Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61(2):69-90.	15	N/A	Review of global cancer statistics.	The global burden of cancer continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries. A substantial proportion of the worldwide burden of cancer could be prevented through the application of existing cancer control knowledge and by implementing programs for tobacco control, vaccination (for liver and cervical cancers), and early detection and treatment, as well as public health campaigns promoting physical activity and a healthier dietary intake. Clinicians, public health professionals, and policy makers can play an active role in accelerating the application of such interventions globally.	4
2. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* 2009; 105(2):107-108.	15	N/A	To describe the main controversies concerning cervical cancer staging that have contributed to the presently revised FIGO staging for cervical cancer.	Reaching a useful and unified cancer staging system depends on its ability to cope with new epidemiological and clinical evidence (ie, the increase in population screening for cancer, the discovery of new treatments, and the use of new molecular biomarkers). There is an increasing demand that more biological prognostic factors (histological grades, lymphovascular space invasion, serum biomarkers, etc) be included in the staging system, with the aim to better identify patients at high and low risk of dying of their disease. For this reason, scientists should improve their understanding of tumor biology as well as their ability to tailor treatment.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
3. Kim SH, Choi BI, Lee HP, et al. Uterine cervical carcinoma: comparison of CT and MR findings. *Radiology* 1990; 175(1):45-51.	9	30 patients	To compare MRI with CT in uterine cervical carcinoma imaging.	MRI was superior to CT in visualization of the tumor. MRI had an accuracy of 77% in the assessment of thickness of cervical stromal invasion. The accuracy rates of these modalities for parametrial evaluation were 78% for clinical evaluation, 70% for CT, and 92% for MRI. The overall accuracy rates for tumor staging were 70% for clinical evaluation, 63% for CT, and 83% for MRI. MRI is superior to clinical evaluation and CT in parametrial evaluation and the staging of uterine cervical carcinoma.	2
4. Bellomi M, Bonomo G, Landoni F, et al. Accuracy of computed tomography and magnetic resonance imaging in the detection of lymph node involvement in cervix carcinoma. *Eur Radiol* 2005; 15(12):2469-2474.	10	62 patients	To retrospectively and blindly evaluate the accuracy of CT and MRI in diagnosing nodal metastases in patients with cervical carcinoma.	Combining the reading results of both observers, CT showed a sensitivity of 64.6% and specificity of 93.3%; MRI a sensitivity of 72.9% and specificity of 93.1%. PPV was 50.8% for CT and 53% for MRI; while NPV was 96% both for CT and MRI. The expert radiologist reviewing the films obtained better results. Inter-observer variability in the lower quadrants was high for each imaging technique (kappa for CT: 0.71; kappa for MRI: 0.84). Both imaging techniques showed similar screening accuracy in identifying nodal metastases. The radiologist's experience is important in determining the performance of the imaging technique. CT and MRI are only moderately sensitive for detection of nodal metastases and the clinical impact of their results in patient's management is limited.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
5. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol* 2006; 24(36):5687-5694.	9	208 patients with biopsy-proven invasive cervical cancer	Multicenter study (25-centers). To compare MRI, CT, and clinical examination for delineating early cervical cancer and for measuring tumor size. Surgical pathology was the standard of reference. Each imaging study was interpreted prospectively by one onsite radiologist and retrospectively by four independent offsite radiologists, who were all blinded to surgical, histopathologic, and other imaging findings.	Neither MRI nor CT was accurate for evaluating cervical stroma. For uterine body involvement, the area under the receiver operating characteristic curve was higher for MRI than for CT for both prospective (0.80 vs 0.66, respectively; P=.01) and retrospective (0.68 vs 0.57, respectively; P=.02) readings. Retrospective readers could measure diameter by CT in 35%-73% of patients and by MRI in 79%-94% of patients. Prospective readers had the highest Spearman correlation coefficient with pathologic measurement for MRI (r(s) = 0.54), followed by CT (r(s) = 0.45) and clinical examination (r(s) = 0.37; P<.0001 for all). Spearman correlation of multiobserver diameter measurements for MRI (r(s) = 0.58; P<.0001) was double that for CT (r(s) = 0.27; P=.03). MRI is superior to CT and clinical examination for evaluating uterine body involvement and measuring tumor size, but no method was accurate for evaluating cervical stroma.	1
6. Choi HJ, Roh JW, Seo SS, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer* 2006; 106(4):914-922.	9	22	Prospective study to determine the accuracy of MRI and PET/CT for detecting lymph node metastases in patients with uterine cervical carcinoma compared with thin-section histopathologic results from systemic lymphadenectomy. Diagnostic standard used was histopathologic evaluation of lymph nodes.	With MRI, the sensitivity, specificity, and accuracy rates for detecting metastatic lymph nodes in each lymph node group were 30.3% (10/33 lymph node groups), 92.6% (112/121 lymph node groups), and 72.7% (122/154 lymph node groups), respectively; with PET/CT, those rates were 57.6% (19/33 lymph node groups), 92.6% (112/121 lymph node groups), and 85.1% (131/154 lymph node groups), respectively. Statistical analysis showed that PET/CT was more sensitive than MRI (P=0.026) but that there were no statistical differences noted with regard to specificity (P=1.000) or accuracy (P=0.180). Power analysis demonstrated that a sample size of 685 lymph node groups (98 patients) would be necessary to demonstrate that PET/CT was more accurate than MRI (alpha = 0.05; beta = 0.80).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
7. Boughanim M, Leboulleux S, Rey A, et al. Histologic results of para-aortic lymphadenectomy in patients treated for stage IB2/II cervical cancer with negative [18F]fluorodeoxyglucose positron emission tomography scans in the para-aortic area. *J Clin Oncol* 2008; 26(15):2558-2561.	4	38 patients	To study histologic results of complete para-aortic lymphadenectomy.	Three patients had histologically proven para-aortic involvement (metastatic nodes with capsular rupture in the para-aortic area), leading to a NPV of 92% for para-aortic nodal involvement. In this study, 3/38 patients with no para-aortic uptake on FDG-PET/CT imaging had histologically proven para-aortic node involvement. PET/CT imaging without histologic examination of the para-aortic area used to determine RT fields in stage IB2/II cervical cancer would overlook 8% of patients with histologic para-aortic nodal involvement.	2
8. Leblanc E, Gauthier H, Querleu D, et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. *Ann Surg Oncol* 2011; 18(8):2302-2309.	10	125 patients from 5 institutions	To evaluate the accuracy of PET at detecting para-aortic lymph node metastases in LACC patients with a negative morphological imaging.	All had an ilio-infrarenal para-aortic lymphadenectomy, either by laparoscopy (n = 117) or laparotomy (n = 8). Twenty-one patients (16.8%) had pathologically proven para-aortic metastases. Among them, 14 (66.7%) had negative PET/CT. Overall morbidity of surgery was 7.2%. All but one of the complications was mild and did not delay chemoradiotherapy. Sensitivity, specificity, and PPV and NPV of the PET/CT were 33.3%, 94.2%, 53.8%, and 87.5%, respectively, for the detection of microscopic lymph node metastases. Laparoscopic staging surgery seems warranted in LACC patients with negative PET scan who are candidates for definitive concurrent chemoradiotherapy or exenteration.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
9. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer* 2008; 112(9):1954-1963.	1	685 total patients 555 surgical PALN (group S) 130 radiography (group R)	Retrospective, randomized trial to evaluate surgical vs radiographic determination of para-aortic lymph node metastases before chemoradiation for LACC.	Patients in the R group had better performance status (P<.01), less advanced stage (P=.023), and smaller tumor size (P=.004) compared with patients in the S group, although patients with stage III and IV disease in the S group had better 4-year PFS (48.9% vs 36.3%) and OS (54.3% vs 40%) compared with patients in the R group. In multivariate analysis, the R group was associated independently with a poorer prognosis compared with the S group (for disease progression: HR, 1.35, 95% CI, 1.01-1.81; for death: HR, 1.46, 95% CI, 1.08-1.99). Surgical exclusion (compared with radiographic exclusion) of positive PALNs in patients with cervical cancer who received chemoradiation (RT plus C-based chemotherapy) had a significant prognostic impact.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Hasenburg A, Salama JK, Van TJ, Amosson C, Chiu JK, Kieback DG. Evaluation of patients after extraperitoneal lymph node dissection and subsequent radiotherapy for cervical cancer. *Gynecol Oncol* 2002; 84(2):321-326.	4	33 patients	To evaluate patients after extraperitoneal lymph node dissection and subsequent RT for cervical cancer.	The combined treatment approach of extraperitoneal lymph node dissection with RT or chemotherapy/RT was without major complications. Nineteen patients showed a temperature elevation, but only one patient had a fever of greater than 39.0 degrees C. Fourteen (48.3%) of 29 patients experienced some degree of proctitis or diarrhea and 3 (10.3%) experienced cystitis during the course of RT. No grade 3 or 4 acute or late genitourinary or gastrointestinal toxicities were noted. Extraperitoneal lymph node dissection changed the clinical management for 6 patients from a radical hysterectomy to RT and for 7 patients from standard-field RT to EFRT. Without extraperitoneal lymph node dissection these 7 patients would have received RT with standard pelvic fields that would not have treated involved lymph node areas at high risk for subsequent failure. Thirteen (44.8%) of 29 patients received a different treatment than would otherwise have been administered with standard treatment planning. Therefore, we suggest that extraperitoneal lymph node dissection should be performed in all patients with cervical cancer prior to radical surgery or RT.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 1997; 350(9077):535-540.	1	343 patients randomized: 172 to surgery and 171 to radical RT	Prospective randomized trial of RT vs surgery to assess the 5-year survival and the rate and pattern of complications and recurrences associated with each treatment.	After a median follow-up of 87 (range 57-120) months, 5-year overall and DFS were identical in the surgery and RT groups (83% and 74%, respectively, for both groups), 86 women developed recurrent disease: 42 (25%) in the surgery group and 44 (26%) in the RT group. Significant factors for survival in univariate and multivariate analyses were: cervical diameter, positive lymphangiography, and adeno-carcinomatous histotype. 48 (28%) surgery-group patients had severe morbidity compared with 19 (12%) RT-group patients (P=0.0004). There is no treatment of choice for early-stage cervical carcinoma in terms of overall or DFS. Combination of surgery and RT has the worst morbidity, especially urological complications.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
12. Eifel PJ, Moughan J, Erickson B, Iarocci T, Grant D, Owen J. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. Int J Radiat Oncol Biol Phys 2004; 60(4):1144-1153.	7	442 patients 59 facilities	To determine the influence of research findings and evolving technology on the practice of RT in patients with carcinoma of the cervix.	Overall, 40.5%, 25.4%, and 33.9% of patients had stage IA-IIA, IIB, or IIIA-IVA disease, respectively. Patients treated at small facilities were significantly more likely to have received a total dose to Point A of <80 Gy, to have had their treatment protracted to >70 days, and to have undergone adjuvant hysterectomy or chemotherapy. In large facilities, RT was less likely to be protracted to >70 days in the 1996-1999 survey than in the 1992-1994 survey (P<0.0001); however, in small facilities, treatment was more likely to be protracted than in the earlier survey (P=0.06), contributing to increasing disparities between the treatments given in large and small facilities. Overall, 92.4% of patients treated with nonpalliative intent were treated with brachytherapy. Of the patients who received brachytherapy, 16.4% had at least part of their brachytherapy delivered at a HDR. The sharp increase in the use of chemotherapy in 1999 suggested rapid application of the results from randomized trials. However, considerable heterogeneity in practice patterns remains, particularly in the use of brachytherapy. The practice at small facilities appears to differ significantly from that at larger facilities in several respects, with a statistically significantly larger proportion of treatments at small facilities failing to meet current guidelines for optimal treatment.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
13. Erickson B, Eifel P, Moughan J, Rownd J, Iarocci T, Owen J. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): a patterns of care study. *Int J Radiat Oncol Biol Phys* 2005; 63(4):1083-1092.	15	408 patients	To analyze the details of brachytherapy practice in patients treated for carcinoma of the cervix in the United States between 1996 and 1999.	Overall, 94% of patients who completed treatment with curative intent received brachytherapy. Of these patients who had brachytherapy, 77.8%, 13.3%, and 0.9%, respectively, were treated with LDR, HDR, or a combination of HDR and LDR brachytherapy; 7.9% had interstitial brachytherapy (5.7% LDR and 1.9% HDR, 0.3% mixed). In facilities that treated >2 patients per year, 15.5% and 9.4% of brachytherapy procedures included HDR or interstitial, respectively; in facilities that treated fewer patients, 3.4% had HDR brachytherapy, and only 1.2% had interstitial brachytherapy. The median duration of treatment and median Point A dose were very similar for patients treated with HDR or LDR. Patients with HDR were treated using a variety of treatment schedules. Different applicator types were favored for LDR vs HDR. Of patients treated with HDR, 73.4% had no brachytherapy bladder or rectal doses recorded, suggesting that full dosimetric calculations were performed only for the first fraction in many institutions. Facility size significantly impacted on referral to another institution for brachytherapy, brachytherapy dose, and treatment duration.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
14. Barillot I, Horiot JC, Cuisenier J, et al. Carcinoma of the cervical stump: a review of 213 cases. Eur J Cancer 1993; 29A(9):1231-1236.	7	213 cases	Multi-institutional prospective cooperative study to evaluate carcinoma of the cervical stump.	• RT alone (external and brachytherapy) was given to 77%, brachytherapy and surgery to 15% and surgery alone to 8%). • FIGO stage distribution was: I (31%), IIa (15%), IIb (27%), IIIa (5%), IIIb (17%) and IV (5%). 5-year locoregional control per stage was 100% in Ia, 85% in Ib, 82% in IIa, 71% in IIb, 45% in IIIa, 54% in IIIb and 30% in IV. • Corrected 5-year survival per stage was 82% in Ib, 78% in IIa, 73% in IIb, 69% in IIIa, 38% in IIIb and 0% in IV. The diameter of disease in stage II strongly influenced the 5-year locoregional control (81% for tumors of <3 cm vs 68% for tumors >3 cm). • Lymphangiogram was associated with a 44.5% 5-year locoregional control when positive vs 74% when non-positive. Brachytherapy was advantageous in obtaining locoregional control in patients receiving external irradiation and brachytherapy: 81.5% vs 38.5% in patients treated with external RT alone. • Radical RT seems to provide similar results of locoregional control and survival at equal stages in carcinoma of the cervical stump compared to carcinoma developed on an intact uterus. The rate of severe complications reported with the French-Italian glossary is 13% for G3 and 3% for G4, which is close to the observed rate during the same period in our series of radical RT to the intact uterus.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys* 1991; 20(4):667-676.	3a	1,558 total patients Stage 1 618 patients Stage 2 632 patients Stage 3 289 patients	Two national surveys of patients treated in 1973 and 1978 for squamous cell cancer of the uterine cervix. In addition, a survey of patients treated in 1973 from selected large facilities was conducted to establish outcome with "optimal" RT.	Multivariate analysis revealed that unilateral parametrial involvement for stage IIB and unilateral sidewall involvement for stage III are significant positive prognostic factors with respect to survival after treatment with RT. Although FIGO staging is the single most important pretreatment prognostic factor with respect to survival and infield pelvic failure, FIGO substaging deserves reappraisal and further refinement. There is a significant relationship between patterns of care study point A dose and complications with the highest rate of complications for patterns of care study point A dose greater than 8500 cGy. A significant relationship between lateral (external iliac lymph nodes or patterns of care study point P) dose and major complications is also found, and doses greater than 5000 cGy are associated with a significant increase in complications. The patterns of care study has established two sequential national benchmarks of treatment outcome for squamous cell carcinoma of the uterine cervix treated with RT with respect to survival, infield pelvic control, and complications.	3

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16. Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC, Aydogan B. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2008; 71(5):1504-1510.	5	7 patients	To compare BMS-IMRT with conventional (four-field box and AP-PA) techniques in the treatment of cervical cancer.	BMS-IMRT was superior to the four-field box technique in reducing the dose to the pelvic bone marrow, small bowel, rectum, and bladder. Compared with AP-PA plans, BMS-IMRT reduced the pelvic bone marrow volume receiving a dose >16.4 Gy. BMS-IMRT reduced the volume of ilium, lower pelvis bone marrow, and bowel receiving a dose >27.7, >18.7, and >21.1 Gy, respectively, but increased dose below these thresholds compared with the AP-PA plans. BMS-IMRT reduced the volume of lumbosacral spine bone marrow, rectum, small bowel, and bladder at all dose levels in all 7 patients. BMS-IMRT reduced RT of pelvic bone marrow compared with the four-field box technique. Compared with the AP-PA technique, BMS-IMRT reduced lumbosacral spine bone marrow RT and reduced the volume of pelvic bone marrow RT to high doses. Therefore BMS-IMRT might reduce acute hematologic toxicity compared with conventional techniques.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
17. 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.	4	10 patients	To evaluate IMRT to determine if it can deliver adequate dose to the target structures while sparing the normal organs and could also allow for dose escalation to grossly enlarged metastatic lymph node in pelvic or para-aortic area without increasing gastrointestinal/genitourinary complications.	The volume of small bowel receiving the prescribed dose (45 Gy) with IMRT technique was as follows: four fields, 11.01 +/- 5.67%; seven fields, 15.05 +/- 6.76%; and nine fields, 13.56 +/- 5.30%. These were all significantly better than with two-field (35.58 +/- 13.84%) and four-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: four fields, 8.55 +/- 4.64%; seven fields, 6.37 +/- 5.19%; nine fields, 3.34 +/- 3.0%; in contrast to 84.01 +/- 18.37% with two-field and 46.37 +/- 24.97% with four-field conventional technique (P<0.001). The fractional volume of bladder receiving the prescribed dose and higher was as follows: four fields, 30.29 +/- 4.64%; seven fields, 31.66 +/- 8.26%; and nine fields, 26.91 +/- 5.57%. It was significantly worse with the two-field (92.89 +/- 35.26%) and with the four-field (60.48 +/- 31.80%) techniques (P<0.05). In this dosimetric study, the researchers demonstrated that with similar target coverage, normal tissue sparing is superior with IMRT in the treatment of cervical cancer.	3
18. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011; 80(5):1436-1445.	4	111 patients	To evaluate disease outcomes and toxicity in cervical cancer patients treated with pelvic IMRT.	Of the patients, 63 had stage I-IIA disease and 48 had stage IIB-IVA disease. The median follow-up time was 27 months. The 3-year OS rate and the DFS rate were 78% (95% CI, 68%-88%) and 69% (95% CI, 59%-81%), respectively. The 3-year pelvic failure rate and the distant failure rate were 14% (95% CI, 6%-22%) and 17% (95% CI, 8%-25%), respectively. Estimates of acute and late Grade 3 toxicity or higher were 2% (95% CI, 0%-7%) and 7% (95% CI, 2%-13%), respectively. IMRT is associated with low toxicity and favorable outcomes, supporting its safety and efficacy for cervical cancer. Prospective clinical trials are needed to evaluate the comparative efficacy of IMRT vs conventional techniques.	2

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19. Beadle BM, Jhingran A, Salehpour M, Sam M, Iyer RB, Eifel PJ. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 2009; 73(1):235-241.	4	16 patients	To evaluate the magnitude of cervix regression and motion during external beam chemoradiation for cervical cancer.	Mean cervical volumes before and after 45 Gy of EBRT were 97.0 and 31.9 cc, respectively; mean volume reduction was 62.3%. Mean maximum changes in the center of mass of the cervix were 2.1, 1.6, and 0.82 cm in the superior-inferior, anterior-posterior, and right-left lateral dimensions, respectively. Mean maximum changes in the perimeter of the cervix were 2.3 and 1.3 cm in the superior and inferior, 1.7 and 1.8 cm in the anterior and posterior, and 0.76 and 0.94 cm in the right and left lateral directions, respectively. Cervix regression and internal organ motion contribute to marked interfraction variations in the intrapelvic position of the cervical target in patients receiving chemoradiation for cervical cancer. Failure to take these variations into account during the application of highly conformal EBRT techniques poses a theoretical risk of underdosing the target or overdosing adjacent critical structures.	3
20. Chan P, Dinniwell R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys* 2008; 70(5):1507-1515.	10	20 patients	To examine the internal movement of the tumor, cervix, and uterus using serial cinematic MRI scans and point-of-interest analysis.	Large interscan motion was found for all three points of interest that was only partially explained by the variations in bladder and rectal filling. The intrascan motion was much smaller. Both inter- and intrascan motion was greatest at the fundus of the uterus, less along the canal, and least at the cervical os. The isotropic internal target margins required to encompass 90% of the interscan motion were 4 cm at the fundus and 1.5 cm at the os. In contrast, smaller margins of 1 cm and 0.45 cm, respectively, were adequate to encompass the intrascan motion alone. Daily soft-tissue imaging with correction for interfractional motion or adaptive replanning will be important if the benefits of IMRT are to be maximized in women with cervical cancer.	3

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21. 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.	4	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. These preliminary data suggest that prone positioning on a belly board can reduce the small bowel dose further in gynecology patients treated with pelvic RT, and that the dose reduction depends on the IMRT technique used.	3

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22. Ahmad R, Hoogeman MS, Bondar M, et al. Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix-uterus displacements: proof of principle. *Radiother Oncol* 2011; 98(3):340-346.	10	13 patients	To prospectively investigate application of pre-treatment established correlations between bladder-filling changes and cervix-uterus displacements in adaptive therapy.	Target displacement in variable bladder filling CT-scans ranged from up to 65 mm in a single direction to almost 0 mm, depending on the patient. For pre-treatment variable bladder filling CT-scans, the linear correlation models predicted the mean 3D position change for the tip of the uterus of 26.1 mm ± 10.8 with a residual of only 2.2 mm ± 1.7. For the marker-center of mass, the 8.4 mm ± 5.3 mean positioning error was predicted with a residual of 0.9 mm ± 0.7. After 40 Gy, the mean tip of the uterus displacement was 26.8 mm ± 15.8, while prediction based on the pre-treatment correlation models yielded a mean residual error of 9.0 mm ± 3.7. Target positioning errors in the fractioned treatments were very large, especially for the tip of the uterus (-18.5mm ± 11.2 for systematic errors in SI-direction). Pre-treatment acquired variable bladder filling CT-scans may be used to substantially enhance treatment precision of cervical cancer patients. Application in adaptive therapy is promising and warrants further investigation. For highly conformal (IMRT) treatments, the use of a full bladder drinking protocol results in unacceptably large systematic set-up errors.	3
23. Higginson DS, Morris DE, Jones EL, Clarke-Pearson D, Varia MA. Stereotactic body radiotherapy (SBRT): Technological innovation and application in gynecologic oncology. *Gynecol Oncol* 2011; 120(3):404-412.	12	6 cases series 16 patients treated	Literature review and experiential data to evaluate SBRT with regard to its use in gynecologic malignancies.	Preliminary follow-up at a median of 11 months (range, 0.3-33 months) demonstrates 79% locoregional control, 43% distant failure, and 50% OS. SBRT boosts to macroscopic periaortic node recurrences and other sites seem to provide local control and a possibility of long-term DFS in carefully selected patients. Previously this had been difficult to achieve with conventional RT because of the proximity of periaortic nodes to small bowel. SBRT also offers a novel approach for minimally invasive treatment in the management of gynecological cancer where current surgical and RT techniques are unsuitable.	4

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24. Mayr NA, Huang Z, Sohn JW, et al. Emerging application of stereotactic body radiation therapy for gynecologic malignancies. *Expert Rev Anticancer Ther* 2011; 11(7):1071-1077.	7	N/A	A review of studies to consider indications for SBRT application in gynecological cancer management, to reflect on outcomes from key SBRT clinical trials and to discuss new therapeutic roles of SBRT for gynecological cancers.	Clinical data on the efficacy and toxicity of SBRT for gynecologic malignancies are emerging: • Preliminary results of SBRT for gynecologic malignancies are encouraging. • The present literature on SBRT in gynecologic cancers does not include persuasive radiobiological data that ablative radiation doses provided by SBRT overcome the lack of reoxygenation in targeted hypoxic cell populations. • It has been challenging to combine SBRT with radiosensitizing and cytotoxic/cytostatic chemotherapy. • It remains unclear whether SBRT can offer the same therapeutic efficacy as LDR and HDR brachytherapy that are more commonly and validated techniques to achieve radiation dose escalation in gynecologic targets.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
25. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004; 22(5):872-880.	1	403 women	Randomized trial to report mature results of a randomized trial that compared EFRT vs pelvic RT with concomitant fluorouracil and cisplatin in women with locoregionally advanced carcinomas of the uterine cervix.	The median follow-up time for 228 surviving patients was 6.6 years. The OS rate for patients treated with concomitant fluorouracil and cisplatin was significantly greater than that for patients treated with EFRT (67% vs 41% at 8 years; P<.0001). There was an overall reduction in the risk of disease recurrence of 51% (95% CI, 36% to 66%) for patients who received concomitant fluorouracil and cisplatin. Patients with stage IB to IIB disease who received concomitant fluorouracil and cisplatin had better OS and DFS than those treated with EFRT (P<.0001); 116 patients with stage III to IVA disease had better DFS (P=.05) and a trend toward better OS (P=.07) if they were randomly assigned to concomitant fluorouracil and cisplatin. The rate of serious late complications of treatment was similar for the two treatment arms. Mature analysis confirms that the addition of fluorouracil and cisplatin to RT significantly improved the survival rate of women with LACC without increasing the rate of late treatment-related side effects.	1
26. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999; 340(15):1154-1161.	1	369 patients 186 in the RT group and 183 in the combined-therapy group	Randomized trial to determine whether weekly infusions of cisplatin during RT improve progression-free and OS among patients with bulky stage IB cervical cancer. Women with bulky stage IB cervical cancers (tumor, ≥4 cm in diameter) were randomly assigned to receive RT alone or in combination with cisplatin (40 mg per square meter of body-surface area once a week for up to six doses; maximal weekly dose, 70 mg), followed in all patients by adjuvant hysterectomy.	Rates of both PFS (P<0.001) and OS (P=0.008) were significantly higher in the combined-therapy group at four years. In the combined-therapy group there were higher frequencies of transient grade 3 (moderate) and grade 4 (severe) adverse hematologic effects (21%, vs 2% in the RT group) and adverse gastrointestinal effects (14% vs 5%). Adding weekly infusions of cisplatin to pelvic RT followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
27. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002; 20(4):966-972.	1	259 patients	Phase III randomized trial to evaluate the effects of cisplatin administered concurrently with standard RT to determine if it improves pelvic control and survival in patients with advanced squamous cell cancer of the cervix.	Median follow-up was 82 months. No significant difference was found in PFS (P=.33). No significant difference in 3- and 5-year survival rates was found (69% vs 66% and 62% vs 58%, respectively; P=.42). The HR for survival (arm 2 to arm 1) was 1.10 (95% CI, 0.75 to 1.62). This study did not show a benefit to either pelvic control or survival by adding concurrent weekly concomitant fluorouracil and cisplatin chemotherapy in a dose of 40 mg/m(2) to radical RT as given in this trial. Careful attention to RT details is important for achieving optimum outcome for patients with this disease.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
28. Roberts KB, Urdaneta N, Vera R, et al. Interim results of a randomized trial of mitomycin C as an adjunct to radical radiotherapy in the treatment of locally advanced squamous-cell carcinoma of the cervix. *Int J Cancer* 2000; 90(4):206-223.	1	160 patients 78 RT with mitomycin C group 82 in RT alone group	Randomized trial to determine the efficacy of mitomycin C as an adjunct to RT for the treatment of LACC.	• Mean follow-up of 46 months. • The 4-year actuarial local recurrence-free survival rates for patients receiving RT with mitomycin C and RT alone were 78% and 63%, respectively (P=0.11). • Differences in 4-year distant recurrence-free survival between RT plus mitomycin C and RT alone were significantly different at 85% vs 61% (P=0.01); this analysis is not adjusted for local failure. • On subgroup analysis, stage III-IVA patients had a 4-year actuarial DFS of 75% for RT plus mitomycin C compared with 35% for RT alone (P=0.03). • In this open phase III trial of mitomycin C as an adjunct to radical RT for squamous-cell carcinoma of the cervix, there were minimal hematologic effects and no increase in acute radiation reactions. A statistically significant difference in favor of patients receiving mitomycin C is shown for DFS. Thus far, there are trends in favor of those patients receiving mitomycin C for survival and local control. Patients with more advanced stage disease, predominantly stage IIIB, appear to have the most benefit. These preliminary results support the hypothesis that targeting hypoxic cells may lead to a therapeutic enhancement in the RT of cervix cancer. This trial continues to accrue patients and follow-up data.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010; (1):CD008285.	7 (meta-analysis)	15 trials	A meta-analysis to assess the effect of chemoradiotherapy and whether it differs by trial or patient characteristics.	On the basis of 13 trials that compared chemoradiotherapy vs the same RT, there was a 6% improvement in 5-year survival with chemoradiotherapy (HR = 0.81, P<0.001). A larger survival benefit was seen for the two further trials in which chemotherapy was administered after chemoradiotherapy. There was a significant survival benefit for both the group of trials that used platinum-based (HR = 0.83, P=0.017) and non-platinum based (HR = 0.77, P=0.009) chemoradiotherapy, but no evidence of a difference in the size of the benefit by RT or chemotherapy dose or scheduling was seen. Chemoradiotherapy also reduced local and distant recurrence and progression and improved DFS. There was a suggestion of a difference in the size of the survival benefit with tumor stage, but not across other patient subgroups. Acute haematological and gastrointestinal toxicity were increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity. These results endorse the recommendations of the NCI alert, but also demonstrate their applicability to all women and a benefit of non-platinum based chemoradiotherapy. Furthermore, although these results suggest an additional benefit from adjuvant chemotherapy this requires testing in randomized controlled trials.	2
30. Gaffney DK, Du Bois A, Narayan K, et al. Practice patterns of radiotherapy in cervical cancer among member groups of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys* 2007; 68(2):485-490.	15	39 surveys returned from 13 different cooperative groups	To describe radiotherapeutic practice of the treatment of cervical cancer in member groups of the Gynecologic Cancer Intergroup (GCIG).	RT practices among member groups of the GCIG are similar in terms of both doses and use of chemotherapy.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
31. Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. *J Clin Oncol* 2002; 20(1):179-188.	1	409 total patients 210 NACT+ radical surgery 199 RT	Phase III randomized trial to evaluate NACT and radical surgery as a possible alternative to conventional RT in LACC.	There was no evidence for any significant excess of severe morbidity in one of the two arms. The 5-year OS and PFS rates were 58.9% and 55.4% for arm A and 44.5% and 41.3% for arm B (P=.007 and P=.02), respectively. Subgroup survival analysis shows OS and PFS rates of 64.7% and 59.7% (stage IB2-IIB, NACT+ radical surgery), 46.4% and 46.7% (stage IB2-IIB, RT) (P=.005 and P=.02), 41.6% and 41.9% (stage III, NACT+ radical surgery), 36.7% and 36.4% (stage III, RT) (P=.36 and P=.29), respectively. Treatment had a significant impact on OS and PFS. Although significant only for the stage IB2 to IIB group, a survival benefit seems to be associated with the NACT+ radical surgery compared with conventional RT.	1
32. Chang TC, Lai CH, Hong JH, et al. Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. *J Clin Oncol* 2000; 18(8):1740-1747.	1	120 total patients 68 in the NACT arm 52 in the RT arm	To compare the efficacy of NACT followed by radical hysterectomy with that of RT for bulky early-stage cervical cancer.	The median duration of follow-up was 39 months. 31% of patients in the NACT arm and 27% in the RT arm had relapse or persistent diseases after treatment, and 21% in each group died of disease. Estimated cumulative survival rates at 2 years were 81% for the NACT arm and 84% for the RT arm; the 5-year rates were 70% and 61%, respectively. There were no significant differences in DFS and OS. NACT followed by radical hysterectomy and primary RT showed similar efficacy for bulky stage IB or IIA cervical cancer. Further study to identify patient subgroups better suited for either treatment modality and to evaluate the concurrent use of cisplatin and radiation without routine hysterectomy is necessary.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. Choi YS, Sin JI, Kim JH, Ye GW, Shin IH, Lee TS. Survival benefits of neoadjuvant chemotherapy followed by radical surgery versus radiotherapy in locally advanced chemoresistant cervical cancer. *J Korean Med Sci* 2006; 21(4):683-689.	4	94 patients	To analyze long-term survivals in patients with stage IB to IIA cervical cancer treated by NACT setting.	All of patients with chemoresponse (complete response, n=15; partial response, n=47) and 16 patients with chemoresistance received radical surgery (RS group). The other 16 patients with chemoresistance received RT for definite treatment (RT group). In the RS group, the 10 year survival estimation in patients with bulky tumors (diameter ≥4 cm, n=26) was similar to that with non-bulky tumors (83.3% vs 89.3%, p=NS). In selected patients with chemoresistance, those treated by RT (n=16) showed significantly poorer survivals than those treated by radical surgery (n=16) (10 year survival rates of RT (25%) vs RS (76.4%), P=0.0111). The results support that a possible therapeutic benefit of NACT plus radical surgery is only in patients with bulky stage IB to IIA cervical cancer. In cases of chemoresistance, radical surgery might be a better definite treatment option.	2
34. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. *Eur J Cancer* 2003; 39(17):2470-2486.	7 (meta-analysis)	21 randomized trials eligible 1st comparison: 18 trials and 2,074 patients. 2nd comparison: 5 trials and 872 patients	Systematic review and meta-analysis of individual patient data to assess the effect of NACT in LACC. Two comparisons made: • First comparison, of NACT followed by radical RT compared with the same RT alone. • Second comparison, of NACT followed by surgery compared with radical RT alone.	The combined results from all trials (HR=0.65, 95% CI=0.53-0.80, P=0.0004) indicated a highly significant reduction in the risk of death with NACT, but there were some differences between the trials in their design and results. Despite some unexplained heterogeneity, the timing and dose intensity of cisplatin-based NACT appears to have an important impact on whether or not it benefits women with LACC and warrants further exploration.	1
35. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev* 2010; (1):CD007406.	7 (meta-analysis)	6 trials (1,072 women)	To assess the role of NACT in women with early or LACC.	PFS was significantly improved with NACT (HR = 0.76, 95% CI = 0.62 to 0.94, P=0.01), no OS rate benefit was observed (HR = 0.85, 95% CI = 0.67 to 1.07, P=0.17). Furthermore, estimates for both local (OR = 0.76, 95% CI = 0.49 to 1.17, P=0.21) and distant (OR = 0.68, 95% CI = 0.41 to 1.13, P=0.13) recurrence and rates of resection (OR = 1.55, 95% CI = 0.96 to 2.50, P=0.07) only tended to be in favor of NACT, and heterogeneity was observed.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
36. Monk BJ, Koh WJ. What is the standard therapy for bulky stage IB cervical cancer? *Int J Gynecol Cancer* 2009; 19(3):480.	15	N/A	Letter to editor on a review article by "Petsuksiri J, Chansilpa Y, Therasakvichya S, et al. Treatment options in bulky stage IB cervical carcinoma. I*nt J Gynecol Cancer*. 2008;18:1153-1162." The study outlines treatment options for women with a diagnosis of bulky stage IB cervical cancer.	Randomized clinical trials, as reviewed by Petsuksiri et al, have established the widely accepted standard therapy for women with FIGO stage IB2 lesions, without metastatic spread beyond the pelvis, as being EBRT to the pelvis, intracavitary brachytherapy, and concomitant cisplatin-based chemotherapy.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
37. 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.	1	367 total patients	To investigate 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). 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. The statistically significant difference in OS at 10 years for the pelvic plus para-aortic irradiation arm, without a difference in DFS, can be explained by the following two factors: 1) a lower incidence of distant failure in complete responders and 2) a better salvage in the complete responders who later failed locally.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001; 51(4):982-987.	4	30 patients	To evaluate the late toxicity and efficacy of twice-daily external irradiation to the pelvis and lumbar para-aortic region with brachytherapy and concurrent chemotherapy for carcinoma of the cervix with positive para-aortic lymph nodes.	30 patients with clinical stages I-IV carcinoma of the cervix with biopsy-proven para-aortic lymph node metastases were enrolled in this study. Hyperfractionated external irradiation was completed in 87% (26/30). RT was completed per protocol in 70%. Three cycles of chemotherapy were given to 23% (7/30); 73% (22/30) received two cycles, and 1 patient did not receive chemotherapy. The acute toxicity from chemotherapy was Grade 1 in 3%, Grade 2 in 17%, Grade 3 in 48%, and Grade 4 in 28%. Acute toxicity from RT was Grade 1 in 7%, Grade 2 in 34%, Grade 3 in 21%, and Grade 4 in 28%. Late toxicity was Grade 1 in 10%, Grade 2 in 17%, Grade 3 in 7%, and Grade 4 in 17%. Grade 5 toxicity occurred in 1 patient during the course of therapy, but none had a late Grade 5 toxicity. The median follow-up time for the 7 patients alive at the time of last follow-up was 57 months. The OS estimates were 46% at 2 years and 29% at 4 years. The probability of local-regional failure was 40% at 1 year and 50% at 2 and 3 years. The probability of disease failure at any site was 46% at 1 year, 60% at 2 years, and 63% at 3 years. The results suggest that twice-daily external irradiation to the pelvis and lumbar para-aortic region with brachytherapy and concurrent chemotherapy resulted in an unacceptably high rate (17%, 5/29) of Grade 4 late toxicity. One patient died of acute complications of therapy. The survival estimates seem no better than standard fractionation irradiation without chemotherapy.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Small W, Jr., Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys* 2007; 68(4):1081-1087.	3a	26 patients	To test the ability of Amifostine to reduce the toxicity of combined chemotherapy with EFRT and brachytherapy (Part 2), after first determining the toxicity rate for the regimen without Amifostine (Part 1).	The median follow-up was 17.1 months (range, 1.8-38.6 months) for all patients and 21.7 months (range, 11.4-38.6 months) for alive patients. The acute Grade 3/4 toxicity rate, excluding Grade 3 leukopenia was 81%. Late Grade 3/4 toxicity was 40%. Eight patients underwent surgery for complications. Sixteen (62%) patients had a complete response for both local and nodal disease. The complete local response was 92%, the complete overall nodal response rate was 62% and the regional and para-aortic nodal response rates were 60% and 71%, respectively. Estimated DFS and OS at 18 months are 46% and 60%. EFRT and intracavitary irradiation with cisplatin for para-aortic or high common iliac metastasis from cervical cancer is associated with significant acute and late toxicity.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
40. Beadle BM, Jhingran A, Yom SS, Ramirez PT, Eifel PJ. Patterns of regional recurrence after definitive radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2010; 76(5):1396-1403.	3a	198 patients	To determine the patterns of regional recurrence in patients treated with definitive RT for cervical cancer.	The median time to regional recurrence was 13 months (range, 2-85 months). Of the 180 patients who had an evaluable regional recurrence, 119 (66%) had a component of marginal failure; 71 patients recurred above-the-field, 2 patients occurred in the inguinal nodes, and 2 patients recurred above-the-field and in the inguinal nodes. In addition, 105 patients (58%) had a component of in-field failure; 59 patients recurred in-field only, 39 patients recurred in-field and above-the-field, 2 patients recurred in-field, above-the-field, and in the inguinal nodes, and 5 patients recurred in-field and in the inguinal nodes. The median survival after regional recurrence was 8 months (range, 0-194 months). Most regional recurrences after definitive RT for cervical cancer include a component of marginal failure, usually immediately superior to the radiation field. These recurrences suggest a deficiency in target volume. Recurrences also occur in-field, suggesting a deficiency in dose. Developments in pretreatment staging, field delineation, dose escalation, and post-treatment surveillance may help to improve outcome in these patients.	2
41. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2003; 89(3):343-353.	1	256 patients randomized: external and intracavitary irradiation (RT, n=124) or attenuated irradiation followed by extrafascial hysterectomy (RT + hysterectomy n=132)	To evaluate, in a randomized clinical trial, the role of adjuvant hysterectomy after standardized radiation in improving PFS and survival for patients with "bulky" stage IB cervical cancer.	No clinically important benefit with the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4-, 5-, and 6-cm tumors may have benefitted from extrafascial hysterectomy (unadjusted relative risk of progression; 0.58; unadjusted relative risk of death, 0.60).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
42. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol* 2007; 197(5):503 e501-506.	1	369 total patients 186 RT alone 183 cisplatin plus RT	To confirm that concurrent cisplatin with RT is associated with improved long-term PFS and OS, compared with RT alone in stage IB bulky carcinoma of the cervix, when both groups' therapy is followed by hysterectomy.	Median duration of follow-up was only 36 months. Patient and tumor characteristics were well balanced between the regimens. The median patient age was 41.5 years; 81% had squamous tumors; 59% were white. Median follow-up is now 101 months. The relative risk for progression was 0.61 favoring CT plus RT (95% CI, 0.43 to 0.85, P<.004). At 72 months, 71% of patients receiving cisplatin plus RT were predicted to be alive and disease free when adjusting for age and tumor size, compared with 60% of those receiving RT alone. The adjusted death HR was 0.63 (95% CI, 0.43 to 0.91, P<.015) favoring cisplatin plus RT. At 72 months, 78% of cisplatin plus RT patients were predicted to be alive, compared with 64% of RT patients. An increased rate of early hematologic and gastrointestinal toxicity was seen with cisplatin plus RT. There was no detectable difference in the frequency of late adverse events. Concurrent weekly cisplatin with RT significantly improves long-term PFS and OS when compared with RT alone. Serious late effects were not increased. The inclusion of hysterectomy has been discontinued on the basis of another trial. Pending further trials, weekly cisplatin with radiation is the standard against which other regimens should be compared.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Nijhuis ER, van der Zee AG, in 't Hout BA, et al. Gynecologic examination and cervical biopsies after (chemo) radiation for cervical cancer to identify patients eligible for salvage surgery. *Int J Radiat Oncol Biol Phys* 2006; 66(3):699-705.	4	169 consecutive patients	To evaluate the efficacy of gynecologic examination under general anesthesia with cervical biopsies after (chemo) radiation for cervical cancer to identify patients with residual disease who may benefit from salvage surgery.	Median follow-up was 3.5 years (interquartile range, 1.5-5.9). In each of 111 patients a biopsy sample was taken, of which 90 (81%) showed no residual tumor. Vital tumor cells were found in 21/111 patients (19%). Salvage surgery was performed in 13/21 (62%) patients; of these patients, 5 (38%) achieved long-term, complete remission after salvage surgery (median follow-up, 5.2 years; range, 3.9-8.8 years). All patients with residual disease who did not undergo operation (8/21) died of progressive disease. Locoregional control was more often obtained in patients who underwent operation (7/13) than in patients who were not selected for salvage surgery (0/8 patients) (P<0.05). Gynecologic examination under anesthesia 8 to 10 weeks after (chemo) radiation with cervical biopsies allows identification of those cervical cancer patients who have residual local disease, of whom a small but significant proportion may be salvaged by surgery.	2
44. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA* 2007; 298(19):2289-2295.	3a	92 patients	Prospective cohort study to validate the association between the metabolic response on the 3-month post-therapy FDG-PET and long-term survival outcome.	Post-therapy FDG-PET showed a complete metabolic response in 65 patients (70%), a partial metabolic response in 15 (16%), and progressive disease in 12 (13%). Their 3-year PFS rates were 78%, 33%, and 0%, respectively (P<.001). Multivariate analysis demonstrated that the HR for risk of recurrence based on the post-therapy metabolic response showing progressive disease was 32.57 (95% CI, 10.22-103.82). A partial metabolic response had an HR of 6.30 (95% CI, 2.73-14.56). These were more predictive of survival outcome than the pretreatment lymph node status (HR, 3.54; 95% CI, 1.54-8.09). In this single-site study population of women with cervical cancer, 3-month post-therapy FDG uptake, as detected by whole-body PET, was predictive of survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
45. Wang JZ, Mayr NA, Zhang D, et al. Sequential magnetic resonance imaging of cervical cancer: the predictive value of absolute tumor volume and regression ratio measured before, during, and after radiation therapy. *Cancer* 2010; 116(21):5093-5101.	10	80 patients	To investigate outcome prediction by measuring absolute tumor volume and regression ratios using serial MRI during RT for cervical cancer and to develop algorithms capable of identifying patients at risk of a poor therapeutic outcome.	Both tumor volume and regression ratio were strongly correlated with LR (P=.06, P = 5×10(-4), P=1×10(-6), and P=2×10(-8) for V1, V2, V3, and V4, respectively; and P=7×10(-5), P=1×10(-6), and P=1×10(-8) for V2/V1, V3/V1, and V4/V1, respectively) and dying of disease (P=.015, P=.004, P=.001, and P=3×10(-4) for V1, V2, V3, and V4, respectively; and P=.03, P=.009, and P=3×10(-4) for V2/V1, V3/V1, and V4/V1, respectively). Algorithms that combined tumor volumes and regression ratios improved predictive power (sensitivity, 61%-89%; specificity, 79%-100%). The strongest predictor, pre-RT volume and regression ratio at MRI3 (V1>40 cm3 and V3/V1>20%, respectively), achieved 89% sensitivity, 87% specificity, and 88% accuracy for LR and achieved 54% sensitivity, 83% specificity, and 73% accuracy for dying of disease. The current results suggested that tumor volume/regression parameters obtained during primary therapy are useful in predicting LR and dying of disease. Both tumor volume and regression ratio provided important information as early outcome predictors that may guide early intervention for patients with cervical cancer who are at high risk of treatment failure.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Huang YT, Wang CC, Tsai CS, et al. Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; 80(2):429-436.	4	148 patients	To study the outcomes of patients with adenocarcinoma/adenosquamous carcinoma of the cervix primarily treated with RT, identify the prognostic factors, and evaluate the efficacy of concurrent chemoradiotherapy or salvage surgery.	The 5-year relapse-free survival rate was 68%, 38%, 49%, 30%, and 0% for those with stage IB/IIA nonbulky, IB/IIA bulky, IIB, III, and IVA disease, respectively, and appeared inferior to that of those with squamous cell carcinoma of the cervix treated using the same RT protocol. Incomplete tumor regression after RT, a low hemoglobin level, and positive lymph node metastasis were independent poor prognostic factors for relapse-free survival. Concurrent chemoradiotherapy with weekly cisplatin did not improve the outcome for our adenocarcinoma/adenosquamous carcinoma patients. Salvage surgery rescued 30% of patients with persistent disease. Patients with adenocarcinoma/adenosquamous carcinoma of the cervix primarily treated with RT had inferior outcomes compared to those with squamous cell carcinoma. Incomplete tumor regression after RT was the most important prognostic factor for local failure. Salvage surgery for patients with persistent tumor should be encouraged for selected patients. Our results did not demonstrate a benefit of concurrent chemoradiotherapy with cisplatin for this disease.	2
47. Lea JS, Coleman RL, Garner EO, Duska LR, Miller DS, Schorge JO. Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. *Gynecol Oncol* 2003; 91(3):558-562.	3a	230 patients	To identify poor prognostic factors of low-risk stage IB1 cervical adenocarcinoma.	Adenosquamous cell type ($P<0.01$) was the only independent risk factor of disease recurrence in the low-risk group (n=178). The 5-year DFS for low-risk adenosquamous patients was 79%, compared to 96% for other histologic subtypes ($P<0.01$). Low-risk case subjects developed fewer disease recurrences than those in the intermediate/high-risk (n=52) category (7% vs 46%; $P<0.01$). The 5-year DFS for intermediate/high-risk patients was 51% and no additional risk factors were identified. Adenosquamous histology is predictive of disease recurrence and decreased survival in low-risk stage IB1 cervical adenocarcinoma. This risk factor should be considered in future clinical trials of adjuvant therapy.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix. *J Clin Oncol* 2011; 29(13):1678-1685.	1	515 patients arm A n=259 arm B n=256	To determine whether addition of gemcitabine to concurrent cisplatin chemoradiotherapy and as adjuvant chemotherapy with cisplatin improves PFS at 3 years compared with current standard of care in LACC.	PFS at 3 years was significantly improved in arm A vs arm B (74.4% vs 65.0%, respectively; P=.029), as were overall PFS (log-rank P=.0227; HR, 0.68; 95% CI, 0.49 to 0.95), OS (log-rank P=.0224; HR, 0.68; 95% CI, 0.49 to 0.95), and time to progressive disease (log-rank P=.0012; HR, 0.54; 95% CI, 0.37 to 0.79). Grade 3 and 4 toxicities were more frequent in arm A than in arm B (86.5% vs 46.3%, respectively; P<.001), including two deaths possibly related to treatment toxicity in arm A. Gemcitabine plus cisplatin chemoradiotherapy followed by BCT and adjuvant gemcitabine/cisplatin chemotherapy improved survival outcomes with increased but clinically manageable toxicity when compared with standard treatment.	1
49. Winter WE, 3rd, Maxwell GL, Tian C, et al. Association of hemoglobin level with survival in cervical carcinoma patients treated with concurrent cisplatin and radiotherapy: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2004; 94(2):495-501.	1	494 patients	To determine if there is an association of hemoglobin level before or during concurrent cisplatin and RT with disease outcome in women with LACC, and to assess if the association is particularly significant at a specific interval or time during treatment.	The pretreatment level was not significant when hemoglobin levels during treatment were included in the multivariate analysis. When the 6-week treatment course was divided into 2-week periods (early, middle, and late), analysis revealed hemoglobin values during the late period were the most predictive of disease progression (P=0.0289). Hemoglobin levels during combined RT and cisplatin were independent predictors of treatment outcome in advanced cervical carcinoma. The pretreatment level was not a significant predictor of outcome when hemoglobin levels during treatment were included in the multivariate regression model. Levels in the last part of treatment were the most predictive of disease recurrence and survival.	1

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
50. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer* 1999; 86(8):1528-1536.	4	605 patients from 7 centers across Canada in 1989, 1990, and 1992	Retrospective study to examine the impact of anemia and blood transfusion on patients with carcinoma of the cervix treated with radical RT.	• The median follow-up was 41 months (range, 0-92 months). Presenting hemoglobin level, average weekly nadir hemoglobin during RT, and blood transfusion were correlated significantly with local control, DFS, and OS on univariate analysis. • The average weekly nadir hemoglobin remained significant on multivariate analysis, whereas hemoglobin at presentation and blood transfusion did not. • The 5-year survival was 74% for patients with an average weekly nadir hemoglobin ≥120 g/L, 52% for patients with average weekly nadir hemoglobin levels 110-119 g/L inclusive, and 45% for patients with average weekly nadir hemoglobin levels <110 g/L (P<0.0001). • At each hemoglobin level, patients who were transfused and maintained a specific hemoglobin level had a survival rate that was not significantly different from patients who were at that level spontaneously. • There was a significant reduction in both pelvic and distant recurrence (P<0.0001 and P<0.0006, respectively) in patients whose average weekly nadir hemoglobin level during RT was ≥120 g/L compared with <120 g/L. A reduction in the rate of distant recurrence was observed in patients with and without pelvic recurrence. • Average weekly nadir hemoglobin is highly predictive of outcome for patients treated with RT for carcinoma of the cervix. Blood transfusion appears to overcome the negative prognostic effects of low presenting hemoglobin levels and average weekly nadir hemoglobin.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
51. Mayr NA, Wang JZ, Zhang D, et al. Synergistic effects of hemoglobin and tumor perfusion on tumor control and survival in cervical cancer. *Int J Radiat Oncol Biol Phys* 2009; 74(5):1513-1521.	4	88 patients	To assess the effects of local tumor perfusion, systemic hemoglobin levels, and their combination on the treatment outcome in cervical cancer.	Local recurrence predominated in the group with both a low mean hemoglobin (<11.2 g/dL) and low perfusion (lowest 10th percentile of signal intensity <2.0 at 20-22 Gy), with a 5-year local control rate of 60% vs 90% for all other groups (P=.001) and a disease-specific survival rate of 41% vs 72% (P=.008), respectively. In the group with both high mean hemoglobin and high perfusion, the 5-year local control rate and disease-specific survival rate was 100% and 78%, respectively. These results suggest that the compounded effects of hemoglobin level and tumor perfusion during RT influence the radioresponsiveness and survival in cervical cancer patients. The outcome was worst when both were impaired. The management of hemoglobin may be particularly important in patients with low tumor perfusion.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
52. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2008; 108(2):317-325.	1	109 patients 52 received cisplatin/RT 57 received cisplatin/RT + recombinant human erythropoietin	Randomized trial to determine whether maintaining hemoglobin levels ≥12.0 g/dL with recombinant human erythropoietin compared to "standard" treatment (transfusion for hemoglobin ≤10.0 g/dL) improves PFS, OS and local control in women receiving concurrent weekly cisplatin and radiation for carcinoma of the cervix. In addition, to determine whether platinum-DNA adducts were associated with clinical characteristics or outcome.	• The study closed prematurely, with <25% of the planned accrual, due to potential concerns for thromboembolic event with recombinant human erythropoietin. • Median follow-up was 37 months (range 9.8-50.4 months). PFS and OS at 3 years should be 65% and 75% for cisplatin/RT and 58% and 61% for cisplatin/RT + recombinant human erythropoietin, respectively. • Thromboembolic event occurred in 4/52 receiving cisplatin/RT and 11/57 with cisplatin/RT + recombinant human erythropoietin, not all considered treatment related. No deaths occurred from thromboembolic event. High-platinum adducts were associated with inferior PFS and local control. • Thromboembolic event is common in cervical cancer patients receiving cisplatin/RT. Difference in thromboembolic event rate between the two treatments was not statistically significant. The impact of maintaining hemoglobin level >12.0 g/dL on PFS, OS and local control remains undetermined.	1
53. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78(1):67-77.	15	N/A	Recommendations from gynaecological (GYN) GEC ESTRO working group (II) on 3D dose-volume parameters for brachytherapy of cervical carcinoma.	It is expected that the therapeutic ratio including target coverage and sparing of organs at risk can be significantly improved, if radiation dose is prescribed to a 3D image-based CTV taking into account dose volume constraints for organs at risk. However, prospective use of these recommendations in the clinical context is needed.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
54. Dimopoulos JC, Potter R, Lang S, et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. *Radiother Oncol* 2009; 93(2):311-315.	4	141 patients	To analyze dose-response relationships for local control of cervical cancer after MR image-guided brachytherapy based on dose-volume histogram parameters.	18 local recurrences in the true pelvis were observed. Dose-response analyses revealed a significant effect of high risk CTV D100 (P=0.02) and D90 (P=0.005). The ED50-values for tumor control were 33 +/- 15 Gy (D100) and 45 +/- 19 Gy (D90). ED90-values were 67 Gy (95% CI [50;104]) and 86 Gy [77;113], respectively. A significant dependence of local control on D100 and D90 for high risk CTV was found. Tumor control rates of >90% can be expected at doses >67 Gy and 86 Gy, respectively.	2
55. Engle DB, Bradley KA, Chappell RJ, Conner JP, Hartenbach EM, Kushner DM. The effect of laparoscopic guidance on gynecologic interstitial brachytherapy. *J Minim Invasive Gynecol* 2008; 15(5):541-546.	2	42 women 28 patients underwent TrIB 14 underwent LAIB	To compare LAIB with TrIB in the treatment of gynecologic malignancies.	Mean follow-up of 24 months. Of the 14 patients undergoing LAIB, 2 (14%) had carcinomatosis and the brachytherapy was aborted. Of patients who proceeded with LAIB, 64% had clinically significant pelvic adhesions necessitating lysis of adhesions. Mean radiation doses were similar for both external beam (LAIB=54 Gy, TrIB=50 Gy; P=.12) and brachytherapy (LAIB=29 Gy, TrIB=30 Gy; P=.8). In regard to long-term grade 3/4 radiation toxicity, 1 (10%) patient undergoing LAIB had a rectovaginal fistula. Six (27%) patients (P=.39; 95% CI, 9%-43%) undergoing TrIB experienced high-grade toxicity, including 2 rectovaginal fistulas, 1 rectal stricture, 1 necrotizing fasciitis, 1 urinary incontinence, and 1 soft-tissue necrosis. The LAIB procedure appears safe, but substantially increases operating department time. No significant decrease in late high-grade toxicities was detected in comparison with TrIB. The LAIB procedure allows for both lysis of adhesions and identification of unknown carcinomatosis.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
56. Shah AP, Strauss JB, Gielda BT, Zusag TW. Toxicity associated with bowel or bladder puncture during gynecologic interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; 77(1):171-179.	3a	36 patients	To examined the researchers' experience with interstitial brachytherapy and investigate the relationship between the visceral puncture and toxicity.	At a median follow-up of 21 months, the crude locoregional control rate was 78%. Bowel puncture was noted in 26 patients and bladder puncture in 19. The mean operating time was 50 min, and 86% of patients were discharged in ≤3 days. The incidence of acute and late toxicity was similar between patients with and without visceral puncture according to the log-rank analysis of Kaplan-Meier curves. No patients with bowel puncture experienced Grade 2 or greater acute gastrointestinal toxicity and only one had Grade 3 or greater late gastrointestinal toxicity. No patients with bladder puncture experienced greater than Grade 2 acute genitourinary toxicity and only two had late Grade 3 or greater genitourinary toxicity. The operating time, length of hospital stay, and treatment-induced morbidity in this cohort compared favorably to series using techniques to avoid visceral puncture. Additionally, visceral puncture did not correlate with the occurrence of acute or late toxicity. These data suggest that visceral puncture in the absence of source loading carries a low risk of morbidity.	2
57. Viani GA, Manta GB, Stefano EJ, de Fendi LI. Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy - a meta-analysis of clinical trials. *J Exp Clin Cancer Res* 2009; 28:47.	7 (meta-analysis)	5 randomized trials (2,065 patients)	Meta-analysis of randomized trials was performed comparing LDR to HDR brachytherapy for cervix cancer treated for RT alone.	Pooled results from randomized trials of HDR brachytherapy in cervix cancer showed no significant increase of mortality (P=0.52), local recurrence (P=0.68), or late complications (rectal; P=0.7, bladder; P=0.95 or small intestine; P=0.06) rates as compared to LDR brachytherapy. Meta-analysis shows there are no differences between HDR and LDR for OS, local recurrence and late complications for clinical stages I, II and III. Recommend the use of HDR for all clinical stages of cervix cancer.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
58. Jones ND, Rankin J, Gaffney DK. Is simulation necessary for each high-dose-rate tandem and ovoid insertion in carcinoma of the cervix? *Brachytherapy* 2004; 3(3):120-124.	3a	14 patients	To evaluate the dose variation in HDR intracavitary brachytherapy for cancer of the cervix when treatment planning is performed prior to each applicator insertion versus when the initial plan is used for each treatment.	An increase in the percent dose to the rectum, bladder, and vaginal surface of 5%, cGy (P=0.038), 6% (P=0.006), and 11%, respectively, were observed when the initial treatment plan was used versus using the optimized treatment plan for each insertion. The greatest single change resulted in a percent increase of 35%, 30%, and 45% to the rectum, bladder, and vaginal surface points, respectively. Increased dose to at-risk structures occurred when individualized treatment planning was not performed. Since a significant increase in dose to the rectum (P=0.038) and bladder (P=0.006) was obtained without customized treatment planning, we continue to advocate individualized treatment planning in HDR tandem and ovoid insertions for the treatment of cervix cancer.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
59. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995; 32(5):1275-1288.	4	1,224 patients	To evaluate the impact of timing of brachytherapy on outcome. To also explore the hypothesis that more extensive tumors technically require prolongation of the course of irradiation; thus, decreased tumor control and survival in these patients may not necessarily be the result of time/dose factor.	There was strong correlation between overall treatment time and tumor stage (≤7 weeks: 81% for stage IB; 74% for stage IIA; 52% for stage IIB; and 47% for stage III). Overall treatment time had a major impact on pelvic tumor control in stages IB, IIA, and IIB; in stage IB 10-year actuarial pelvic failure rates were 7% with overall treatment time ≤7 weeks, 22% with 7.1 to 9 weeks, and 36% with >9 weeks (P≤0.01). In multivariate analysis of patients with stage IB and IIA, overall treatment time and clinical stage were the most important prognostic factors for pelvic tumor control, DFS, and cause-specific survival. Tumor size was a prognostic factor for cause-specific survival. In stages IIB and III, overall treatment time, clinical stage, unilateral or bilateral parametrial invasion, and dose to point A were significant prognostic factors for pelvic tumor control, DFS, and cause-specific survival. Prolongation of treatment time in patients with stage IB, IIA, IIB, and III carcinoma of the uterine cervix has a significant impact on pelvic tumor control and cause-specific survival. The effect of overall treatment time was present regardless of tumor size except in stage IB tumors ≤3 cm.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
60. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1995; 32(5):1301-1307.	4	209 patients	To retrospectively analyze the effect of total treatment time in relation to pelvic control and OS for squamous cell carcinomas of the uterine cervix.	The median treatment duration was 55 days. For all stages combined, the 5-year survival and pelvic control rates were significantly different with treatment times <55 days vs ≥55 days: 65% and 54% (P=0.03), 87% and 72% (P=0.006), respectively. By stage, a shorter treatment duration (ie, <55 days vs ≥55 days) was significant for 5-year OS and pelvic control for stages IB/IIA and III, but not for stage IIB: stage IB/IIA (81% and 67%, 96% and 84%), stage III disease (52% and 42%, 76% and 55%) and stage IIB (43% and 50%, 74% and 80%, respectively). Survival decreased 0.6%/day and pelvic control decreased 0.7%/day for each additional day of treatment beyond 55 days for all stages of disease. Additionally, significant late complications were not influenced by treatment time. These results suggest that prolongation of treatment time is associated with decreased local control and survival in patients with cervical carcinoma. This is consistent with emerging data from other institutions. Therapeutic implications include avoidance of unnecessary treatment breaks, the design of fractionation schemes that decrease treatment duration, and possibly the use of tumor cytostatic drugs during conventional radiation.	2

Definitive Therapy for Early Stage Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
61. Miller BE, Copeland LJ, Hamberger AD, et al. Carcinoma of the cervical stump. *Gynecol Oncol* 1984; 18(1):100-108.	3a	263 patients	Retrospective analysis to evaluate patients with carcinoma of the cervical stump.	Symptomatology, stage distribution, and histology of carcinoma of the cervical stump showed no significant differences from cervical carcinoma of the intact uterus. Depending on the tumor stage, tumor volume, and distorted anatomy, treatment consisted of various combinations of intracavitary radium and transvaginal and external radiation. The 5-year survival was 100% in stage 0, 91% in stage I, 77% in stage II, 46% in stage III, and 37% in stage IV. The results achieved are similar to those in cervical cancer of the intact uterus. The complication rate was 30% and there were 9 (3.7%) deaths related to radiation complications.	2

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

AP-PA = Anteroposterior-posteroanterior

BMS = Bone marrow-sparing

CI = Confidence interval

CT = Computed tomography

CTV = Clinical target volume

DFS = Disease-free survival

EBRT = External-beam radiation therapy

ED = Equivalent dose

EFRT = Extended-field radiation therapy

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

HDR = High-dose-rate

HR = Hazard ratio

IMRT = Intensity-modulated radiotherapy

LACC = Locally advanced cervical cancer

LAIB = Laparoscopic-assisted interstitial brachytherapy

LDR = Low-dose-rate

MRI = Magnetic resonance imaging

NACT = Neoadjuvant chemotherapy

NPV = Negative predictive value

OR = Odds ratio

OS = Overall survival

PET = Positron emission tomography

PFS = Progression-free survival

PPV = Positive predictive value

RHPPL = Radical hysterectomy and pelvic/para-aortic lymphadenectomy

RT = Radiation therapy

SBRT = Stereotactic body radiotherapy

TrIB = Traditional interstitial brachytherapy