Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62(1):10-29.	15	N/A	An estimate of the numbers of new cancer cases and deaths expected in the United States in the current year from the American Cancer Society with a compilation of the most recent data on cancer incidence, mortality, and survival based on incidence data from the National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics.	A total of 1,638,910 new cancer cases and 577,190 deaths from cancer are projected to occur in the United States in 2012. During the most recent 5 years for which there are data (2004-2008), overall cancer incidence rates declined slightly in men (by 0.6% per year) and were stable in women, while cancer death rates decreased by 1.8% per year in men and by 1.6% per year in women. Over the past 10 years of available data (1999-2008), cancer death rates have declined by more than 1% per year in men and women of every racial/ethnic group with the exception of American Indians/Alaska Natives, among whom rates have remained stable.	3
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/vulva.html, based on November 2010 SEER data submission, posted to the SEER web site, 2012. Accessed 20 June 2012.	7	N/A	SEER Cancer Statistics Review, 1978 to 2008. A report of the most recent cancer incidence, mortality, survival, prevalence, and lifetime risk statistics.	SEER Incidence: From 2005-2009, the median age at diagnosis for cancer of the vulva was 68 years of age. US Mortality: From 2005-2009, the median age at death for cancer of the vulva was 79 years of age. Survival and Stage: The overall 5-year relative survival for 2002-2008 from 18 SEER geographic areas was 71.5%. Lifetime Risk: Based on rates from 2007-2009, 0.27% of women born today will be diagnosed with cancer of the vulva at some time during their lifetime.	4
3. Hacker NF. Revised FIGO staging for carcinoma of the vulva. *Int J Gynaecol Obstet* 2009; 105(2):105-106.	7	(varied by study)	Revised FIGO staging for carcinoma of the vulva.	Stage IA will remain unchanged because this is the only group of patients with a negligible risk of lymph node metastases, but stage I and II have been combined. The number and morphology of the involved nodes have been taken into account, and the bilaterality of positive nodes has been discounted. In the future, account may need to be taken of patients having sentinel node biopsies without full groin dissection, and molecular markers may provide even better discrimination between prognostic groups.	4

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4. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* 2009; 105(2):107-108.	7	N/A	Review/analysis of surgical cancer staging guidelines.	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.	4
5. Piura B, Rabinovich A, Cohen Y, Friger M, Glezerman M. Squamous cell carcinoma of the vulva in the south of Israel: a study of 50 cases. *J Surg Oncol* 1998; 67(3):174-181.	7	50 patient medical files were reviewed: mean age 67.1 years	To investigate the clinical findings, treatment, and outcome of patients with vulvar squamous cell carcinoma in the south of Israel.	The most prevailing presenting symptoms were vulvar lump, ulcer, and itching. Mean patient delay in seeking medical help was 48.2 months. Clinical palpation as a test for detecting groin lymph node metastases had a sensitivity and specificity of 57.1% and 61.5%, respectively. The 5-year survival rate was 60.3% overall. By means of univariate analysis, a significant worsening in survival was demonstrated with advancing stage of disease ($P<0.001$), tumor >4 cm ($P<0.001$), and positivity of surgical margins ($P<0.0001$). In a multivariate analysis (Cox proportional hazards model) in a group of 45 patients, stage of disease was the strongest and the only significant predictor of survival ($P=0.0098$).	4
6. Hall TB, Barton DP, Trott PA, et al. The role of ultrasound-guided cytology of groin lymph nodes in the management of squamous cell carcinoma of the vulva: 5-year experience in 44 patients. *Clin Radiol* 2003; 58(5):367-371.	2	44 consecutive patients with primary squamous cell carcinoma of the vulva	To assess the accuracy of US combined with fine-needle aspiration cytology in the detection of lymph node metastasis in patients with squamous cell carcinoma of the vulva.	Histology demonstrated metastatic disease in 28 groins and no evidence of metastatic disease in 45. US agreed with the histology in 67/73 groins (92%), with two false-positives, four false-negatives and two indeterminate appearances. Cytology agreed with the histology in 65/72 fine-needle aspiration cytology samples obtained (90%), with six false-negatives, and one indeterminate result. No false-positive cytology results were seen. US and fine-needle aspiration cytology together failed to detect metastatic disease in four groins, one with an indeterminate US appearance, another with indeterminate cytology, the two others each having a single positive inguinal node despite a negative US and fine-needle aspiration cytology.	3

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7. Moskovic EC, Shepherd JH, Barton DP, Trott PA, Nasiri N, Thomas JM. The role of high resolution ultrasound with guided cytology of groin lymph nodes in the management of squamous cell carcinoma of the vulva: a pilot study. *Br J Obstet Gynaecol* 1999; 106(8):863-867.	2	24 women, 43 groins dissected	The accuracy of high resolution US with guided fine needle aspiration cytology in detecting inguinal lymph node involvement was assessed in women undergoing radical vulvectomy and groin node dissection for squamous cell vulval cancer.	Of the 43 groins dissected, US correctly diagnosed the lymph node status in 36, with five false positive and two false negative results. Cytology in 40 groins showed no false positive and five false negative results. The sensitivity and specificity for the combined techniques were 83% and 82% respectively. Assessed together, the combined technique failed to detect metastatic disease in two groins; in both cases the extent of nodal metastatic involvement was a solitary focus <3 mm in diameter. The US and fine needle aspiration procedure is safe and well tolerated and can be repeated as needed for surveillance.	3
8. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol* 2001; 19(17):3745-3749.	7	101 consecutive patients with carcinoma of the cervix	To compare the results of CT and FDG-PET for lymph node staging in patients with carcinoma of the cervix and to evaluate the relationship of the imaging findings to prognosis.	CT demonstrated abnormally enlarged pelvic lymph nodes in 20 (20%) and para-aortic lymph nodes in 7 (7%) of the 101 patients. PET demonstrated abnormal FDG uptake in pelvic lymph nodes in 67 (67%), in para-aortic lymph nodes in 21 (21%), and in supraclavicular lymph node in 8 (8%). The 2-year PFS, based solely on para-aortic lymph node status, was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive patients, and 14% in CT-positive and PET-positive patients (P<.0001).	4
9. Grigsby PW, Siegel BA, Dehdashti F, Mutch DG. Posttherapy surveillance monitoring of cervical cancer by FDG-PET. *Int J Radiat Oncol Biol Phys* 2003; 55(4):907-913.	4	76 patients	Retrospective review to evaluate the effect of irradiation and chemotherapy for carcinoma of the uterine cervix on post-treatment tumor uptake of FDG-PET and to assess the utility of FDG-PET for surveillance monitoring.	After treatment, persistent abnormal FDG uptake in the cervix was found in 18% (14/76), in the pelvic lymph nodes in 16% (9/55), in the paraaortic lymph nodes in 45% (5/11), and in the supraclavicular lymph nodes in 75% (3/4). 11 patients developed new sites of increased FDG uptake. In relation to the findings on post-treatment PET, the 2-year PFS rate was 86% for patients with no abnormal FDG uptake at any site and 40% for those with persistent abnormal uptake; there were no survivors at 2 years among patients who developed new sites of abnormal FDG uptake (P<0.0001).	3

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10. Rose PG, Adler LP, Rodriguez M, Faulhaber PF, Abdul-Karim FW, Miraldi F. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol* 1999; 17(1):41-45.	10	32 patients with stage IIB (n=6), IIIB (n=24), and IVA (n=2) tumors	To evaluate PET scanning in detecting para-aortic nodal metastasis in patients with locally advanced cervical carcinoma and no evidence of extrapelvic disease before planned surgical staging lymphadenectomy.	FDG was taken up by 91% of the cervical tumors. 6/8 patients with positive para-aortic node metastasis had PET scan evidence of para-aortic nodal metastasis. One of the two false-negatives had only one microscopic focus of metastatic cancer. In the para-aortic nodes, PET scanning had a sensitivity of 75%, a specificity of 92%, a PPV of 75%, and a NPV of 92%. FDG para-aortic nodal uptake conferred a relative risk of 9.0 (95% CI, 2.3 to 36.0) for para-aortic nodal metastasis. All 10/17 patients with metastasis were predicted by PET scanning (P<.001); 5 of these patients had abnormalities on CT scans.	2
11. Sironi S, Buda A, Picchio M, et al. Lymph node metastasis in patients with clinical early-stage cervical cancer: detection with integrated FDG PET/CT. *Radiology* 2006; 238(1):272-279.	10	47 consecutive women aged 29-71 years with clinical stage IA or IB cervical carcinoma	To prospectively determine the accuracy of combination PET/CT in lymph node staging in patients with early-stage cervical cancer, with histopathologic results as the reference standard.	15 (32%) patients had metastatic lymph nodes at histopathologic examination, and 32 (68%) had no histopathologically confirmed nodal metastasis. Of the total 1081 lymph nodes histopathologically sampled, 18 were found to be positive for malignant cells. The overall node-based sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 72% (13/18), 99.7% (1060/1063), 81% (13/16), 99.5% (1060/1065), and 99.3% (1073/1081), respectively. Corresponding values for PET/CT-based diagnosis of lymph nodes >0.5 cm in diameter were 100% (13/13), 99.6% (675/678), 81% (13/16), 100% (675/675), and 99.6% (688/691), respectively. The overall patient-based sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 73% (11/15), 97% (31/32), 92% (11/12), 89% (31/35), and 89% (42/47), respectively.	3
12. Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. *Int J Radiat Oncol Biol Phys* 2006; 65(3):720-725.	9	41 consecutive patients	A comparison of FDG-PET/CT in the staging of carcinoma of the anal canal, with special emphasis on determination of spread to inguinal lymph nodes.	FDG-PET/CT detected 91% of nonexcised primary tumors, whereas CT visualized 59%. FDG-PET/CT detected abnormal uptake in pelvic nodes of 5 patients with normal pelvic CT scans. FDG-PET/CT detected abnormal nodes in 20% of groins that were normal by CT, and in 23% without abnormality on physical examination.	4

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13. Schwarz JK, Siegel BA, Dehdashti F, Myerson RJ, Fleshman JW, Grigsby PW. Tumor response and survival predicted by post-therapy FDG-PET/CT in anal cancer. *Int J Radiat Oncol Biol Phys* 2008; 71(1):180-186.	2	53 consecutive patients with anal cancer	To evaluate the response to therapy for anal carcinoma using post-therapy imaging with FDG-PET and to compare the metabolic response with patient outcome.	The post-therapy PET scan did not show any abnormal FDG uptake (complete metabolic response) in 44 patients. Persistent abnormal FDG uptake (partial metabolic response) was found in the anal tumor in 9 patients. The 2-year cause-specific survival rate was 94% for patients with a complete vs 39% for patients with a partial metabolic response in the anal tumor (P=0.0008). The 2-year PFS rate was 95% for patients with complete vs 22% for patients with a partial metabolic response in the anal tumor (P<0.0001). A Cox proportional hazards model of survival outcome indicated that a complete metabolic response was the most significant predictor of PFS in our patient population (P=0.0003).	2
14. Cohn DE, Dehdashti F, Gibb RK, et al. Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer. *Gynecol Oncol* 2002; 85(1):179-184.	10	15 patients, 29 groins were evaluated	To determine the ability of FDG-PET to detect groin lymph node metastases from vulvar cancer.	6 patients had positive scans, suggesting metastases in 8 groins. Pathologically, 5 patients had metastases in 9 groins, with PET demonstrating metastases in 4/5 patients and 6 of 9 groins with disease. On a patient-by-patients basis, PET had a sensitivity of 80%, specificity of 90%, PPV of 80%, and NPV of 90% in demonstrating metastases. On a groin-by-groin basis, PET had a sensitivity of 67%, specificity of 95%, PPV of 86%, and NPV of 86%. PET was more accurate in detecting extranodal metastases than disease confined within the groin nodes (P=0.048).	2

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15. Sohaib SA, Richards PS, Ind T, et al. MR imaging of carcinoma of the vulva. *AJR Am J Roentgenol* 2002; 178(2):373-377.	10	22 patients (range, 21-85 years; median, 74 years)	To describe the MR imaging features of cancer of the vulva and to determine the accuracy of MR imaging in staging the disease.	The tumors were isointense to muscle on T1-weighted images and showed intermediate-to-high signal intensity on T2-weighted scans. After IV gadolinium was administered to four patients, tumor enhancement was seen in two (50%). MR imaging correctly staged the primary site in 14 (70%) of the 20 patients. If superficial inguinal nodes 10 mm or greater in short-axis diameter are considered abnormal, then the sensitivity for detection of malignant nodes was 40% and the specificity, 97%. If deep inguinal nodes 8 mm or greater in short-axis diameter are considered abnormal, then the sensitivity for detection of malignant nodes was 50% and the specificity, 100%.	3
16. Singh K, Orakwue CO, Honest H, Balogun M, Lopez C, Luesley DM. Accuracy of magnetic resonance imaging of inguinofemoral lymph nodes in vulval cancer. *Int J Gynecol Cancer* 2006; 16(3):1179-1183.	10	59 medical records of women were reviewed	To assess the accuracy of MRI in predicting inguinofemoral lymph nodes metastasis in women with vulval cancer.	MRI had a LR+ of 4.8 (95% CI of 2.7-8.6) and LR- of 0.17 (0.06-0.49). It had a sensitivity of 85.7% (63.7-97), specificity of 82.1% (69.6-91.1), PPV of 64.3% (44.1-81.4), and NPV of 93.9% (83.1-98.7). Clinical examination had an LR+ of 6.1 (1.8-21.6) and LR- of 0.69 (0.5-0.96). It had a sensitivity of 35% (15.3-59.4), specificity of 94.3% (84.3-98.8), PPV of 70% (34.7-93.3), and NPV of 79.4% (67.3-88.5).	3
17. Hacker NF. Surgery for gynaecological cancer: results since the introduction of radical operations. *Aust N Z J Obstet Gynaecol* 1990; 30(1):24-28.	7	N/A	Summary of historical radical and nonradical approaches to cervical and ovarian cancer treatments.	Surgical and nonsurgical approaches (both successful and unsuccessful) are discussed.	4
18. Homesley HD, Bundy BN, Sedlis A, et al. Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). *Am J Obstet Gynecol* 1991; 164(4):997-1003; discussion 1003-1004.	15	588	Analysis (review of survival rates) for patients with vulvar carcinoma: four risk groups delineated by the proportional hazards model.	The 5-year relative survival rates were 98%, 87%, 75%, and 29% for the risk group categories of minimal (negative groin nodes and lesion diameter ≤2 cm), low (one positive groin node and lesion diameter ≤2 cm or negative groin nodes and fewer than two lesions ≤8 cm diameter), intermediate (negative groin nodes and lesion diameter >8 cm diameter, one positive groin node and lesion diameter >2 cm, or two unilaterally positive groin nodes and lesion diameter ≤8 cm), and high (three or more positive groin nodes or two bilaterally positive groin nodes), respectively.	4

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19. Bipat S, Fransen GA, Spijkerboer AM, et al. Is there a role for magnetic resonance imaging in the evaluation of inguinal lymph node metastases in patients with vulva carcinoma? *Gynecol Oncol* 2006; 103(3):1001-1006.	10	60 patients with diagnosed vulva carcinoma	To study the accuracy of MRI in lymph node detection in patients with vulva carcinoma.	119 groins were examined either by sentinel node procedure or surgery, of which 23 groins were malignant. Sensitivity, specificity, PPVs and NPVs were 52%, 85%, 46% and 87% for observer 1 and 52% 89%, 52% and 89% for observer 2. The interobserver agreement was 104/119 (kappa 0.62), representing good agreement.	2
20. Oonk MH, Hollema H, de Hullu JA, van der Zee AG. Prediction of lymph node metastases in vulvar cancer: a review. *Int J Gynecol Cancer* 2006; 16(3):963-971.	12	N/A	To review the literature on currently available non- and minimally-invasive diagnostic methods and analysis of primary tumor characteristics for prediction of inguinofemoral lymph node metastases in patients with primary squamous cell carcinoma of the vulva.	Currently no noninvasive imaging techniques exist that are able to predict lymph node metastases with a high enough NPV. A depth of invasion ≤1 mm is the only histopathologic parameter that can exclude patients for complete inguinofemoral lymphadenectomy. No other clinicopathologic parameter allows exclusion of lymph node metastases with a high enough NPV.	4
21. Fons G, ter Rahe B, Sloof G, de Hullu J, van der Velden J. Failure in the detection of the sentinel lymph node with a combined technique of radioactive tracer and blue dye in a patient with cancer of the vulva and a single positive lymph node. *Gynecol Oncol* 2004; 92(3):981-984.	12	1 patient: 75-year-old with a clinical T2N0M0 squamous cell carcinoma replacing the clitoris	Study using the sentinel lymph node procedure with a radioactive tracer as a new diagnostic tool to predict lymph node status in early stage vulvar cancer.	A sentinel node was detected only at one groin. An exploration of the other groin showed a positive lymph node totally replaced by tumor. Stasis of the lymph flow might be the leading cause of the failure of the sentinel lymph node procedure.	4
22. Raspagliesi F, Ditto A, Fontanelli R, et al. False-negative sentinel node in patients with vulvar cancer: a case study. *Int J Gynecol Cancer* 2003; 13(3):361-363.	14	1 patient: underwent sentinel node biopsy, then bilateral inguino-femoral node dissection, and, lastly, radical vulvectomy	A study of the sentinel node biopsy technique as a useful solution for detecting lymph node status for primary vulvar cancer without having to perform radical inguinal lymphadenectomy.	The histologic analysis showed a well differentiated squamous cell carcinoma with metastases in one right inguinal node and one left inguinal node and a false-negative right sentinel node. The use of preoperative lymphoscintigraphy and the intraoperative use of the gamma probe combined with blue dye helps considerably in identifying lymphatic drainage and the sentinel node for vulvar cancer.	4

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23. Hefler LA, Grimm C, Six L, et al. Inguinal sentinel lymph node dissection vs. complete inguinal lymph node dissection in patients with vulvar cancer. *Anticancer Res* 2008; 28(1B):515-517.	7	29: inguinal sentinel lymph node dissection 46: complete inguinal lymph node dissection	Retrospective study to ascertain the postoperative morbidity in patients with vulvar cancer undergoing sentinel lymph node vs complete inguinal lymph node dissection.	Inguinal sentinel lymph node dissection was associated with a shorter operation time, a reduced rate of inguinal seromas, wound breakdown and wound infection, fewer days of inguinal drainage, and reduced postoperative lymphatic secretion.	3
24. Levenback CF, Ali S, Coleman RL, et al. Lymphatic Mapping and Sentinel Lymph Node Biopsy in Women With Squamous Cell Carcinoma of the Vulva: A Gynecologic Oncology Group Study. *J Clin Oncol* 2012:[E-pub ahead of print].	2	452 women	To determine the safety of sentinel lymph node biopsy as a replacement for inguinal femoral lymphadenectomy in selected women with vulvar cancer.	There were 132 node-positive women, including 11 (8.3%) with false-negative nodes. 23% of the true-positive patients were detected by immunohistochemical analysis of the sentinel lymph node. The sensitivity was 91.7% (90% lower confidence bound, 86.7%) and the false-NPV (1-NPV) was 3.7% (90% upper confidence bound, 6.1%). In women with tumor <4 cm, the false-NPV was 2.0% (90% upper confidence bound, 4.5%).	2
25. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 2008; 26(6):884-889.	4	623 groins of 403 assessable patients	To investigate the safety and clinical utility of the sentinel node procedure in early-stage vulvar cancer patients.	In 259 patients with unifocal vulvar disease and a negative sentinel node (median follow-up time, 35 months), six groin recurrences were diagnosed (2.3%; 95% CI, 0.6% to 5%), and 3-year survival rate was 97% (95% CI, 91% to 99%). Short-term morbidity was decreased in patients after sentinel node dissection only when compared with patients with a positive sentinel node who underwent inguinofemoral lymphadenectomy (wound breakdown in groin: 11.7% vs 34.0%, respectively; P<.0001; and cellulitis: 4.5% vs 21.3%, respectively; P<.0001). Long-term morbidity also was less frequently observed after removal of only the sentinel node compared with sentinel node removal and inguinofemoral lymphadenectomy (recurrent erysipelas: 0.4% vs 16.2%, respectively; P<.0001; and lymphedema of the legs: 1.9% vs 25.2%, respectively; P<.0001).	2

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26. Oonk MH, van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. *Lancet Oncol* 2010; 11(7):646-652.	15	723 sentinel nodes in 260 patients (2.8 sentinel nodes per patient) were reviewed	To assess the association between size of sentinel-node metastasis and risk of metastases in non-sentinel nodes, and risk of disease-specific survival in early stage vulvar cancer.	Our data show that the risk of non-sentinel-node metastases increases with size of sentinel-node metastasis. No size cutoff seems to exist below which chances of non-sentinel-node metastases are close to zero. Therefore, all patients with sentinel-node metastases should have additional groin treatment. The prognosis for patients with sentinel-node metastasis larger than 2 mm is poor, and novel treatment regimens should be explored for these patients.	2
27. Boronow RC. Combined therapy as an alternative to exenteration for locally advanced vulvo-vaginal cancer: rationale and results. *Cancer* 1982; 49(6):1085-1091.	4	During the period from 1968-1980, 33 cancers have been treated: 26 primary and 7 recurrent cases	The rationale and results from combined therapy as an alternative to exenteration for locally advanced vulvo-vaginal cancer.	The apparent advantages of this combined therapeutic approach over exenterative surgery include bladder and/or rectal preservation, low primary mortality, low treatment morbidity, and good results in cancer control.	3
28. Boronow RC, Hickman BT, Reagan MT, Smith RA, Steadham RE. Combined therapy as an alternative to exenteration for locally advanced vulvovaginal cancer. II. Results, complications, and dosimetric and surgical considerations. *Am J Clin Oncol* 1987; 10(2):171-181.	4	48 treated cases (37 primary cases and 11 cases of recurrent disease)	Updates on the experience using surgery for the vulvar (external genital) phase of this disease presentation, combined with RT for the internal genital phase (with adequate overlap of fields to protect surgical margins).	One patient had a total pelvic exenteration for local failure, and one had a posterior exenteration for local failure. One bladder and one rectum were lost to permanent diversion because of radiation injury. Thus, 5 of these major viscera were lost of the 96 total, and 91 (94.8%) were retained. Radiation therapy and surgical details have been reviewed relevant to local control and local failure and complications.	3

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29. Hacker NF, Berek JS, Juillard GJ, Lagasse LD. Preoperative radiation therapy for locally advanced vulvar cancer. *Cancer* 1984; 54(10):2056-2061.	4	8 patients	Study of preoperative radiation therapy for locally advanced vulvar cancer.	Satisfactory shrinkage of tumor occurred in 7/8 patients (87.5%), thus allowing conservative surgical excision. In 4 patients (50%), there was no viable tumor in the surgical specimen. Moist desquamation of the vulva occurred in all patients and was of sufficient severity to require temporary cessation of radiation in 4 patients (50%). Five received groin radiation, and one (20%) subsequently developed bilateral hip fractures. No other major morbidity occurred. 5/8 patients (62.5%) are alive without evidence of disease at intervals ranging from 15 months to 10 years.	3
30. Shimizu Y, Hasumi K, Masubuchi K. Effective chemotherapy consisting of bleomycin, vincristine, mitomycin C, and cisplatin (BOMP) for a patient with inoperable vulvar cancer. *Gynecol Oncol* 1990; 36(3):423-427.	5	1 patient: 57-year-old with FIGO stage IV (T3N3 + M1B) squamous cell carcinoma of the vulva	Evaluation of chemotherapy consisting of bleomycin, vincristine, mitomycin C, and cisplatin as treatment for a patient with inoperable vulvar cancer.	After three courses of bleomycin, vincristine, mitomycin C, and cisplatin therapy, the patient achieved a complete response with few toxic effects and subsequently could undergo radical vulvectomy with bilateral inguinal and pelvic lymphadenectomy. On microscopic examination, only a minute focus of viable squamous cell carcinoma was observed in the vulvar lesion and regional lymph nodes, which was surrounded by fibrotic or necrotic tissues. The patient received a further two courses of bleomycin, vincristine, mitomycin C, and cisplatin as postoperative chemotherapy. Five courses of bleomycin, vincristine, mitomycin C, and cisplatin were extremely tolerable and did not require special care. She has been free of disease for 20 months and her present performance status is 0.	4

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31. Durrant KR, Mangioni C, Lacave AJ, et al. Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynaecological Cancer Cooperative Group (GCCG). *Gynecol Oncol* 1990; 37(3):359-362.	4	31 patients	To test a low-dose chemotherapy schedule based on one used for cervical cancer in the treatment of advanced or recurrent vulvar cancer to determine response rates, toxicity, and subsequent operability.	18/28 evaluable patients showed a response (64%), 3 of them being complete and 15 partial. Response rates for patients with primary tumors (12/18) and for those with recurrences (6/10) were similar. No responses were seen in 3 patients of performance status grade 0 (WHO), 11 of 17 patients of grade 1 performance status showed objective response and 7/8 grade 2 performance status patients also showed objective response. After chemotherapy eight patients were found to have resectable disease and seven in fact had surgery.	3
32. Wagenaar HC, Colombo N, Vergote I, et al. Bleomycin, methotrexate, and CCNU in locally advanced or recurrent, inoperable, squamous-cell carcinoma of the vulva: an EORTC Gynaecological Cancer Cooperative Group Study. European Organization for Research and Treatment of Cancer. *Gynecol Oncol* 2001; 81(3):348-354.	4	25 patients: median age of 66 years (range, 39-82 years)	To investigate tumor response rate and treatment toxicity of a modified combination chemotherapy consisting of bleomycin, methotrexate, and CCNU for patients with locally advanced, squamous-cell carcinoma of the vulva (not amenable to resection by standard radical vulvectomy) or recurrent disease (after incomplete resection). Tumor resectability was reassessed in patients who had responded to chemotherapy.	Two complete and 12 partial responses were observed (response rate, 56%; 95% confidence limits, 35%-76%). The bleomycin, methotrexate, and CCNU regimen was associated with major hematological side effects and mild signs of bleomycin-related pulmonary toxicity. At a median follow-up of 8 months, 3 patients were alive, 18 had died due to malignant disease, 2 had died due to toxicity, and 2 had died due to intercurrent disease and unknown cause. The median PFS was 4.8 months and the median survival was 7.8 months. The 1-year survival was 32% (95% confidence limits, 13%-51%).	2

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33. Benedetti-Panici P, Greggi S, Scambia G, Salerno G, Mancuso S. Cisplatin (P), bleomycin (B), and methotrexate (M) preoperative chemotherapy in locally advanced vulvar carcinoma. *Gynecol Oncol* 1993; 50(1):49-53.	4	21 patients	Evaluation of Cisplatin, bleomycin, and methotrexate preoperative chemotherapy in locally advanced vulvar carcinoma.	2 patients (10%) had a partial response in the primary tumor and 14 (67% complete response + partial response) in the inguinal nodes. The operability rate following neoadjuvant chemotherapy was 90% (pathological downstaging rate, 33%) but surgery was really radical in 79% of cases. Pathological node response was significantly related to the pathological T downstaging, and a persistently high node positivity rate was detected (inguinal, 81%; pelvic, 47%). Neoadjuvant chemotherapy + radical surgery had an acceptable morbidity but the therapeutic results were less encouraging than expected with a 3-year survival of 24% and stage, pathological T downstaging, and node status all significantly affected survival. 68% of the operated patients recurred 3-17 months from the end of treatment and 50% of them had a distant relapse.	3
34. Geisler JP, Manahan KJ, Buller RE. Neoadjuvant chemotherapy in vulvar cancer: avoiding primary exenteration. *Gynecol Oncol* 2006; 100(1):53-57.	5	14 patients with advanced vulvar cancer: median age of 63 years	To determine whether neoadjuvant cisplatin and 5-FU chemotherapy can be used to preserve the anal sphincter and/or urethra in patients with advanced vulvar cancer involving these sites.	13 patients received a median of 3 cycles (range 2-4) of neoadjuvant chemotherapy. 10 patients received cisplatin and 5-FU, while 3 received cisplatin alone. The median time from diagnosis to surgery was 77 days (range 54-143). All patients with cisplatin and 5-FU chemotherapy underwent surgery except one patient who had a synchronous renal cell carcinoma and died prior to surgery. Patients receiving cisplatin alone showed no measurable response, while all patients receiving cisplatin and 5-FU demonstrated at least a partial response. 2 patients had no residual invasive carcinoma on final pathology. All patients receiving cisplatin and 5-FU followed by surgery are disease-free, while two of three receiving cisplatin have progressive disease. The anal sphincter and urethra were conserved in all patients receiving cisplatin and 5-FU.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
35. Domingues AP, Mota F, Durao M, Frutuoso C, Amaral N, de Oliveira CF. Neoadjuvant chemotherapy in advanced vulvar cancer. *Int J Gynecol Cancer* 2010; 20(2):294-298.	3b	25 patients	Analysis of 3 neoadjuvant chemotherapy schemes, bleomicine, paclitaxel, and 5-FU/cisplatin, used in patients with locally advanced vulvar tumors in a 12-year period.	Of the 25 patients included, 10 underwent an neoadjuvant chemotherapy regimen with bleomicine (Group A); 5, with paclitaxel (Group B); and 10, with a combination of 5-FU/cisplatin (Group C). In Group A, there was a 60% response rate. Mortality was 70%, with an OS rate of 70%, 40%, and 30% at 12, 24, and 60 months, respectively. The mean survival was 46.7 (15.4) months. In Group B, the response rate was 40%, with an 80% mortality rate and a survival rate of 60% and 20% at 12 and 24 months, respectively. The mean survival was 17.0 (3.8) months. In Group C, 20% of the responses were observed and the mortality was 90%, with an OS rate of 10% at 12 and 24 months and a mean survival of 7.6 (2.0) months.	3
36. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet* 1996; 348(9034):1049-1054.	1	856 patients: randomly put into three different treatment groups	To compare CMT with RT alone in patients with epidermoid anal cancer.	In the RT and CMT arms, respectively, five and three were ineligible, and six and nine died 6 weeks after initial treatment. After a median follow-up of 42 months (interquartile range 28-62), 164/279 (59%) RT patients had a local failure compared with 101/283 (36%) CMT patients. This gave a 46% reduction in the risk of local failure in the patients receiving CMT (relative risk 0.54, 95% CI 0.42-0.69, P<0.0001). The risk of death from anal cancer was also reduced in the CMT arm (0.71, 0.53-0.95, P=0.02). There was no OS advantage (0.86, 0.67-1.11, P=0.25). Early morbidity was significantly more frequent in the CMT arm (P=0.03), but late morbidity occurred at similar rates.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
37. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008; 299(16):1914-1921.	1	682 patients	To compare the efficacy of cisplatin-based (experimental) therapy vs mitomycin-based (standard) therapy in treatment of anal canal carcinoma.	A total of 644 patients were assessable. The median follow-up for all patients was 2.51 years. Median age was 55 years, 69% were women, 27% had a tumor diameter >5 cm, and 26% had clinically positive nodes. The 5-year disease-free survival rate was 60% (95% CI, 53%-67%) in the mitomycin-based group and 54% (95% CI, 46%-60%) in the cisplatin-based group (P=.17). The 5-year OS rate was 75% (95% CI, 67%-81%) in the mitomycin-based group and 70% (95% CI, 63%-76%) in the cisplatin-based group (P=.10). The 5-year local-regional recurrence and distant metastasis rates were 25% (95% CI, 20%-30%) and 15% (95% CI, 10%-20%), respectively, for mitomycin-based treatment and 33% (95% CI, 27%-40%) and 19% (95% CI, 14%-24%), respectively, for cisplatin-based treatment. The cumulative rate of colostomy was significantly better for mitomycin-based than cisplatin-based treatment (10% vs 19%; P=.02). Severe hematologic toxicity was worse with mitomycin-based treatment (P<.001).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997; 15(5):2040-2049.	1	110 patients were randomized between RT alone and a combination of RT and chemotherapy	To investigate the potential gain of the concomitant use of RT and chemotherapy in improving local control and reducing the need for colostomy, a randomized phase III trial was performed in patients with locally advanced anal cancer.	The addition of chemotherapy to RT resulted in a significant increase in the complete remission rate from 54% for RT alone to 80% for RT and chemotherapy, and from 85% to 96%, respectively, if results are considered after surgical resections. This led to a significant improvement of locoregional control and colostomy-free interval (P=.02 and P=.002, respectively), both in favor of the combined modality treatment. The locoregional control rate improved by 18% at 5 years, while the colostomy-free rate at that time increased by 32% by the addition of chemotherapy to RT. No significant difference was found when severe side effects were considered, although anal ulcers were more frequently observed in the combined-treatment arm. The survival rate remained similar in both treatment arms. Skin ulceration, nodal involvement, and sex were the most important prognostic factors for both local control and survival. Event-free survival, defined as free of locoregional progression, no colostomy, and no severe side effects or death, showed significant improvement (P=.03) in favor of the combined-treatment modality. The 5-year survival rate was 56% for the whole patient group.	1
39. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 1996; 14(9):2527-2539.	1	310 patients randomized to receive RT and 5-FU or RT, 5-FU, and mitomycin	To determine the importance of mitomycin in the standard chemoradiation regimen and to assess the role of salvage chemoradiation in patients who have residual tumor following chemoradiation.	Post-treatment biopsies were positive in 15% of patients in the 5-FU arm vs 7.7% in the mitomycin arm (P=.135). At 4 years, colostomy rates were lower (9% vs 22%; P=.002), colostomy-free survival higher (71% vs 59%; P=.014), and disease-free survival higher (73% vs 51%; P=.0003) in the mitomycin arm. A significant difference in OS has not been observed at 4 years. Toxicity was greater in the mitomycin arm (23% vs 7% grade 4 and 5 toxicity; P≤.001). Of 24 assessable patients who underwent salvage chemoradiation, 12 (50%) were rendered disease-free.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
40. Nigro ND, Vaitkevicius VK, Considine B, Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 1974; 17(3):354-356.	7	3 past cases of anal cancer	Combined therapy for cancer of the anal canal: a preliminary report.	Report and discussion of 3 past cases of anal cancer.	4
41. Berek JS, Heaps JM, Fu YS, Juillard GJ, Hacker NF. Concurrent cisplatin and 5-fluorouracil chemotherapy and radiation therapy for advanced-stage squamous carcinoma of the vulva. *Gynecol Oncol* 1991; 42(3):197-201.	5	12 patients	A phase II trial of concurrent cisplatin and 5-FU chemotherapy and RT was conducted for the primary treatment of patients with retrospective surgical FIGO stages III-IV squamous carcinoma of the vulva.	Complete tumor responses were seen in 8/12 (67%) patients. Responses were observed in 6/8 (75%) stage III patients and 2/4 (50%) stage IV patients. Partial response was observed in 3 patients, and 1 patient had persistent disease. At the completion of concurrent chemoradiation therapy, radical vulvectomy or excision was used in 3 patients and posterior exenteration in 1. With a median follow-up of 37 months (range, 7-60 months), 10 patients are alive and free of disease, and 2 patients died at 12 and 15 months. There were no treatment-related deaths and no grade 4 toxicity. The morbidity included moist desquamation of the vulva in all patients, with grade 2 toxicity in 10 patients and grade 3 in 2 patients. One patient had a deep venous thrombosis that responded to anticoagulation therapy.	3
42. Cunningham MJ, Goyer RP, Gibbons SK, Kredentser DC, Malfetano JH, Keys H. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. *Gynecol Oncol* 1997; 66(2):258-261.	5	14 patients with primary squamous carcinoma of the vulva (not candidates for standard radical vulvectomy), treated with RT with cisplatin and 5-FU chemo-therapy, mean age 68 years	To evaluate a regimen of RT and chemotherapy as an alternative for those patients in whom the location and extent of advanced vulvar carcinoma makes pelvic exenteration the only surgical option.	Acute complications included desquamation requiring treatment interruptions in 5 patients and deep venous thrombosis in 1 patient. Delayed complications were limited to small bowel obstruction and colonic stricture in one patient. There was a 92% response rate with complete responses in 9 patients (64%). Among patients with complete clinical response, there has been only one recurrence with follow-up of 7-81 months, mean 36.5. All patients with partial responses died, with survival of 8-25 months, mean 15.7.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Eifel PJ, Morris M, Burke TW, Levenback C, Gershenson DM. Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva. *Gynecol Oncol* 1995; 59(1):51-56.	5	12 patients ages 37-85 years (mean, 59 years)	Evaluation of prolonged continuous infusion cisplatin and 5-FU with radiation as treatment for locally advanced carcinoma of the vulva.	Chemoradiation was well tolerated with virtually no hematologic toxicity and no unscheduled breaks in treatment. 11/12 patients had at least a partial clinical response; 1 patient had a minimal response of unresectable vulvar disease. Of 8 patients who underwent vulvar resection 6 weeks after chemoradiation, 4 had no residual disease in the resected vulvar specimen and remain disease-free 17, 20, 25, and 37 months, respectively, after surgery. Another patient is disease-free 28 months after a complete clinical response without vulvar resection. However, of 4 patients who had residual disease in the vulvar surgical specimen, disease has recurred within the irradiation field in three. Overall, 6 of 12 patients treated with this chemoradiation regimen remain disease-free 17-30 months after treatment.	3
44. Evans LS, Kersh CR, Constable WC, Taylor PT. Concomitant 5-fluorouracil, mitomycin-C, and radiotherapy for advanced gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 1988; 15(4):901-906.	4	19 patients were treated definitively and 6 patients were treated with palliative intent (24 primary, 1 recurrent), median age of 57 years	Evaluation of treatment by a combined modality approach; Mitomycin-C and 5-FU given concomitantly with RT for advanced gynecologic malignancies.	In the definitive patient group, there was no reduction in the therapeutic dose. Only 4 patients underwent surgical therapy. With a minimum follow-up of 8 months and a median follow-up of 28 months, the survival for the entire population was 56%. 14/19 patients (74%) treated definitively are surviving with 12 patients having no evidence of disease. Survival by site in the definitive therapy group was cervix 70%, vulva 100%, and vagina 66%. The overall response rate was 84% at 3 and 9 months (3 months; complete response 36%, partial response 48%, and 9 months; complete response 60%, partial response 24%). There were no local recurrences in the 12 patients who achieved a complete response. Three patients died of metastatic disease alone and the overall local control was 60%.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
45. Gerszten K, Selvaraj RN, Kelley J, Faul C. Preoperative chemoradiation for locally advanced carcinoma of the vulva. *Gynecol Oncol* 2005; 99(3):640-644.	4	18 patients with vulvar cancer	Retrospective review of the outcomes of a twice daily radiation treatment schedule (interval of 4-6 hours) delivered concurrent with chemotherapy for advanced or critically located carcinoma of the vulva was modeled on the schema developed by the Gynecology Oncology Group (GOG).	All patients responded. There were 13/18 complete clinical responses, of whom 12 remained NED at 25 months. Of the five partial clinical response patients, two have suffered local recurrences, despite surgical resection in one and electron boost in the other. All patients developed a desquamative perineal skin reaction necessitating a mean treatment break of 15 days. No severe hematological toxicity was encountered, and only one patient had grade 3 small bowel toxicity. One patient required surgical debridement for groin wound breakdown.	4
46. Koh WJ, Wallace HJ, 3rd, Greer BE, et al. Combined radiotherapy and chemotherapy in the management of local-regionally advanced vulvar cancer. *Int J Radiat Oncol Biol Phys* 1993; 26(5):809-816.	4	20 patients with locally extensive primary or recurrent carcinoma of the vulva	To determine, in a retrospective single institutional study, the role of concurrent RT and chemotherapy in the treatment of local-regionally advanced vulvar cancer.	10 patients had complete resolution of tumor to initial chemoradiotherapy, and 8 of these have remained free of tumor relapse. Eight other patients had partial responses, with tumor bulk reduced by >50%, while the remaining 2 patients had local-regionally progressive disease. Six of the patients with partial responses had residual tumor successfully resected, although four subsequently recurred. For the entire group of 20 patients, the actuarial 3- and 5-year local control rates were 48% each, and the corresponding disease-specific survival rates were 59% and 49%.	4
47. Landoni F, Maneo A, Zanetta G, et al. Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma. *Gynecol Oncol* 1996; 61(3):321-327.	2	58 total patients: primary (41) or recurrent (17) disease	To prospectively evaluate the feasibility and efficacy of neoadjuvant chemoradiotherapy in locally advanced or recurrent vulvar carcinoma.	89% of patients completed the chemoradiotherapeutic treatment, whereas 72% underwent surgery. Objective responses were observed in 80% of vulvar diseases and in 79% of groin metastases. Pathologic complete response of both the vulvar and inguinal disease was confirmed in 13 patients (31%). Early severe toxicity was recorded in 3 patients and severe worsening of performance status in 3. Three deaths occurred shortly after treatment and at least one is directly related to toxic effects. This treatment allows good control of locally advanced and recurrent vulvar cancer with acceptable side effects.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Mulayim N, Foster Silver D, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. *Gynecol Oncol* 2004; 93(3):659-666.	4	17 patients: medical chart review	To investigate the acute and late toxicities associated with the use of chemoradiation therapy with 5-FU and mitomycin C or mitomycin C alone for primary, adjuvant, and salvage therapy for vulvar cancer.	6 patients had grade 4 neutropenia. In 3 patients, life-threatening neutropenic sepsis developed after the second cycle of chemotherapy. Severe enterocolitis was a direct cause of death in two patients. In 4 patients, the second cycle of chemotherapy was cancelled because of severe toxicity associated with the first cycle. 1 patient had grade 4 skin toxicity in the vulvar-perineal area. 6 patients had grade 3 and 7 patients had grade 2 acute skin toxicity. Skin toxicity necessitated the interruption of chemoradiation therapy in 9 patients at a median dose of 32.4 Gy. One patient developed bowel perforation and colovaginal fistula 1.5 years after completion of chemoradiation therapy.	4
49. Russell AH, Mesic JB, Scudder SA, et al. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cancer of the vulva. *Gynecol Oncol* 1992; 47(1):14-20.	2	18 previously untreated patients: 1 was stage II, 10 were stage III, 6 were stage IVA, and 1 was stage IVB	Evaluation of EBRT and synchronous, radiopotentiating chemotherapy to treat 25 women with locoregionally advanced or locoregionally recurrent squamous cancer of the vulva.	Complete clinical response was obtained in 16/18 previously untreated patients (89%) and in 4/7 patients with recurrent disease following vulvar surgery (57%). Of 20 patients achieving a complete clinical response, 3 patients have relapsed within the irradiated volume at 11, 38, and 48 months following completion of treatment. 14 patients remain alive and continuously cancer free from 2-52 months after completion of treatment (median follow-up 24 months).	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
50. Thomas G, Dembo A, DePetrillo A, et al. Concurrent radiation and chemotherapy in vulvar carcinoma. *Gynecol Oncol* 1989; 34(3):263-267.	2	33 patients	The role of radiation with concurrent infusional 5-FU with or without mitomycin C was examined in patients with vulvar cancer.	9 received adjuvant postsurgical chemotherapy-RT and none has relapsed in the radiation field. Seven are alive disease free. Two have died of distant metastases. Of the 9 receiving definitive primary chemotherapy-RT, 6 had initial complete response with subsequent vulvar relapse developing in 3. 7/9 remain disease free after chemotherapy-RT alone (in 3) or with the addition of a local excision of residual or recurrent disease (in 6). One patient did not respond to chemotherapy-RT and required a radical vulvectomy and groin node dissection. 15 received chemotherapy-RT for disease recurrence following primary surgery. Disease was present in the vulva only in 11, vulva and inguinal nodes in 1 and nodes only in 3. 8/15 had a complete response and no relapses occurred in the treated sites. 4/8 dying of disease developed pulmonary metastases. Serious late complications developed in 2 patients, 1 avascular hip necrosis and 1 proctitis requiring a defunctioning colostomy.	3
51. Wahlen SA, Slater JD, Wagner RJ, et al. Concurrent radiation therapy and chemotherapy in the treatment of primary squamous cell carcinoma of the vulva. *Cancer* 1995; 75(9):2289-2294.	2	19 patients	To evaluate the potential role of combined radiation and chemotherapy with or without local excision as primary treatment for squamous cell carcinoma of the vulva, the outccomes of patients with this disease treated with combination therapy were reviewed.	The median follow-up was 34 months. Responses were determined clinically 1 month after completion of the radiation and chemotherapy. Clinically, complete responses were obtained in 10 patients (53%), partial responses in 7 (37%), and no response in 1; 1 patient progressed during treatment. The CMT (radiation/chemotherapy/with or without wide local excision) resulted in a local control rate of 74% (14/19). All 5 treatment failures occurred within 6 months of treatment. Four of these patients were rendered disease free by radical vulvectomy and/or exenteration, for an overall local control rate of 95% (18/19).	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
52. Gaffney DK, Du Bois A, Narayan K, et al. Patterns of care for radiotherapy in vulvar cancer: a Gynecologic Cancer Intergroup study. *Int J Gynecol Cancer* 2009; 19(1):163-167.	15	32 surveys were returned from 12 different cooperative groups	This study aimed to describe radiotherapeutic practice in the treatment of vulvar cancer in member study groups of the Gynecologic Cancer Intergroup (GCIG).	The most common indications for neoadjuvant RT include unresectable disease or International Federation of Gynecology and Obstetrics stage ≥III. For the neoadjuvant treatment of vulvar cancer, pelvic doses were 48.2 +/- 5.0 Gy (mean +/- standard deviation). The upper border of the pelvic field was L4/5 in 4, L5/S1 in 12, and not specified in 4. Of 21 groups that perform neoadjuvant RT, 17 use concomitant chemotherapy and 4 individualize treatment. Weekly cisplatin was the most commonly used chemotherapy. For the neoadjuvant RT treatment of the inguinal region, doses were 49.9 +/- 5.5 Gy (mean +/- standard deviation). 16/18 groups used CT simulation for planning. After initial surgery, the most common indications for RT included positive lymph nodes or positive margins. Chemotherapy was not routinely used after surgery.	4
53. Moore DH, Thomas GM, Montana GS, Saxer A, Gallup DG, Olt G. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. *Int J Radiat Oncol Biol Phys* 1998; 42(1):79-85.	2	73 patients with clinical stage III-IV squamous cell vulvar carcinoma	To determine the feasibility of using preoperative chemoradiotherapy to avert the need for more radical surgery for patients with T3 primary tumors, or the need for pelvic exenteration for patients with T4 primary tumors, not amenable to resection by standard radical vulvectomy.	Following chemoradiotherapy, 33/71 (46.5%) patients had no visible vulvar cancer at the time of planned surgery and 38/71 (53.5%) had gross residual cancer at the time of operation. Five of the latter 38 patients had positive resection margins and underwent: further radiation therapy to the vulva (3 patients); wide local excision and vaginectomy necessitating colostomy (1 patient); no further therapy (1 patient). Using this strategy of preoperative, split-course, twice-daily radiation combined with cisplatin plus 5-FU chemotherapy, only 2/71 (2.8%) had residual unresectable disease. In only 3 patients was it not possible to preserve urinary and/or gastrointestinal continence. Toxicity was acceptable, with acute cutaneous reactions to chemoradiotherapy and surgical wound complications being the most common adverse effects.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
54. Montana GS, Thomas GM, Moore DH, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 2000; 48(4):1007-1013.	2	46 patients	To determine if patients with carcinoma of the vulva, with N2/N3 lymph nodes, could undergo resection of the lymph nodes and primary tumor following preoperative chemo-radiation.	Following chemo-radiation, the disease in the lymph nodes became resectable in 38/40 patients. Two patients who completed the course of chemo-radiation did not undergo surgery as per protocol because of pulmonary metastasis. One underwent radical vulvectomy and unilateral node dissection and the other radical vulvectomy only. The specimen of the lymph nodes was histologically negative in 15/37 patients. 19 patients developed recurrent and/or metastatic disease. The sites of failure were as follows: primary area only, 9; lymph node area only, 1; primary area and distant metastasis, 1; distant metastasis only, 8. Local control of the disease in the lymph nodes was achieved in 36/37 and in the primary area in 29/38 of the patients. 20 patients are alive and disease-free, and five have expired without evidence of recurrence or metastasis. Two patients died of treatment-related complications.	3
55. Parsons JT, Bova FJ, Million RR. A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 1980; 6(12):1645-1652.	7	468 consecutive patients: 214 split-course and 254 continuous-course method of treatment	A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck, with 208 additional patients.	Primary lesions regressed or stabilized during the rest interval in patients who received split-course treatment; no tumor was observed to enlarge. Metastatic neck nodes usually stabilized, but occasionally regressed during the split; none enlarged. Split-course treatment patients reported alleviation of acute symptoms after 10-12 days of rest; mucous membranes appeared near normal when the patients returned to resume therapy.	4
56. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol* 2012; 124(3):529-533.	2	40 patients completed the study treatment	To determine the efficacy and toxicity of radiation therapy and concurrent weekly cisplatin chemotherapy in achieving a complete clinical and pathologic response when used for the primary treatment of locally-advanced vulvar carcinoma.	Reasons for prematurely discontinuing treatment included: patient refusal (n=4), toxicity (n=9), death (n=2), other (n=3). There were 37 patients with a complete clinical response (37/58; 64%). Among these women there were 34 who underwent surgical biopsy and 29 (78%) who also had a complete pathological response. Common adverse effects included leukopenia, pain, radiation dermatitis, pain, or metabolic changes.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
57. Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulval cancer. *Cochrane Database Syst Rev* 2011; (4):CD003752.	7	One randomized control trial and two non-randomized studies met the inclusion criteria and included a total of 141 women	To evaluate the effectiveness and safety of neoadjuvant and primary chemoradiation for women with locally advanced primary vulval cancer compared to other primary modalities of treatment such as primary surgery or primary radiation.	One randomized control trial found that neoadjuvant chemoradiation did not appear to offer longer survival compared to primary surgery in advanced vulval tumors (relative risk = 1.29, 95% CI, 0.87 to 1.91). There was also no statistically significant difference in survival between primary chemoradiation and primary surgery in a study that included 63 women (pooled adjusted hazard ratio = 1.09, 95% CI, 0.37 to 3.17) and in another study that only included 12 eligible women and compared the same interventions (hazard ratio was non-informative when statistical adjustment was made). In the randomized control trial there was no observed statistically significant difference between neoadjuvant chemoradiation and primary surgery.	4
58. Landrum LM, Skaggs V, Gould N, Walker JL, McMeekin DS. Comparison of outcome measures in patients with advanced squamous cell carcinoma of the vulva treated with surgery or primary chemoradiation. *Gynecol Oncol* 2008; 108(3):584-590.	3b	63 patients: stage III (n=47) and IV (n=16) carcinoma of the vulva	To review outcome measures including OS, PFS, and patterns of recurrence in patients with advanced vulvar cancer managed by primary surgery or primary chemoradiation as well as population characteristics for the two groups.	Patients treated with primary chemoradiation were younger (61 vs 72 years; P=0.09), had less metastasis to lymph nodes (54% vs 83%, P=0.01), and larger tumors (6 vs 3.5 cm, P=0.0001) compared to patients treated with primary surgery. Despite these differences, OS for the primary surgery and primary chemoradiation groups was 69% and 76%, respectively, with median follow-up at 31 months. There were no differences in PFS or recurrence rates between the two groups.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
59. Maneo A, Landoni F, Colombo A, Villa A, Caspani G. Randomised Study Between Neoadjuvant Chemoradiotherapy and Primary Surgery for the Treatment of Advanced Vulvar Cancer. *International Journal of Gynecological Cancer* 2003; 13(Suppl 1):6, Abstrast PL 19.	2	Surgical arm: 37 patients, Chemo-RT arm: 30 patients	Since 1994 to 2000 68 cases with operable advanced vulvar cancer (T2>4 cm, T3, any case with positive nodes) were randomized between primary radical surgery (followed by RT in patients with more than one lymph node metastasis) vs concomitant RT (50 Gy) and chemotherapy (5-FU 750 mg/sqm day 1-5, mitomycin-C 15 mg/sqm day 1, 2 courses every 3 weeks) followed by surgery.	Surgical arm: Node metastases were found in 24 cases (65%) and RT was delivered to 15 cases. Overall morbidity rate was 46% (17/37 patients) and 10 cases presented wound diastasis. Chemo-RT arm: Neoadjuvant treatment was delivered to 28 cases. Surgical therapy was feasible in 24 cases (inguinal lymphadenectomy in 18). Pathological complete response was recorded in 5/24 vulvar specimens (21%) and in 6/18 groins (33%). Overall morbidity rate was 54% (13/24 patients) and 10 cases presented wound diastasis. After a mean follow-up of 42 months patients alive with no evidence of disease are 22 (58%) in the surgical arm and 10 (42%) in the chemo-RT arm. 5-year survival is respectively 49% and 30% (P=0.19).	1
60. McCall AR, Olson MC, Potkul RK. The variation of inguinal lymph node depth in adult women and its importance in planning elective irradiation for vulvar cancer. *Cancer* 1995; 75(9):2286-2288.	15	100 women without inguinal adenopathy or prior inguinal surgery	The depths of inguinal lymph nodes were evaluated with CT scans in adult women.	Only 18% of women had all inguinal lymph nodes measured at a depth of 3 cm or less.	3
61. Beriwal S, Coon D, Heron DE, et al. Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma. *Gynecol Oncol* 2008; 109(2):291-295.	2	18 patients	To assess the clinical outcome in patients with locally-advanced vulvar cancers treated using preoperative chemotherapy with IMRT.	The median follow-up time was 22 months (2-60 months). Fourteen patients had surgery performed with pathological complete response (pCR) in 9 (64%) patients and partial response (pPR) in 5 patients. There were no recurrences in the 9 patients who achieved pCR whereas 3/5 with pPR had local recurrence (p=0.027). Four patients did not have surgery: one patient died a week after treatment while 2 of the remaining 3 patients had local recurrences. Acute desquamative skin reactions in the vulva and perineum were seen in all patients. Three of the 14 patients who had surgery had prolonged wound complications requiring debridement. No patients had radiation-related acute or late toxicity of grade = 3. The 2-year cause specific and OSs were 75% and 70% respectively.	2

Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
62. Bloemers MC, Portelance L, Ruo R, Parker W, Souhami L. A dosimetric evaluation of dose escalation for the radical treatment of locally advanced vulvar cancer by intensity-modulated radiation therapy. *Med Dosim* 2012.	5	5 vulvar cancer patients treated in the postoperative setting and 5 patients treated with definitive intent (def-group)	To determine whether IMRT reduces the radiation dose to organs at risk when compared with 3D-CRT in patients with vulvar cancer treated by irradiation. This study also investigated the use of sequential IMRT boost and simultaneous integrated boost for dose escalation in the treatment of locally advanced vulvar cancer.	IMRT significantly (all $P<0.05$) reduced the D(mean), V30, and V40 for all organs at risk in the adjuvant setting. The V45 was also significantly reduced for all organs at risk except the bladder. For patients treated in the def-group, all IMRT techniques significantly reduced the D(mean), V40, and V45 for all organs at risk. The mean femur doses with simultaneous integrated boost-IMRT and simultaneous integrated boost-IMRT-esc were 47% and 49% lower compared with 3D-CRT. Simultaneous integrated boost-IMRT-esc reduced the doses to the organs at risk compared with sequential-3D-CRT but increased the D(max.) for the small bowel, rectum, and bladder.	2
63. De Ieso PB, Mullassery V, Shrimali R, Lowe G, Bryant L, Hoskin PJ. Image-guided vulvovaginal interstitial brachytherapy in the treatment of primary and recurrent gynecological malignancies. *Brachytherapy* 2012; 11(4):306-310.	3a	37 patients	To evaluate interstitial high-dose-rate brachytherapy to the vulvovaginal region both alone and in combination with EBRT for primary or recurrent gynecological malignancy.	26% of the patients treated with radical intent relapsed locally and 30% were treated with either radical or palliative intent recurred locally. The 2- and 5-year local PFS was 74% and 63.4%, respectively. The total PFS, which includes local, locoregional/nodal, and distant recurrence, at 2 and 5 years, was 73.6% and 45.6%, respectively. With a mean follow-up of 27 months (3.8-111.9 months), the median survival for the patient group was 16.6 months with a 2- and 5-year OS of 47.7% and 36.4%, respectively. Acute Grade 3 toxicity was seen in 13 (35%) of the 37 patients (skin: 10, urinary: 2, genital: 2, gastrointestinal: 0). No acute Grade 4 toxicities were seen. A total of 10 of the 37 patients (27%) developed late Grade 3 toxicities. Five of the 22 patients (22%) treated for recurrent disease with radical intent developed Grade 3 toxicity (skin: 4, urinary: 2, genital: 1, radiation-induced fracture of acetabulum: 1, and gastrointestinal: 0), whereas 1 of the 6 patients treated with palliative intent had Grade 3 toxicity affecting skin. No late Grade 4 toxicities were seen.	4

Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
64. Tewari K, Cappuccini F, Syed AM, et al. Interstitial brachytherapy in the treatment of advanced and recurrent vulvar cancer. *Am J Obstet Gynecol* 1999; 181(1):91-98.	4	11 patients	To evaluate the role of interstitial brachytherapy in vulvar cancer management.	11 patients received interstitial brachytherapy, with (n=5) or without (n=6) EBRT, for locally advanced (n=5) or recurrent (n=6) vulvar cancer. Local control was achieved in all patients. 10 patients have died of disease at a mean interval of 33 months from the time of treatment, with 9 patients having maintenance of local control at death. One patient is alive without disease after 77 months of follow-up. There were 2 cases of local necrosis (18%) and 1 case of rectovaginal fistula (9%).	4
65. Scheistroen M, Trope C. Combined bleomycin and irradiation in preoperative treatment of advanced squamous cell carcinoma of the vulva. *Acta Oncol* 1993; 32(6):657-661.	2	42 patients with advanced squamous cell carcinoma of the vulva	Evaluation of combined bleomycin and irradiation in preoperative treatment of advanced squamous cell carcinoma of the vulva.	20 patients had primary lesions, and 22 patients had recurrent disease. 15 (75%) of the patients with primary disease showed objective response (5 complete and 10 partial response). 4 underwent surgery. Of these, one is alive after 60 months with no evidence of disease. 2 have died of unrelated causes without signs of recurrence. 17 relapsed and died of carcinoma of the vulva. Median survival for patients treated for primary disease was 8.0 months. 13 (59%) of 22 patients treated for recurrence showed objective response (2 complete and 11 partial responses). None underwent surgery. All these patients died of carcinoma of the vulva. Median survival was 6.4 months. Toxicity was acceptable, and there were no treatment-related deaths.	3
66. Levin W, Goldberg G, Altaras M, Bloch B, Shelton MG. The use of concomitant chemotherapy and radiotherapy prior to surgery in advanced stage carcinoma of the vulva. *Gynecol Oncol* 1986; 25(1):20-25.	5	6 patients	Evaluation of the use of concomitant chemotherapy and RT prior to surgery in advanced stage carcinoma of the vulva.	All 6 patients had satisfactory early tumor response. 3 patients received one course of chemotherapy + RT and 3 were given two courses. One patient died suddenly of unknown causes 6 days after completing the chemotherapy + RT. One patient with fixed groin nodes was treated with palliative intent. She maintained a complete local response but died 6 months later of liver metastases. The remaining 4 patients underwent surgery without healing complications and are alive with no evidence of disease at 1, 4, 14, and 26 months.	3

Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
67. Sebag-Montefiore DJ, McLean C, Arnott SJ, et al. Treatment of advanced carcinoma of the vulva with chemoradiotherapy - can exenterative surgery be avoided? *Int J Gynecol Cancer* 1994; 4(3):150-155.	2	37 patients with advanced FIGO stage (17 stage III, 20 stage IV) carcinoma of the vulva	Evaluation of treatment for advanced carcinoma of the vulva with chemoradiotherapy to ascertain if exenterative surgery can be avoided.	15 (47%) complete and 11 (34%) partial responses were seen at 3 months after completion of treatment. Of the 15 patients with complete response, 10 remained disease-free for a median of 24 months (range 6-36 months). The median survival for complete and partial responding patients was 15 and 11 months, respectively (range 2-37 months). Acute toxicity included moist perineal desquamation, diarrhea and myelosupression. One death secondary to neutropaenic sepsis occurred in the split course group. WHO grade 3 radiation enteritis occurred in one patient (14%) in the split course and two patients (6%) in the continuous CRT groups.	3
68. Lupi G, Raspagliesi F, Zucali R, et al. Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. *Cancer* 1996; 77(8):1472-1478.	2	31 patients with squamous cell carcinoma of the vulva	Results of a pilot study on concurrent chemoradiotherapy followed by radical surgery for patients with locally advanced squamous cell carcinomas of the vulva.	An objective response was observed in 22/24 primary cases (91.6%) and in 7/7 recurrent cases. All but two unresponsive patients underwent radical surgery. The postoperative morbidity rate was 65% (19/29 patients), and the mortality rate was 13.8% (4/29 patients). 5/9 patients (55%) with biopsy-proven inguinal lymph node metastases showed no residual lymph node disease in the surgical specimen. The recurrence rate was 31.8% and the medial follow-up time was 34 months.	3

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

3D-CRT = 3D conventional radiation therapy
5-FU = 5-fluorouracil
CI = Confidence interval
CMT = Combined modality therapy
CT = Computed tomography
EBRT = External beam radiotherapy
FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography
IMRT = Intensity-modulated radiation therapy
LR = Likelihood ratio
MRI = Magnetic resonance imaging
NPV = Negative predictive value
OS = Overall survival
PFS = Progression-free survival
PPV = Positive predictive value
RT = Radiotherapy
US = Ultrasound