Advanced Cervical Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. 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
2. 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

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3. Hancke K, Heilmann V, Straka P, Kreienberg R, Kurzeder C. Pretreatment staging of cervical cancer: is imaging better than palpation?: Role of CT and MRI in preoperative staging of cervical cancer: single institution results for 255 patients. *Ann Surg Oncol* 2008; 15(10):2856-2861.	9	255 patients 164 had CT, 101 had MRI, and 90 had both CT and MRI	To retrospectively analyze files of patients with biopsy-proven cervical carcinoma receiving primary surgical treatment to determine whether imaging is better than palpation. Standard of reference was surgicopathologic findings.	The accuracy, sensitivity, and specificity were 75%, 66%, and 81% for clinical staging, 59%, 43%, and 71% for CT, and 58%, 52%, and 63% for MRI, respectively. After stratification for palpation, the results with CT and MRI were no better than with palpation (accuracy: CT 61% and 54%, MRI 61% and 56%, respectively). The sensitivity of CT and MRI for detecting lymph node metastasis was also poor (36% and 35%, respectively). Clinical examination was better than CT and MRI for pretreatment evaluation of early invasive cervical cancer.	2
4. 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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5. Park W, Park YJ, Huh SJ, et al. The usefulness of MRI and PET imaging for the detection of parametrial involvement and lymph node metastasis in patients with cervical cancer. *Jpn J Clin Oncol* 2005; 35(5):260-264.	9	36	Retrospectively evaluate the diagnostic accuracies of MRI and PET for the detection of parametrial involvement and lymph node metastasis by comparing their results with surgical specimens in patients with early cervical cancer.	The accuracy of FIGO and MRI staging was 67% and 84.4%, respectively. The accuracy for detecting pelvic lymph node metastasis was better for PET than for MRI (78% vs 67%, respectively). MRI provides an improved evaluation of local tumor extension, but PET is more useful for the evaluation of pelvic lymph nodes than MRI; however, PET still misses microscopic disease. Further studies needed to evaluate the usefulness of PET/CT for the accuracy of the disease extension and the cost-effectiveness of MRI, PET or PET/CT in patients with cervical cancer.	2
6. Kitajima K, Murakami K, Yamasaki E, Kaji Y, Sugimura K. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. *Eur Radiol* 2009; 19(6):1529-1536.	9	45 patients 2 readers	To evaluate the accuracy of integrated FDG-PET/CT with intravenous contrast medium in detecting pelvic and para-aortic lymph node metastasis in patients with uterine cancer, with surgical and histopathological findings used as the reference standard.	The overall node-based sensitivity, specificity, PPV, NPV and accuracy of PET/CT for detecting nodal metastases were 51.1% (23/45), 99.8% (1,927/1,931), 85.2% (23/27), 98.9% (1,927/1,949) and 98.7% (1,950/1,976), respectively. The sensitivity for detecting metastatic lesions ≤4 mm in short-axis diameter was 12.5% (2/16), that for between 5 and 9 mm was 66.7% (16/24), and that for ≥10 mm was 100.0% (5/5). The overall patient-based sensitivity, specificity, PPV, NPV, and accuracy were 50% (6/12), 90.9% (30/33), 66.7% (6/9), 83.3% (30/36) and 80.0% (36/45), respectively. Integrated FDG-PET/contrast-enhanced CT is superior to conventional imaging, but only moderately sensitive in predicting lymph node metastasis preoperatively in patients with uterine cancer.	2

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7. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. *Gynecol Oncol* 2007; 106(1):29-34.	10	120 consecutive patients 27 had radical surgery	Prospective study to examine the clinical value of PET/CT as a supplement to FIGO staging in patients with cervical cancer stage ≥1B.	22 patients had true negative PET/CT scans concerning pelvic lymph nodes. One patient had a false negative node. For these patients, PPV was 75%, NPV 96%, sensitivity 75%, specificity 96%. Regarding para-aortal nodal disease in the total population of 119 patients, 15 patients had true positive scans. The number of true negatives was 103, resulting in PPV 94%, NPV 100%, and sensitivity 100%, and specificity 99%. PET/CT scans showed distant metastases in 19 patients, 10 were true positive and nine were false positive. The remaining 100 patients were considered true negative for distant metastases and for these patients, we found PPV 63%, NPV 100%, sensitivity 100%, and specificity 94%. Whole-body FDG-PET/CT scanning for newly diagnosed cervical cancer FIGO stage ≥1B has a high sensitivity and specificity, and can be a valuable supplement to the FIGO staging procedure.	2
8. Grigsby PW. PET/CT imaging to guide cervical cancer therapy. *Future Oncol* 2009; 5(7):953-958.	12	N/A	Review role of PET/CT imaging in patients with carcinoma of the uterine cervix.	PET/CT is useful in the management of patients with cervical cancer.	4
9. Small W, Jr., Vern TZ, Rademaker A, et al. A prospective trial comparing lymphangiogram, cross-sectional imaging, and positron emission tomography scan in the detection of lymph node metastasis in locally advanced cervical cancer. *Am J Clin Oncol* 2010; 33(1):89-93.	9	20 patients had lymphangiogram, CT/MRI, and PET	To prospectively evaluate the use of lymphangiogram, CT/MRI, and PET imaging of lymph node metastasis in patients receiving definitive chemoradiotherapy for cervical cancer.	Agreement between imaging was most consistent in the common iliacs (P<0.001) and least in the para-aortic region (P=0.41). DFS at one year was statistically associated with positive PET imaging (25%) vs negative PET imaging (86%) (P=0.033) in the common iliac lymph node region. One-year DFS in patients with any positive areas on PET imaging was 50% compared with 90% in patients with negative PET imaging (P=0.02). Seven patients were noted to have no metastasis in any region by all 3 of the imaging modalities; the 1-year DFS in these 7 patients was 100% compared with 59% in the 13 patients with any positive nodal area (P=0.05).	3

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10. 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
11. Eddy GL, Bundy BN, Creasman WT, et al. Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. *Gynecol Oncol* 2007; 106(2):362-369.	1	288 patients randomly allocated to RHPPL (N=143) or NACT+RHPPL (N=145)	Randomized phase III trial to determine if NACT prior to RHPPL could improve PFS and OS, as well as operability, with acceptable levels of toxicity.	The NACT+RHPPL group had very similar recurrence rates (relative risk: 0.998) and death rates (relative risk: 1.008) when compared to the RHPPL group. There were 79% that had surgery in the RHPPL group compared to 78% in the NACT+RHPPL group. There were 52% who received postoperative RT in the RHPPL group compared to 45% in the NACT+RHPPL group (not statistically significant). There is no evidence from this trial that NACT offered any additional objective benefit to patients undergoing RHPPL for suboptimal stage IB cervical cancer.	1
12. Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. *Gynecol Oncol* 2008; 110(3):308-315.	1	142	Randomized study to assess the efficacy of preoperative NACT with short cycle-length, high-dose agents for LACC.	The modified preoperative NACT is well tolerated and beneficial in reducing tumor size, eliminating pathological risk factors, and improving prognosis for responders. It also avoids the delay of effective treatment for non-NACT responders.).	1
13. 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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14. Fanfani F, Fagotti A, Ferrandina G, et al. Neoadjuvant chemoradiation followed by radical hysterectomy in FIGO Stage IIIB cervical cancer: feasibility, complications, and clinical outcome. *Int J Gynecol Cancer* 2009; 19(6):1119-1124.	4	39	To demonstrate the efficacy and feasibility of preoperative chemoradiation followed by radical surgery in a consecutive series of patients with stage IIIB cervical cancer.	Median follow-up was 33 months (range, 3-80 months). The percentages of 3-year DFS and OS were 67.6% and 70.0%, respectively. Patients with complete response and microscopic disease showed better prognosis than patients with partial response and no change (3-year DFS, 100% vs 31%; and 3-year OS, 100% vs 39%).	3
15. 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
16. Tierney JF, Vale C, Symonds P. Concomitant and neoadjuvant chemotherapy for cervical cancer. *Clin Oncol (R Coll Radiol)* 2008; 20(6):401-416.	7 (systematic search)	N/A	To examine whether using cytotoxic chemotherapy either alongside RT or in advance of local treatment improves outcome in cervical cancer. Study is based on existing systematic reviews and randomized trials.	There is a strong basis for the use platinum-based chemoradiotherapy, the current standard of care, but little convincing evidence as to the therapeutic benefits of using concomitant HU.	2
17. Glynne-Jones R, Hoskin P. Neoadjuvant cisplatin chemotherapy before chemoradiation: a flawed paradigm? *J Clin Oncol* 2007; 25(33):5281-5286.	7	N/A	To examine whether NACT reduces metastases, improves local control and selects out good responders for nonsurgical treatment in the following sites: head and neck, esophagus, cervix, anus, nasopharynx, and bladder; as well as non-small-cell lung cancer.	NACT has almost invariably failed to deliver an improved outcome in terms of DFS or OS when delivered before RT or chemoradiotherapy in all solid tumor sites. The evidence that NACT may improve outcome in terms of DFS or OS is strongest when it is administered before surgical resection, but remains scant before RT or chemoradiotherapy. Taxane-containing regimens look more promising than does cisplatin NACT, but have not been shown to improve on concurrent chemoradiotherapy.	4
18. 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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19. Grigsby PW, Singh AK, Siegel BA, Dehdashti F, Rader J, Zoberi I. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys* 2004; 59(3):706-712.	3a	208	Retrospective record review to evaluate pretreatment lymph node size, irradiation dose, and failure patterns.	Mean pelvic lymph node doses were: PET negative nodes, ≤1 cm, 66.8 Gy, and 0/76 failures; PET positive nodes, ≤1 cm, 66.8 Gy, and 3/89 failures; 1.1 to ≤2 cm, 66.9 Gy, and 0/21 failures; 2.1 to ≤3 cm, 69.4 Gy, and 2/15 failures; and 3.1 to ≤4 cm, 74.1 Gy, and 0/5 failures. The mean para-aortic lymph node dose was 43.3 Gy and there were no para-aortic failures for 24 patients with PET positive ≤1 cm nodes, 0/5 failures for 1.1 to ≤2 cm, and 0/4 failures for 2.1 to ≤3 cm. The most common site of failure was distant metastases. Positive lymph nodes of any size at diagnosis were the most significant predictor for developing distant metastases.	2
20. 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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21. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; 340(15):1137-1143.	1	403 patients 201 assigned to receive RT and concurrent chemotherapy, and 202 assigned to receive RT alone	Randomized trial to compare the effect of RT to a pelvic and para-aortic field with that of pelvic radiation and concurrent chemotherapy with 5-FU and cisplatin in women with advanced cervical cancer. Women with advanced cervical cancer confined to the pelvis (stages IIB through IVA or stage IB or IIa with a tumor diameter of at least 5 cm or involvement of pelvic lymph nodes) were randomly assigned to receive either 45 Gy of radiation to the pelvis and para-aortic lymph nodes or 45 Gy of radiation to the pelvis alone plus two cycles of 5-FU and cisplatin (days 1 through 5 and days 22 through 26 of radiation).	Estimated cumulative rates of survival at 5 years were 73% among patients treated with RT and chemotherapy and 58% among patients treated with RT alone (P=0.004). Cumulative rates of DFS at 5 years were 67% among patients in the combined-therapy group and 40% among patients in the RT group (P<0.001). The rates of both distant metastases (P<0.001) and locoregional recurrences (P<0.001) were significantly higher among patients treated with RT alone. The seriousness of side effects was similar in the two groups, with a higher rate of reversible hematologic effects in the combined-therapy group.	1
22. 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.	1	243 patients 127 RT + chemotherapy and 116 RT	Randomized trial 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. Patients were randomized to receive RT or RT + chemotherapy.	Projected PFS at 4 years are 63% with RT and 80% with RT + chemotherapy. The projected OS rate at 4 years is 71% with RT and 81% with RT + chemotherapy. Addition of concurrent cisplatin-based chemotherapy to RT significantly improves progression-free and OS for high-risk, early-stage patients who undergo RHPPL for carcinoma of the cervix.	1
23. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999; 17(5):1339-1348.	1	368 patients 177 were randomized to cisplatin and 191 to HU	Protocol comparing primary RT plus HU to irradiation plus 5-FU and cisplatin for the treatment of patients with LACC. The goals were to determine the superior chemoradiation regimen and to quantitate the relative toxicities. Patients were randomized to receive standard whole pelvic RT with concurrent 5-FU infusion and bolus cisplatin or the same RT plus oral HU.	For patients with LACC, the combination of 5-FU and cisplatin with RT offers patients better progression fee survival and OS than HU, and with manageable toxicity.	1

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24. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; 340(15):1144-1153.	1	526 women	To perform a randomized trial of radiotherapy in combination with three concurrent chemotherapy regimens — cisplatin alone; cisplatin, 5-FU, and hydroxyurea; and hydroxyurea alone — in patients with locally advanced cervical cancer.	The median duration of follow-up was 35 months. Both groups that received cisplatin had a higher rate of PFS than the group that received hydroxyurea alone (P<0.001 for both comparisons). The relative risks of progression of disease or death were 0.57 (95% CI, 0.42-0.78) in group 1 and 0.55 (95% CI, 0.40-0.75) in group 2, as compared with group 3. The OS rate was significantly higher in groups 1 and 2 than in group 3, with relative risks of death of 0.61 (95% CI, 0.44-0.85) and 0.58 (95% CI, 0.41-0.81), respectively.	1
25. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; 26(35):5802-5812.	7 (systematic review and meta-analysis)	15 trials (3,452 women) – main analysis	Systematic review and meta-analysis of individual patient data to examine the effect of chemoradiotherapy on all outcomes. Authors prespecified analyses to investigate whether the effect of chemoradiotherapy differed 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<.001). A larger survival benefit was seen for the two 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=.017) and non-platinum-based (HR = 0.77, P=.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.	1
26. Greer BE, Koh WJ, Abu-Rustum N, et al. Cervical cancer. *J Natl Compr Canc Netw* 2008; 6(1):14-36.	15	N/A	Guidelines based on consensus of authors regarding their views of accepted approaches to treatment of cervical cancer.	Effective treatment for cervical cancer like surgery and concurrent chemoradiation can yield cures in 80% of women with early stage disease (stages I and II) and in 60% with stage III disease.	4
27. Logsdon MD, Eifel PJ. Figo IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; 43(4):763-775.	3a	1,096 total 983 patients treated with curative intent and 113 treated only to achieve palliation of symptoms	Retrospective study to define patient, tumor, and treatment factors that influence the outcome of patients with FIGO stage IIIB squamous cell carcinoma of the intact uterine cervix.	Aggressive use of intracavitary irradiation, carefully balanced with pelvic EBRT, is necessary to achieve the best ratio between tumor control and complications for patients with FIGO stage IIIB carcinoma of the cervix. The highest disease specific survival rates and the lowest complication rates were achieved with a combination of 40-45 Gy of EBRT combined with intracavitary irradiation.	2

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28. 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
29. 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
30. Rogers CL, Freel JH, Speiser BL. Pulsed low dose rate brachytherapy for uterine cervix carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 43(1):95-100.	3a	46 patients analyzed	To analyze the outcome and complication rates for patients treated with curative-intent pulsed LDR brachytherapy and EBRT for uterine cervical carcinoma.	Actuarial 4-year DFS rates are 66% for the entire group: stage Ib 100%, stage II 69%, stage III/IVa 68%, and 43% in patients treated for recurrences after surgery for initial stage Ib disease. Pulsed LDR brachytherapy is a safe and effective brachytherapy method in the treatment of cervix carcinoma.	3
31. 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	442 patients' records reviewed in 59 facilities	To analyze the details of brachytherapy practice in patients treated for carcinoma of the cervix in the United States between 1996 and 1999. Radiation facilities were selected from a stratified random sample. Patients were randomly selected from lists of eligible patients treated at each facility.	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.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. 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.	3c	14 patients with carcinoma of the cervix treated with chemoradio-therapy followed by 5 intracavitary tandem and ovoid insertions of 600 cGy/fraction	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 vs 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. Study supports the individualized treatment planning in HDR tandem and ovoid insertions for the treatment of cervix cancer.	3
33. Demanes DJ, Rodriguez RR, Bendre DD, Ewing TL. High dose rate transperineal interstitial brachytherapy for cervical cancer: high pelvic control and low complication rates. *Int J Radiat Oncol Biol Phys* 1999; 45(1):105-112.	3a	62 patients with LACC or early stage carcinoma	Retrospective study. To report the clinical outcome for cervical carcinoma treated with EBRT to the pelvis and interstitial HDR brachytherapy.	• Overall local tumor control was 94%. Local control rates by FIGO stage were stage I (12/12) 100%, stage II (25/27) 93%, stage III (18/19) 95%, and stage IV (3/4) 75%. • The regional pelvic control rates were overall 81%, stage I (12/12) 100%, stage II (22/27) 81%, stage III (15/19) 79%, and stage IV (1/4) 25%. Distant metastasis developed in 20 patients (32%). • The actuarial 5-year DFS was for all patients 48%, stage I 81%, stage II 47%, stage III 39%, and stage IV O%. • Grade 3-4 delayed morbidity resulting from treatment, occurred in 6.5% (4/62) of patients. A fistula without local recurrence occurred in 1.6% (1/62) patients.	2
34. Syed AM, Puthawala AA, Abdelaziz NN, et al. Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2002; 54(1):67-78.	3a	185 patients 21 had stage IB (barrel), 77 stage II, 77 stage III, and 10 stage IV disease	Retrospective study (20-year period) to determine the outcome of interstitial LDR brachytherapy in the treatment of bulky or LACC.	• Clinical local control was achieved in 152 (82%) of the 185 patients. • A 5-year DFS rate of 65%, 67%, 49%, and 17% was achieved for patients with stage IB, II, III, and IV disease, respectively. • Eighteen (10%) of the 185 patients developed Radiation Therapy Oncology Group Grade 3 or 4 late complications. • Patients with LACC, or with distorted anatomy, may be treated adequately with interstitial brachytherapy to achieve excellent locoregional control and a reasonable chance of cure with acceptable morbidity.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
35. Potter R, Dimopoulos J, Kirisits C, et al. Recommendations for image-based intracavitary brachytherapy of cervix cancer: the GYN GEC ESTRO Working Group point of view: in regard to Nag et al. (Int J Radiat Oncol Biol Phys 2004;60:1160-1172). *Int J Radiat Oncol Biol Phys* 2005; 62(1):293-295; author reply 295-296.	15	N/A	Comment on "Guidelines for image-based intracavitary brachytherapy for cervical carcinoma" which was published by The Image-Guided Brachytherapy Group.	To promote efficiently the field of image-based brachytherapy in gynecology, a valid and common language should be agreed upon in particular for gross tumor volume, clinical target volume at a given time, and for meaningful dose–volume parameters.	4
36. Durrance FY, Fletcher GH, Rutledge FN. Analysis of central recurrent disease in stages I and II squamous cell carcinomas of the cervix on intact uterus. *Am J Roentgenol Radium Ther Nucl Med* 1969; 106(4):831-838.	3a	1,341 patients 471 with stage I and 870 with stage II squamous cell carcinomas of the cervix	To analyze central recurrent disease in patients with stages I and II squamous cell carcinomas of the cervix on intact uterus.	• Central failures in stage I cervical cancer is so rare that a definite cause cannot be determined. • Majority of central failures in stage II cervical cancer occurred in patients who had central bulky disease, endocervical disease, or a positive endometrial biopsy. • Almost none of the patients who had a conservative hysterectomy for bulky endocervical disease had central recurrences.	2
37. Mendenhall WM, McCarty PJ, Morgan LS, Chafe WE, Million RR. Stage IB or IIA-B carcinoma of the intact uterine cervix greater than or equal to 6 cm in diameter: is adjuvant extrafascial hysterectomy beneficial? *Int J Radiat Oncol Biol Phys* 1991; 21(4):899-904.	3a	150 total patients Irradiation alone: 75 patients, Irradiation followed by surgery: 75 patients	Analysis of patients with stage IB or IIA-B carcinoma of the intact uterine cervix ≥6 cm in diameter treated with irradiation alone or irradiation followed by surgery.	5-year survival rates for irradiation alone vs irradiation plus surgery were as follows: cause specific, 62% and 55%, and absolute, 54% and 52%. The proportion of patients who developed treatment complications necessitating hospitalization or a second operation was 4/75 (5%) after irradiation alone and 12/75 (16%) after irradiation and surgery. Routine use of adjuvant extrafascial hysterectomy is not warranted in this patient population.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Thoms WW, Jr., Eifel PJ, Smith TL, et al. Bulky endocervical carcinoma: a 23-year experience. *Int J Radiat Oncol Biol Phys* 1992; 23(3):491-499.	3a	371 patients initial treatment for bulky endocervical carcinomas of the uterine cervix 361 patients treated with curative intent by either RT (244 patients), or RT + surgery (117 patients)	To examine treatment of patients who had bulky endocervical carcinoma.	No significant difference in survival rate between 70 patients treated with RT alone and 64 patients treated with RT + surgery (P=0.46). At 10 years, pelvic control rates were 88% and 85% for patients treated with RT and RT + surgery, respectively (P=0.68).	2
39. 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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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
40. 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
41. Singh AK, Grigsby PW, Rader JS, Mutch DG, Powell MA. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. *Int J Radiat Oncol Biol Phys* 2005; 61(2):450-455.	3a	816	Retrospective review to determine the effect of concurrent chemoradiotherapy on the outcome of invasive cervical carcinoma patients with disease recurrence isolated to the para-aortic lymph nodes.	14/816 patients had clinically or radiographically detected isolated para-aortic lymph node metastases. All 7 patients with a classic finding of recurrence, none of whom had been treated to at least 45 Gy and concurrent chemotherapy, were dead of disease within 1.5 years. The 7 patients without a classic finding of recurrence, all of whom had been treated with salvage full-dose concurrent chemoradiotherapy, had a 5-year OS rate of 100% (P<0.01).	2
42. Maggioni A, Roviglione G, Landoni F, et al. Pelvic exenteration: ten-year experience at the European Institute of Oncology in Milan. *Gynecol Oncol* 2009; 114(1):64-68.	4	106 consecutive patients: pelvic exenteration performed for cancer of the cervix (62), vagina (21), vulva (9), endometrium (9), ovary (4) and 1 uterine sarcoma. Mean age 53.6 (30-78) years	To retrospectively analyze morbidity and survival after pelvic exenteration in patients with gynecologic malignancies.	Pelvic exenteration is a feasible technique with no postoperative mortality and high percentage of long-survivors, although the morbidity rate still remains significantly high. Careful patient selection, preoperative and postoperative care and optimal surgical skills in a Gynecologic Oncologic Center are the cornerstones to further improve quality of life and survival for these patients.	2

Advanced Cervical Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Marnitz S, Dowdy S, Lanowska M, Schneider A, Podratz K, Kohler C. Exenterations 60 years after first description: results of a survey among US and German Gynecologic Oncology Centers. *Int J Gynecol Cancer* 2009; 19(5):974-977.	15	40 clinics 38 teaching hospitals	To evaluate the current patterns of care, a questionnaire with 48 items was sent to 40 Society of Gynecologic Oncologists member clinics with fellowship programs and 38 German teaching hospitals for gynecologic oncology.	Before exenteration, PET/CT is mostly performed in the US, while MRI is preferred in Germany. Staging is more often done surgically in the United States (61%) compared with Germany (32%). None of the US institutions recommend an exenteration for patients with International FIGO stage IVA in contrast to 43% in Germany. In the case of fistula to the bladder and/or rectum, exenteration was recommended only by 29% and 61% in US and German clinics, respectively. In Germany, interdisciplinary with general surgeons, urologists, plastic surgeons, and radio-oncologists are more common. There is consensus to apply adjuvant therapy after exenteration in patients with positive margins and/or positive lymph nodes. However, adjuvant therapy is more frequently recommended in Germany (93%) than in the United States (74%).	3
44. Puthawala AA, Syed AM, Fleming PA, DiSaia PJ. Re-irradiation with interstitial implant for recurrent pelvic malignancies. *Cancer* 1982; 50(12):2810-2814.	3a	40 patients	To examine re-irradiation with interstitial implant in patients with a diagnosis of recurrent pelvic malignancy.	26/40 patients received interstitial implant at the time of exploratory laparotomy. A complete local control of implanted pelvic tumors was achieved in 27/40 patients (67%). 13/40 patients (33%) remained alive and disease-free to a minimum follow-up period of 2 years. Serious complications such as soft-tissue necrosis and fistulae occurred in 15% of the patients.	3
45. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Cancer* 1981; 48(4):899-903.	3c	34	Phase II study to examine the benefit of using Cis-platinum in the treatment of patients with advanced or recurrent squamous cell carcinoma of the cervix no longer amenable to control with surgery and/or RT.	Among 22 patients who had received no prior chemotherapy, 3 complete and 8 partial responses were observed (response rate 50%), whereas only two partial responses were observed among 12 patients who had received prior chemotherapy (response rate 17%). The observed response rate was marginally significantly higher among those with no prior chemotherapy (P=0.059). The overall frequency of response was 38% (13/34). Cis-platinum thus appears to be a highly active agent in the treatment of squamous cell carcinoma of the cervix at the dose and schedule tested.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Long HJ, 3rd, Bundy BN, Grendys EC, Jr., et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 2005; 23(21):4626-4633.	1	294 patients enrolled: 146 to CPT and 147 to CT	Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix. Patients were randomly allocated to receive cisplatin 50 mg/m(2) every 3 weeks; cisplatin 50 mg/m(2) day 1 plus topotecan 0.75 mg/m(2) days 1 to 3 every 3 weeks; or methotrexate 30 mg/m(2) days 1, 15, and 22, vinblastine 3 mg/m(2) days 2, 15, and 22, doxorubicin 30 mg/m(2) day 2, and cisplatin 70 mg/m(2) day 2 every 4 weeks.	Patients receiving cisplatin 50 mg/m(2) day 1 plus topotecan 0.75 mg/m(2) days 1 to 3 every 3 weeks had statistically superior outcomes to those receiving cisplatin 50 mg/m(2) every 3 weeks, with median OS of 9.4 and 6.5 months (P=.017), median progression fee survival of 4.6 and 2.9 months (P=.014), and response rates of 27% and 13%, respectively.	1
47. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 2009; 27(28):4649-4655.	1	513	Randomized phase III trial to assess toxicity and efficacy of cisplatin doublet combinations in advanced and recurrent cervical carcinoma. Patients were randomly assigned to paclitaxel 135 mg/m(2) over 24 hours plus cisplatin 50 mg/m(2) day 2 every 3 weeks (PC, reference arm); vinorelbine 30 mg/m(2) days 1 and 8 plus cisplatin 50 mg/m(2) day 1 every 3 weeks (VC); gemcitabine 1,000 mg/m(2) day 1 and 8 plus cisplatin 50 mg/m(2) day 1 every 3 weeks (GC); or topotecan 0.75 mg/m(2) days 1, 2, and 3 plus cisplatin 50 mg/m(2) day 1 every 3 weeks (TC).	Experimental-to-PC HRs of death were 1.15 (95% CI, 0.79 to 1.67) for VC, 1.32 (95% CI, 0.91 to 1.92) for GC, and 1.26 (95% CI, 0.86 to 1.82) for TC. The HRs for PFS were 1.36 (95% CI, 0.97 to 1.90) for VC, 1.39 (95% CI, 0.99 to 1.96) for GC, and 1.27 (95% CI, 0.90 to 1.78) for TC. Response rates for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection, and alopecia. Conclusion: VC, GC, and TC are not superior to PC in terms of OS. However, the trend in Response rates, progression fee survival, and OS rates favors PC. Differences in chemotherapy scheduling, pre-existing morbidity and toxicity are important in individualizing therapy.	1

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

5-FU = Fluorouracil

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EBRT = External-beam radiation therapy

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

HDR = High-dose-rate

HR = Hazard ratio

HU = Hydroxyurea

LACC = Locally advanced cervical cancer

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