young patients with early stage cervical cancer. *BMC Cancer.* 2011;11:157.	Observational-Dx	68 women	To assess the feasibility and accuracy of sentinel lymph nodes detection using 99mTc phytate in predicting pelvic lymph nodes status for radical abdominal trachelectomy in patients with early stage cervical cancer.	Sentinel lymph nodes were identified in 64/68 patients (94.1%). Of these, sentinel lymph nodes of 8 patients (11.8%) were positive on frozen sections and proved to be metastasis by final pathologic examination. The sensitivity, accuracy, and false negative rates were 100%, 100%, and 0%, respectively. All 60 patients with negative sentinel lymph nodes underwent radical abdominal trachelectomy successfully. 2 relapses occurred and no one died of tumor progression during follow-up. 5/15 patients with procreative desire conceived 8 pregnancies (3 term delivery, 2 premature birth, 1 spontaneous abortion, and 2 were still in the duration of pregnancy) after surgery.	3
13. Wolfson AH, Varia MA, Moore D, et al. ACR Appropriateness Criteria(R) role of adjuvant therapy in the management of early stage cervical cancer. *Gynecol Oncol.* 2012;125(1):256-262.	Review/Other-Tx	N/A	The use of adjuvant treatment(s) following initial hysterectomy and retroperitoneal nodal harvesting of patients with clinical stage I and II cervical carcinoma is (are) presently based on the pathological assessment of surgical specimens. This report sought to delineate further the clinical application of potential therapeutic interventions and associated follow-up investigations of this patient cohort.	N/A	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Delgado G, Bundy BN, Fowler WC, Jr., et al. A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 1989;35(3):314-320.	Review/Other-Tx	940 patients: 732 had squamous carcinoma	Prospective study of the surgical and pathological data on patients with primary, previously untreated, histologically confirmed stage I cervical cancer.	For patients undergoing pelvic and para-aortic lymphadenectomy and radical hysterectomy, 5 risk factors were significantly associated with microscopic pelvic lymph node metastasis: depth of invasion (P=0.0001), parametrial involvement (P=0.0001), capillary-lymphatic space invasion (P=0.0001), tumor grade (P=0.01), and gross vs occult primary tumor (P=0.009).The factors identified as independent risk factors for pelvic lymph node metastasis by multivariate analysis were capillary-lymphatic space involvement (P<0.0001), depth of invasion (P<0.0001), parametrial involvement (P=0.0005), and age (P=0.02).	4
15. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1990;38(3):352-357.	Observational-Tx	645 patients	Prospective surgical-pathological study of disease-free interval in patients with stage IB SCC of the cervix.	The 3-year disease-free interval for the 545 patients with negative pelvic nodes was 85.6%, and for the 100 with positive pelvic nodes, 74.4%. Disease-free interval correlated strongly with depth of tumor invasion, both in absolute terms (mm) and infractional thirds. Disease-free interval was 94.6% for ≤5 mm, 86.0% for 6-10 mm, 75.2% for 11-15 mm, 71.5% for 16-20 mm, and 59.5% ≥21 mm. In fractional terms, the disease-free interval was 94.1% for superficial third, 84.5% for middle third, and 73.6% for deep third invasion. With respect to clinical tumor size, the disease-free intervals were 94.8%, 88.1%, and 67.6% for occult, ≤3 cm, and >3 cm, respectively. Disease-free interval was 77.0% for those with positive capillary-lymphatic spaces and 88.9% for those with negative capillary-lymphatic spaces. Tumor grade and parametrial status correlated with disease-free interval. Disease-free interval was not significantly different for age, disease status of the surgical margins, tumor description, quadrant involved with tumor, uterine extension, and keratinizing status of tumor cells.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Yeo RM, Chia YN, Namuduri RP, et al. Tailoring adjuvant radiotherapy for stage IB-IIA node negative cervical carcinoma after radical hysterectomy and pelvic lymph node dissection using the GOG score. *Gynecol Oncol.* 2011;123(2):225-229.	Observational-Tx	126 patients	A report on the use of the Gynecologic Oncology Group (GOG) score to tailor treatment decisions.	61 patients underwent either small field RT or standard field RT. There were only 2 known relapses and 1 death due to inter current illness. The median follow up was 57 months and the 5 year DFS was 98.2%. There was no documented Grade 3 or 4 chronic toxicities. There were significantly less (P=0.025) patients with lower limb lymphedema in the small field RT group compared to standard field RT.	2
17. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol.* 1999;73(2):177-183.	Experimental-Tx	277 patients; 137 randomized to pelvic RT and140 to no further treatment	Randomized study to evaluate the benefits and risk of adjuvant pelvic RT aimed at reducing recurrence in women with stage IB cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy.	21 (15%) in the RT group and 39 (28%) in the no further treatment group had a cancer recurrence, 18 of whom were vaginal/pelvic in the RT and 27 in the no further treatment group. Life table analysis indicated a statistically significant (47%) reduction in risk of recurrence (RR = 0.53, P=0.008, one-tail) among the RT group, with recurrence-free rates at 2 years of 88% vs 79% for the RT and no further treatment groups, respectively. Severe or life-threatening (GOG grade 3 or 4) urologic adverse effects occurred in 4 (3.1%) in the RT group and 2 (1.4%) in the no further treatment group; 3 (2.3%) and 1 (0.7%) hematologic; 4 (3.1%) and 0 GI; and 1 (0.8%) and 0 neurologic, respectively. Adjuvant pelvic RT following radical surgery reduces the number of recurrences in women with stage IB cervical cancer at the cost of 6% grade 3/4 adverse events vs 2.1% in the no further treatment group.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys*. 2006;65(1):169-176.	Experimental-Tx	277 patients; 137 randomized to pelvic RT and 140 randomized to observation	To investigate, in a phase III randomized trial, whether postoperative EBRT to the standard pelvic field improves the recurrence-free interval and OS in women with stage IB cervical cancers with negative lymph nodes and certain poor prognostic features treated by radical hysterectomy and pelvic lymphadenectomy.	Of the 67 recurrences, 24 were in the RT arm and 43 were in the observation arm. RT arm showed a statistically significant (46%) reduction in risk of recurrence (HR = 0.54, 90% CI = 0.35 to 0.81, P=0.007) and a statistically significant reduction in risk of progression or death (HR = 0.58, 90% CI = 0.40 to 0.85, P=0.009). With RT, 8.8% of patients (3/34) with adenosquamous or adenocarcinoma tumors recurred vs 44.0% (11/25) in observation. Fewer recurrences were seen with RT in patients with adenocarcinoma or adenosquamous histologies relative to others (HR for RT by histology interaction = 0.23, 90% CI = 0.07 to 0.74, P=0.019).After an extensive follow-up period, 67 deaths have occurred: 27 RT patients and 40 observation patients. The improvement in OS (HR = 0.70, 90% CI = 0.45 to 1.05, P=0.074) with RT did not reach statistical significance. Pelvic RT after radical surgery significantly reduces the risk of recurrence and prolongs PFS in women with stage IB cervical cancer. RT appears to be particularly beneficial for patients with adenocarcinoma or adenosquamous histologies. Circumstances that may have influenced the OS differences are considered.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Rogers L, Siu SS, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. *Cochrane Database Syst Rev.* 2012;5:CD007583.	Review/Other-Tx	2 randomized control trials, 397 women	To evaluate the effectiveness and safety of adjuvant therapies (RT, chemotherapy followed by RT, chemoradiation) after radical hysterectomy for early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stages IB1, IB2 or IIA).	2 randomized control trials, which compared adjuvant RT with no adjuvant RT, met the inclusion criteria; they randomized and assessed 397 women with stage IB cervical cancer. Meta-analysis of these 2 randomized control trials indicated no significant difference in survival at 5 years between women who received radiation and those who received no further treatment (RR = 0.8; 95% CI, 0.3 to 2.4). However, women who received radiation had a significantly lower risk of disease progression at 5 years (RR 0.6; 95% CI, 0.4 to 0.9).Although the risk of serious adverse events was consistently higher if women received RT rather than no further treatment, these increased risks were not statistically significant, probably because the rate of adverse events was low.	4
20. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000;18(8):1606-1613.	Experimental-Tx	243 patients (127 RT + chemotherapy patients and 116 RT patients)	Randomized study to determine whether the addition of cisplatin-based chemotherapy to pelvic RT will improve the survival of early-stage, high-risk patients with cervical carcinoma.	HR for PFS and OS in the RT only arm vs the RT + chemotherapy arm are 2.01 (P=.003) and 1.96 (P=.007), respectively. Projected PFS at 4 years are 63% with RT and 80% with RT + chemotherapy. Projected OS rate at 4 years is 71% with RT and 81% with RT + chemotherapy. Grades 3 and 4 hematologic and GI toxicity were more frequent in the RT + chemotherapy group. The addition of concurrent cisplatin-based chemotherapy to RT significantly improves PFS and OS for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
21. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol.* 2005;96(3):721-728.	Observational-Tx	243 (RT = 116; RT + chemotherapy = 127)	To retrospectively analyze data from a previously reported randomized trial of pelvic RT or RT + chemotherapy in patients undergoing radical hysterectomy and pelvic lymphadenectomy with positive pelvic lymph nodes, parametrial involvement, or surgical margins; to explore associations between RT + chemotherapy; and to investigate histopathologic and clinical factors which might be predictive of recurrence.	The absolute improvement in 5-year survival for adjuvant chemotherapy in patients with tumors ≤2 cm was only 5% (77% vs 82%), while for those with tumors >2 cm it was 19% (58% vs 77%). Similarly, the absolute 5-year survival benefit was less evident among patients with 1 nodal metastasis (79% vs 83%) than when at least 2 nodes were positive (55% vs 75%). In this exploratory, hypothesis-generating analysis, adding chemotherapy to RT after radical hysterectomy, appears to provide a smaller absolute benefit when only 1 node is positive or when the tumor size is <2 cm. Further study of the role of chemotherapy after radical hysterectomy in patients with a low risk of recurrence may be warranted.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Rosa DD, Medeiros LR, Edelweiss MI, Pohlmann PR, Stein AT. Adjuvant platinum-based chemotherapy for early stage cervical cancer. *Cochrane Database Syst Rev.* 2012;6:CD005342.	Review/Other-Tx	3 trials, 368 women	To evaluate the effectiveness and safety of platinum-based chemotherapy after radical hysterectomy, RT, or both in the treatment of early stage cervical cancer.	3 trials including 368 evaluable women with early cervical cancer were included in the meta-analyses. The median follow-up period in these trials ranged from 29 to 42 months. All women had undergone surgery first. 2 trials compared chemotherapy combined with RT to RT alone; and 1 trial compared chemotherapy followed by RT to RT alone. It was not possible to perform subgroup analyses by stage or tumor size. Compared with adjuvant RT, chemotherapy combined with RT significantly reduced the risk of death (2 trials, 297 women; HR = 0.56, 95% CI: 0.36 to 0.87) and disease progression (2 trials, 297 women; HR = 0.47, 95% CI: 0.30 to 0.74), with no heterogeneity between trials (I(2) = 0% for both meta-analyses). Acute grade 4 toxicity occurred significantly more frequently in the chemotherapy plus RT group than in the RT group (RR 5.66, 95% CI: 2.14 to 14.98). The authors considered this evidence to be of a moderate quality due to small numbers and limited follow-up in the included studies. In addition, it was not possible to separate data for bulky early stage disease. In the 1 small trial that compared adjuvant chemotherapy followed by RT with adjuvant RT alone there was no significant difference in disease recurrence between the groups (HR = 1.34; 95% CI: 0.24 to 7.66) and OS was not reported. The authors considered this evidence to be of a low quality. No trials compared adjuvant platinum-based chemotherapy with no adjuvant chemotherapy after surgery for early cervical cancer with risk factors for recurrence.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
23. Cheng X, Cai SM, Li ZT, et al. Concurrent chemotherapy and adjuvant extended field irradiation after radical surgery for cervical cancer patients with lymph node metastases. *Int J Gynecol Cancer.* 2008;18(4):779-784.	Observational-Tx	25 patients with FIGO stage IB-IIB (IB, 3; IIA, 15; and IIB, 7) cervical carcinoma	Retrospective study to report experience with concurrent chemotherapy and adjuvant extended field irradiation after radical surgery for cervical carcinoma patients with common iliac node and/or multiple pelvic lymph nodes metastases.	3-year PFS and OS rates were 63% and 76%, respectively. PFS rates with multiple pelvic node and common iliac node metastases were 69% and 61%, respectively. Pelvic recurrence rate was 8% (2/25) and that for distant metastases was 32% (8/25). The median interval from the surgery to the recurrence was 14 months (range, 5-29 months). 19 (76%) patients experienced grades 1-2 and 4 (16%) experienced grades 3-4 neutropenia.15 patients (60%) experienced grades 1-2 and 1 (4%) experienced grades 3-4 GI toxicity. Concurrent chemotherapy and adjuvant extended field irradiation after radical surgery achieved good local control with acceptable toxicity. However, subsequent distant metastasis was still the predominant form of treatment failure even after consolidation chemotherapy.	2
24. Demirci S, Ozsaran Z, Ozsaran A, et al. Evaluation of treatment results and prognostic factors in early-stage cervical carcinoma patients treated with postoperative radiotherapy or radiochemotherapy. *Eur J Gynaecol Oncol.* 2012;33(1):62-67.	Observational-Tx	256 Stage IB and II cervical cancer patients	To investigate the clinical features, prognostic factors, and treatment outcome in early-stage cervical carcinoma patients treated with postoperative RT/radiochemotherapy.	Median follow-up duration was 60.5 months (range: 6–202 months). 5-year locoregional control, DFS, disease specific survival and OS rates were 90.8%, 83.4%, 91.2%, and 85%, respectively. In multivariate analysis; bulky tumor (>4 cm) was shown as an important prognostic factor for locoregional control, DFS and disease specific survival. Pretreatment hemoglobin level (<10 g/dL) was associated with lower OS rate. Endometrial involvement was associated with lower locoregional control and DFS. Treatment break >14 days showed significance for DFS and disease specific survival. Metastatic lymph node ratio was found as a valuable prognostic factor for all endpoints (locoregional control, DFS, disease specific survival and OS). The rate of grade 3-4 late toxicity was 3.6% and 2%, respectively.	2

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
25. Takeshima N, Umayahara K, Fujiwara K, Hirai Y, Takizawa K, Hasumi K. Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIA cervical cancer. *Gynecol Oncol.* 2006;103(2):618-622.	Observational-Tx	65 patients	To determine the effectiveness of chemotherapy alone as postoperative adjuvant therapy for intermediate- and high-risk cervical cancer.	Estimated 5-year DFS was 93.3% for the 30 patients with intermediate-risk tumors (100% for those with SCC and 71.4% for those with adenosquamous carcinoma) and 85.7% for the 35 patients with high-risk tumors (89.3% for those with SCC and 71.4% for those with adenosquamous carcinoma). The incidence of locoregional recurrence was 3.3% in the intermediate-risk group and 8.6% in the high-risk group. Side effects of chemotherapy and complications of the combined therapy were within acceptable limits. No patient had severe bleomycin-related pulmonary toxicity. Only 1.5% of patients developed small bowel obstruction, which was cured by conservative therapy.	1
26. Mabuchi S, Okazawa M, Matsuo K, et al. Impact of histological subtype on survival of patients with surgically-treated stage IA2-IIB cervical cancer: adenocarcinoma versus squamous cell carcinoma. *Gynecol Oncol.* 2012;127(1):114-120.	Observational-Tx	520 patients	To evaluate the significance of adenocarcinoma compared with SCC with regard to the survival of surgically-treated early stage cervical cancer patients.	Adenocarcinoma histology was associated with significantly decreased disease specific survival compared with SCC histology in the intermediate- and high-risk groups (HR: 3.06 and 2.88, respectively, both $P<0.05$) while there was no survival difference in the low-risk group ($P=0.1$). Among patients who received any types of adjuvant RT, disease specific survival of adenocarcinoma histology patients were significantly poorer than SCC histology. Multivariate analysis demonstrated adenocarcinoma histology to be an independent predictor of decreased disease specific survival in both concurrent chemoradiotherapy and RT groups. Moreover, pelvic nodal metastasis significantly predicted the poor survival of patients with AC histology who received concurrent chemoradiotherapy in multivariate analysis.	2

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
27. Matsuo K, Mabuchi S, Okazawa M, et al. Utility of risk-weighted surgical-pathological factors in early-stage cervical cancer. *Br J Cancer.* 2013;108(6):1348-1357.	Observational-Tx	540 cases	To evaluate the survival outcomes of surgically treated early-stage cervical cancer patients by surgical–pathological risk factors examining the effects of number and HR for survival. Its utility of scoring was further examined to assess the treatment response of postoperative adjuvant therapy.	HRs for risk factors relating to DFS was: lympho-vascular space invasion 3.95, nodal metastasis 3.88, adenocarcinoma 3.40, large tumor 2.36, positive margin 1.99, deep stromal invasion 1.29, and parametria invasion 1.21. The HR-weighted scoring method showed a high predictive value for recurrence (area-under-curve 0.836, P<0.001). HR-weighted scores were negatively correlated to DFS, and the cases with score ≥12.5 showed 5-year DFS rate of 23.8%. Tumors with larger score offset the benefits of concurrent chemoradiotherapy over RT alone for postoperative adjuvant treatment (P<0.001).	2
28. Lee HJ, Han S, Kim YS, et al. Individualized prediction of overall survival after postoperative radiation therapy in patients with early-stage cervical cancer: a Korean Radiation Oncology Group study (KROG 13-03). *Int J Radiat Oncol Biol Phys.* 2013;87(4):659-664.	Observational-Tx	1,702 patients	To construct a nomogram to predict 5-year OS after postoperative RT for stage IB to IIA cervical cancer.	The median follow-up period for surviving patients was 75.6 months, and the 5-year OS probability was 87.1%. The final model was constructed using the following variables: age, number of positive pelvic lymph nodes, parametrial invasion, lymphovascular invasion, and the use of concurrent chemotherapy. The nomogram predicted the 5-year OS with a c-index of 0.69, which was superior to the predictive power of the FIGO staging system (c-index of 0.54).	2
29. Small W, Jr., Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys.* 2008;71(2):428-434.	Review/Other-Tx	N/A	To develop an atlas of the CTV definitions for postoperative RT of endometrial and cervical cancer to be used for planning pelvic IMRT.	The committee achieved a consensus CTV definition for postoperative therapy for endometrial and cervical cancer. The CTV should include the common, external, and internal iliac lymph node regions. The upper 3.0 cm of the vagina and paravaginal soft tissue lateral to the vagina should also be included. For patients with cervical cancer, or endometrial cancer with cervical stromal invasion, it is also recommended that the CTV include the presacral lymph node region.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Klopp AH, Moughan J, Portelance L, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys.* 2013;86(1):83-90.	Observational-Tx	83 patients	To investigate hematologic toxicity in Radiation Therapy Oncology Group (RTOG) 0418, a prospective study to test the feasibility of delivering postoperative IMRT for cervical and endometrial cancer in a multi-institutional setting.	Patients with cervical cancer treated with weekly cisplatin and pelvic IMRT had grades 1-5 HT (23%, 33%, 25%, 0%, and 0% of patients, respectively). Among patients with cervical cancer, 83% received 5 or more cycles of cisplatin, and 90% received at least 4 cycles of cisplatin. The median percentage volume of bone marrow receiving 10, 20, 30, and 40 Gy in all 83 patients, respectively, was 96%, 84%, 61%, and 37%. Among cervical cancer patients with a V40 >37%, 75% had grade 2 or higher HT compared with 40% of patients with a V40 ≤37% (P =.025). Cervical cancer patients with a median bone marrow dose of >34.2 Gy also had higher rates of grade ≥2 HT than did those with a dose of ≤34.2 Gy (74% vs 43%, P=.049).	2
31. Ohara K, Tsunoda H, Satoh T, Oki A, Sugahara S, Yoshikawa H. Use of the small pelvic field instead of the classic whole pelvic field in postoperative radiotherapy for cervical cancer: reduction of adverse events. *Int J Radiat Oncol Biol Phys.* 2004;60(1):258-264.	Review/Other-Tx	72 patients treated with small pelvic field (small pelvic group) and 46 patients treated with whole pelvic field (whole pelvic group)	Retrospective study to determine whether use of small pelvic field encompassing only the pericervical regions and upper stream lymphatic will reduce the adverse events that occur with classic whole pelvic field, in postoperative RT for cervical cancer.	Diarrhea (Grades 2-3) and leukopenia (Grades 1-3) occurred significantly more often in whole pelvic group (32.4% and 80.5%, respectively) than in small pelvic group (9.2% and 52.2%, respectively). Among the late events, lymphedema occurred most often overall (5-year rate: small pelvic, 47.0%; whole pelvic, 49.1%). Only ileus occurred at a significantly higher rate in The whole pelvic group than in small pelvic group (5-year rate: 16.2% vs 3.2%). Use of the small pelvic field tailored for node-negative status was suggested to reduce adverse events involving the intestine and hemopoietic system.	4
32. Geller MA, Argenta PA, Thomas SG, Dusenbery KE, Judson PL, Boente MP. Feasibility and morbidity of using saline filled tissue expanders to reduce radiation-induced bowel injury in patients with gynecologic malignancies. *Eur J Obstet Gynecol Reprod Biol.* 2009;143(2):93-97.	Review/Other-Tx	10 patients	To evaluate the feasibility and morbidity of using saline filled tissue expanders to displace the small bowel during RT in patients with gynecologic malignancies.	Tissue expander's placement can successfully isolate small bowel from the pelvis. Usage should be individualized to minimize the likelihood of short and long-term complications, particularly in patients at higher risk of morbidity.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Ghosh K, Padilla LA, Murray KP, Downs LS, Carson LF, Dusenbery KE. Using a belly board device to reduce the small bowel volume within pelvic radiation fields in women with postoperatively treated cervical carcinoma. *Gynecol Oncol.* 2001;83(2):271-275.	Review/Other-Tx	21 patients with cervical cancer, positive nodal disease (n=11), lymph-vascular space invasion (n=2), poor histology (n=3), parametrial disease (n=4), and positive vaginal margin (n=1)	To attempt to reduce the small bowel volume in cervical cancer patients undergoing RT using the belly board device and a 4-field technique.	Median follow-up was 37 months (24–65 months). No significant acute GI or genitourinary toxicity was experienced and no patients have experienced a bowel obstruction to date. The belly board device may offer a means for positioning the mobile small intestine out of the radiation field and improving the tolerance of RT. The belly board device provides a noninvasive technique for reduction of acute and chronic GI morbidity.	4
34. Adli M, Mayr NA, Kaiser HS, et al. Does prone positioning reduce small bowel dose in pelvic radiation with intensity-modulated radiotherapy for gynecologic cancer? *Int J Radiat Oncol Biol Phys.* 2003;57(1):230-238.	Observational-Tx	16 patients	To determine whether the combination of both IMRT and prone positioning on a belly board can reduce small bowel dose further in gynecologic cancer patients undergoing pelvic RT.	Prone positioning on a belly board decreased the small bowel dose in gynecologic pelvic IMRT, and the magnitude of improvement depended on the specific IMRT technique used. With the limited arc technique, prone positioning significantly decreased the irradiated small bowel volume at the 25–50 Gy dose levels compared with supine positioning. Small bowel volumes receiving ≥45 Gy decreased from 19% to 12.5% (P=0.005) with prone positioning. With the extended arc technique, the decrease in irradiated small bowel volume was less marked, but remained detectable in the 35–45 Gy dose levels. Small bowel volumes receiving ≥45 Gy decreased from 13.6% to 10.1% (P=0.03) with prone positioning. The effect of prone positioning on large bowel and bladder was variable. Large bowel volumes receiving ≥45 Gy increased with prone positioning from 16.5% to 20.6% (P=0.02) in the limited arc technique and was unaffected in the extended arc technique.	2

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Taylor A, Powell ME. Conformal and intensity-modulated radiotherapy for cervical cancer. *Clin Oncol (R Coll Radiol)*. 2008;20(6):417-425.	Review/Other-Tx	N/A	To discuss the evidence for the current use and potential applications of these techniques in the treatment of cervical cancer.	There is a high risk of a geographical miss and dose-limiting normal tissue toxicity when treating cervical cancer with conventional RT. With accurate target volume delineation, 3-D RT planning techniques can improve outcomes by ensuring adequate target coverage throughout treatment while reducing doses to the organs at risk. Dose escalation can therefore be considered and further clinical trials are awaited on the various strategies with simultaneous integrated boost-IMRT.	4
36. McAlpine J, Schlaerth JB, Lim P, Chen D, Eisenkop SM, Spirtos NM. Radiation fields in gynecologic oncology: correlation of soft tissue (surgical) to radiologic landmarks. *Gynecol Oncol*. 2004;92(1):25-30.	Review/Other-Tx	100 patients	To determine if radiation fields defined by bony structure landmarks correlate to anatomic boundaries of lymph node dissection marked intraoperatively; and to determine if a patient's body mass index correlates with these anatomic or radiographic boundaries.	Radiation fields defined by traditional bony landmarks would adequately encompass the para-aortic lymph nodes in the majority of patients (91%). For pelvic radiation fields, there was a significant "miss" (39%) of common iliac lymph nodes. Approximately one quarter (26%) of patients would receive inadequate coverage of one or both of the lateral boundaries of pelvic radiation. No apparent correlation of body mass index to vascular or bony landmarks. Radiation fields determined by traditional bony landmarks do not adequately reflect the anatomic (surgical) landmarks associated with the lymphatic drainage of the female reproductive organs.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys.* 2003;56(5):1354-1360.	Observational-Tx	36 patients	To provide a preliminary analysis of chronic GI toxicity in gynecology patients treated with IM-WPRT.	The IM-WPRT and WPRT groups were well balanced in terms of most patient and treatment factors, including age, site, stage, chemotherapy, WPRT dose, and brachytherapy, except for a higher frequency of surgery (75 vs 54%, P=0.02) in the IM-WPRT group. Overall, IM-WPRT patients had a lower rate of chronic GI toxicity (11.1 vs 50.0%, P=0.001) than WPRT patients. The percentage of IM-WPRT patients with Grade 1, 2, and 3 toxicity were 8.3%, 2.8%, and 0%, respectively. Corresponding percentages in the WPRT group were 30.0%, 16.7%, and 3.3%, respectively. The only other factor correlated with chronic GI toxicity was age (P=0.02). On multivariate (logistic regression) analysis controlling for age and other clinical factors, IM-WPRT retained its statistical significance (P=0.01; odds ratio 0.16; 95% CI: 0.04, 0.67).	1
38. Roeske JC, Bonta D, Mell LK, Lujan AE, Mundt AJ. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol.* 2003;69(2):201-207.	Review/Other-Tx	50 patients	To identify dosimetric factors correlated with acute GI toxicity in gynecology patients undergoing IM-WPRT.	14 women (28%) developed clinically significant acute GI toxicity. None of the patient factors were correlated with acute GI toxicity. In addition, the volume of rectum receiving 25%, 50%, 75%, 90%, 100% and 110% of the prescription dose did not reach statistical significance. In contrast, a correlation was observed between the volume of small bowel irradiated and acute GI toxicity, particularly the small bowel volumes receiving 90% and 100% of the prescription dose (P=0.009 and P=0.009, respectively). Controlling for patient and other dosimetric factors, the small bowel volume receiving the 100% of the prescription dose remained the sole significant factor on multivariate analysis (P=0.012).	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51(1):261-266.	Observational-Tx	10 patients with cervical cancer	To determine whether IMRT can achieve adequate dose coverage to the different lymph node regions in the pelvic and para-aortic areas while sparing more effectively than conventional beam arrangement the small bowel, rectum, and bladder.	The volume of small bowel receiving the prescribed dose (45 Gy) with IMRT technique was as follows: 4 fields, 11.01 +/- 5.67%; 7 fields, 15.05 +/- 6.76%; and 9 fields, 13.56 +/- 5.30%. These were all significantly better than with 2-field (35.58 +/- 13.84%) and 4-field (34.24 +/- 17.82%) conventional techniques (P<0.05).The fraction of rectal volume receiving a dose greater than the prescribed dose was as follows: 4 fields, 8.55 +/- 4.64%; 7 fields, 6.37 +/- 5.19%; 9 fields, 3.34 +/- 3.0%; in contrast to 84.01 +/- 18.37% with 2-field and 46.37 +/- 24.97% with 4-field conventional technique (P<0.001).The fractional volume of bladder receiving the prescribed dose and higher was as follows: 4 fields, 30.29 +/- 4.64%; 7 fields, 31.66 +/- 8.26%; and 9 fields, 26.91 +/- 5.57%. It was significantly worse with the 2-field (92.89 +/- 35.26%) and with the 4-field (60.48 +/- 31.80%) techniques (P<0.05).Normal tissue sparing is superior with IMRT in the treatment of cervical cancer.	3
40. Heron DE, Gerszten K, Selvaraj RN, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms small star, filled. *Gynecol Oncol.* 2003;91(1):39-45.	Observational-Tx	10 patients	To evaluate the feasibility of pelvic IMRT in the adjuvant treatment of gynecologic malignancies and to compare the dose-volume histograms and determine the potential impact on acute and long-term toxicity based on the dose to target and nontarget tissues for both planning techniques.	The volume of each organ of interest (small bowel, bladder, and rectum) receiving doses in excess of 30 Gy was compared in the 3D and IMRT treatment plans. The mean volume of small bowel receiving doses in excess of 30 Gy was reduced by 52% with IMRT compared with 3D. A similar advantage was noted for the rectum (66% reduction) and the bladder (36% reduction). The nodal regions at risk and the upper vagina all received the prescribed dose of 45.0 Gy.	3

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Igdem S, Ercan T, Alco G, et al. Dosimetric comparison of intensity modulated pelvic radiotherapy with 3D conformal radiotherapy in patients with gynecologic malignancies. *Eur J Gynaecol Oncol.* 2009;30(5):547-551.	Review/Other-Tx	10 consecutive patients with cervical and endometrial cancer	To prospectively evaluate the potential benefits of IMRT by dose volume histogram comparison of IMRT and 3D conformal RT plans.	IMRT reduced the volume of small bowel receiving more than 45 Gy in all patients. The average absolute volume of small bowel receiving 45 Gy was significantly reduced from 318 cc to 33 cc. No significant increase in the volume of small bowel receiving <20 Gy was observed. IMRT significantly reduces the volume of normal tissues irradiated to high doses without compromising the target coverage. This may potentially lead to a reduction in treatment related toxicities.	4
42. Mundt AJ, Roeske JC, Lujan AE, et al. Initial clinical experience with intensity-modulated whole-pelvis radiation therapy in women with gynecologic malignancies. *Gynecol Oncol.* 2001;82(3):456-463.	Review/Other-Tx	15 women with cervical (9) or endometrial (6) cancer received IM-WPRT; 25 patients treated with conventional WPRT	To describe initial experience with IM-WPRT in gynecologic malignancies.	IM-WPRT plans provided excellent coverage of the target structures in all patients and were highly conformal, providing considerable sparing of the bladder, rectum, and small bowel. Treatment was well tolerated, with grade 0-1 GI and genitourinary toxicity in 46% and 93% of patients, respectively. IM-WPRT patients had a lower rate of grade 2 GI toxicity (53.4% vs 96%, P=0.001) than those treated with conventional WPRT. Moreover, the percentage of women requiring no or only infrequent antidiarrheal medications was lower in the IM-WPRT group (73.3% vs 20%, P=0.001).While grade 2 genitourinary toxicity was also lower in the IM-WPRT patients (6.7% vs 16%), this difference did not reach statistical significance (P=0.38).	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1330-1337.	Review/Other-Tx	40 gynecology patients had IM-WPRT; 35 previously treated conventional WPRT patients	To describe initial clinical experience with IM-WPRT in women with gynecologic malignancies.	IM-WPRT plans provided excellent planning target volume coverage, with considerable sparing of the surrounding normal tissues. On average, 98.1% of the planning target volume received the prescription dose. The average percentage of the planning target volume receiving 110% and 115% of the prescription dose was 9.8% and 0.2%, respectively. IM-WPRT was well tolerated, with no patient developing Grade 3 toxicity. Grade 2 acute GI toxicity was less common in the IM-WPRT group (60 vs 91%, P=0.002) than in the conventional WPRT group. Moreover, the percentage of IM-WPRT and WPRT patients requiring no or only infrequent antidiarrheal medications was 75% and 34%, respectively (P=0.001). Although less Grade 2 genitourinary toxicity was seen in the IM-WPRT group (10% vs 20%), this difference was not statistically significant (P=0.22).	3
44. Folkert MR, Shih KK, Abu-Rustum NR, et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. *Gynecol Oncol.* 2013;128(2):288-293.	Observational-Tx	34 patients	To report a single-institution experience using postoperative pelvic IMRT with concurrent chemotherapy in intermediate- and high-risk early stage cervical cancer.	With a median follow-up of 44 months, 3 patients have recurred; 1 vaginal recurrence, 1 regional and distant, and 1 distant. The 3- and 5-year DFS was 91.2% (95% CI, 81.4%–100%) and OS was 91.1% (95% CI, 81.3%–100%). All failures and all deaths were in the high-risk group (n=3/26). There was 32.3% Grade 3-4 hematologic toxicity, 2.9% acute Grade 3 GI toxicity, and no acute Grade 3 or higher genitourinary toxicity. There were no chronic Grade 3 or higher toxicities.	2
45. Kim JH, Choi JH, Ki EY, et al. Incidence and risk factors of lower-extremity lymphedema after radical surgery with or without adjuvant radiotherapy in patients with FIGO stage I to stage IIA cervical cancer. *Int J Gynecol Cancer.* 2012;22(4):686-691.	Review/Other-Tx	75 patients developed lower-extremity lymphedema	To determine the incidence and risk factors of lower-extremity lymphedema in women who had radical surgery with or without adjuvant RT for FIGO stage I to stage IIA cervical cancer.	The incidence was high in patients with adjuvant RT (odds ratio, 3.47; 95% CI, 2.086–5.788; P = 0.000), with 78.7% of the patients with lower-extremity lymphedema having developed the condition within 3 years after initial treatment.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Ballon SC, Berman ML, Lagasse LD, Petrilli ES, Castaldo TW. Survival after extraperitoneal pelvic and paraaortic lymphadenectomy and radiation therapy in cervical carcinoma. *Obstet Gynecol.* 1981;57(1):90-95.	Observational-Tx	95 patients with invasive squamous carcinoma of the cervix	To examine survival after extraperitoneal pelvic and para-aortic lymphadenectomy and RT in cervical carcinoma.	Operative staging can be performed safely by the extraperitoneal route and RT can be modified on the basis of the true extent of disease. RT fails to cure patients because of distant dissemination of disease as well as an inability of conventional radiotherapeutic techniques to sterilize a large primary tumor volume.	2
47. Varia MA, Bundy BN, Deppe G, et al. Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys.* 1998;42(5):1015-1023.	Observational-Tx	85 patients	A multicenter trial of chemoradiation therapy to evaluate the feasibility of extended field RT with 5-FU and cisplatin, and to determine the progression-free interval, OS, and recurrence sites in patients with biopsy-confirmed para-aortic node metastases from cervical carcinoma.	85/86 patients completed RT and 90% of patients completed both courses of chemotherapy. GOG grade 3-4 acute toxicity were GI (18.6%) and hematologic (15.1%). Late morbidity actuarial risk of 14% at 4 years primarily involved the rectum. Initial sites of recurrence were pelvis alone, 20.9%; distant metastases only, 31.4%; and pelvic plus distant metastases, 10.5%. The 3-year OS and progression-free interval rate were 39% and 34%, respectively, for the entire group. OS was stage I; 50%, stage II; 39%, and stage III/IVA; 38%.	1
48. Haie C, Pejovic MH, Gerbaulet A, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol.* 1988;11(2):101-112.	Experimental-Tx	441 patients with cervical carcinoma	Results of a randomized trial where patients were randomized between pelvic irradiation and pelvic and para-aortic irradiation. This is to determine whether prophylactic para-aortic irradiation is worthwhile in the treatment of advanced cervical carcinoma.	The 4-year no evidence of disease survival rate was 51%. The incidence of severe digestive complications was significantly higher in patients receiving para-aortic irradiation (para-aortic group). Routine para-aortic irradiation for all high risk patients with cervical carcinoma is of limited value, but patients with a high probability of local control can benefit from extended field irradiation, despite an increase in severe digestive complications.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Rotman M, Pajak TF, Choi K, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA.* 1995;274(5):387-393.	Experimental-Tx	337 patients (167 in the pelvic only irradiation arm and 170 in the pelvic plus para-aortic irradiation arm)	10-year results of RTOG 79-20. Randomized trial to determine whether irradiation to the standard pelvic field only improves the response rate and survival in comparison with pelvic plus para-aortic irradiation in patients with high-risk cervical carcinoma, and to investigate patterns of failure and treatment-related toxicity.	10-year OS was 44% for the pelvic only irradiation arm and 55% for the pelvic plus para-aortic irradiation am (P=.02). Cumulative incidence of death due to cervical cancer was estimated as significantly higher in the pelvic only arm at 10 years (P=.01). DFS was similar in both arms; 40% for the pelvic only arm and 42% for the pelvic plus para-aortic arm. Locoregional failures were similar at 10 years for both arms (pelvic only, 35%; pelvic plus para-aortic, 31%; P=.44). In complete responders, the patterns of locoregional failures were the same for both arms, but there was a lower cumulative incidence for first distant failure in the pelvic plus para-aortic irradiation arm (P=.053). Survival following first failure was significantly higher in the pelvic plus para-aortic arm (P=.007). A higher percentage of local failures were salvaged long-term on the pelvic plus para-aortic arm compared with the pelvic only arm (25% vs 8%). The cumulative incidence of grade 4 and 5 toxicities at 10 years in the pelvic plus para-aortic arm was 8%, compared with 4% in the pelvic only arm (P=.06). The death rate due to RT complications was higher in the pelvic plus para-aortic arm (4 [2%] of 170) compared with the pelvic only arm (1 [1%] of 167) (P=.38). The proportion of deaths due to RT complications in the pelvic plus para-aortic arm was higher than in the pelvic only arm (4 [6%] of 67 vs 1 [1%] of 85; P=.24). If the patient had abdominal surgery prior to para-aortic irradiation, the estimated cumulative incidence of grade 4 and 5 complications was 11%, compared with 2% in the pelvic only arm.	1

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Matsuura Y, Kawagoe T, Toki N, Tanaka M, Kashimura M. Long-standing complications after treatment for cancer of the uterine cervix--clinical significance of medical examination at 5 years after treatment. *Int J Gynecol Cancer.* 2006;16(1):294-297.	Review/Other-Tx	109 patients	To examine the side effect in patients who survived for more than 5 years after initial treatment for invasive cervical cancer. Patients were divided into 3 groups: radical surgery alone (group A), RT alone (group B), and radical surgery with postoperative RT (group C).	Dysuria was seen in 8%, and positive catheterized urine culture was noted in about 20% of groups A and C. Hydronephrosis was seen in 2% and 9% of groups A and B, respectively. Colitis or ulcer detected by proctosigmoidoscopy was noted in 15%, 50%, and 43% of groups A, B, and C, respectively, frequently observed in RT group (P=0.0029). Lymphocyst was still present in 6% of group A, and leg edema was noted in 14%, 6%, and 15% of groups A, B, and C, respectively.	4
51. Pieterse QD, Maas CP, ter Kuile MM, et al. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. *Int J Gynecol Cancer.* 2006;16(3):1119-1129.	Observational-Tx	94 women 224 aged matched control	To evaluate the problems with miction, defecation, and sexuality after a radical hysterectomy with or without adjuvant RT for the treatment of cervical cancer stage I-IIA. Study included an observational longitudinal study of self-reported bladder, defecation, and sexual problems with a baseline score.	Patients showed significantly more negative effects on sexual function compared with both the controls and their situation before the treatment throughout 24 months of follow-up. Up to 12 months after the treatment, the patients complained significantly more of little or no urge to urinate and diarrhea as compared with the controls. Adjuvant RT did not increase the risk of bladder dysfunction, colorectal motility disorders, and sexual functions. A radical hysterectomy for the treatment of early-stage cervical carcinoma is associated with adverse effects mainly on sexual functioning.	2
52. Wolf JK. Prevention and treatment of vaginal stenosis resulting from pelvic radiation therapy. *Community Oncology.* 2006;3(10):665-671.	Review/Other-Tx	N/A	Review prevention and treatment of vaginal stenosis.	No results stated.	4

Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Buekers TE, Anderson B, Sorosky JI, Buller RE. Ovarian function after surgical treatment for cervical cancer. *Gynecol Oncol.* 2001;80(1):85-88.	Review/Other-Tx	102 cervical cancer patients; 83 patients had radical hysterectomy and 19 patients had staging laparatomy	Patients were treated with radical hysterectomy and/or lymphadenectomy and ovarian preservation. A retrospective chart review was conducted, followed by a survey to determine the time of menopause.	Mean follow-up for premenopausal patients was 87.0 months. After ovarian transposition without RT, 98.0% of patients retained ovarian function for a mean of 126 months with menopause at a mean of 45.8 years. When ovarian transposition and RT were added, 41% retained ovarian function for a mean of 43 months and a mean age at menopause of 36.6 years. Radical hysterectomy with bilateral ovarian preservation and without ovarian transposition does not significantly reduce the age of menopause. The addition of unilateral oophorectomy or ovarian transposition to this treatment reduces ovarian function appreciably. The addition of RT after ovarian transposition dramatically shortens ovarian function.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

5-FU = Fluorouracil

CI = Confidence interval

CTV = Clinical target volume

DFS = Disease-free survival

EBRT = External-beam radiation therapy

GI = Gastrointestinal

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

IM-WPRT = Intensity-modulated whole pelvic radiation therapy

MRI = Magnetic resonance imaging

OS = Overall survival

PFS = Progression-free survival

RR = Relative risk

RT = Radiation therapy

SCC = Squamous cell carcinoma

WPRT = Whole pelvic radiotherapy