

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. <i>CA Cancer J Clin.</i> 2015;65(1):5-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2015 nationally and for each state, as well as a comprehensive overview of cancer incidence, mortality, and survival rates and trends using the most current population-based data. The article also estimates the total number of deaths averted nationally during the past 2 decades and by state in 2011 as a result of the continual decline in cancer death rates and present actual number of deaths reported in 2011 by age for the 10 leading causes of death and for the 5 leading causes of cancer death.	Cancer death rates have been continuously declining for the past 2 decades. Overall, the risk of dying from cancer decreased by 22% between 1991 and 2011. Regionally, progress has been most rapid for residents of the Northeast, among whom death rates have declined by 25% to 30%, and slowest in the South, where rates declined by about 15%. Further reductions in cancer death rates can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those in the lowest socioeconomic bracket and other disadvantaged populations.	4
2. Beller U, Quinn MA, Benedet JL, et al. Carcinoma of the vulva. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. <i>Int J Gynaecol Obstet.</i> 2006;95 Suppl 1:S7-27.	Review/Other-Tx	N/A	To review carcinoma of the vulva.	No results reported in abstract.	4
3. Farias-Eisner R, Cirisano FD, Grouse D, et al. Conservative and individualized surgery for early squamous carcinoma of the vulva: the treatment of choice for stage I and II (T1-2N0-1M0) disease. <i>Gynecol Oncol.</i> 1994;53(1):55-58.	Observational-Tx	74 patients	To expand the analysis of stage I patients and add those with stage II squamous carcinoma of the vulva treated with modified radical vulvectomy.	Reviews of both patient charts and histopathology reports were correlated with recurrence and survival. Factors analyzed included FIGO stage and grade, histology, lesion size and depth of invasion, surgical procedure, RT, lymph node status, interval to and site of recurrence, and survival. 39 patients had stage I disease and 35 had stage II. The primary operation was a radical local excision (modified radical vulvectomy) in 56 patients and radical vulvectomy in 18 patients; 13 underwent ipsilateral inguinal-femoral lymphadenectomy and 58 bilateral lymphadenectomy, each through separate groin incisions. The survival of those treated conservatively (97% and 90% for stages I and II, respectively) is the same as those undergoing a radical vulvectomy (100% and 75% for stages I and II, respectively) with only the presence of inguinal-femoral lymph node metastases impacting negatively on survival. In the entire group, the survival for negative and positive nodes was 98% and 45%, respectively.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. <i>Gynecol Oncol.</i> 1990;38(3):309-314.	Observational-Tx	135 patients	To assess the risk of local recurrence after primary surgery for vulvar carcinoma in patients.	62 cases were stage I, 48 stage II, 18 stage III, and 7 stage IV. 21 patients developed a local vulvar recurrence after primary radical resection. 91 patients had a surgical tumor-free margin $\geq 8$ mm on tissue section and none had a local vulvar recurrence. 44 patients had a margin $< 8$ mm; 21 had a local recurrence and 23 did not ( $P < 0.0001$ ). Of the 23 patients with $< 8$ mm who did not recur locally, 14 remained free of disease, and 9 had either advanced disease, declining health, or short follow-up. Depth of invasion is associated with local recurrence, with a 9.1-mm reference value correctly predicting outcome in 81.5% of cases. Increasing tumor thickness is associated with local recurrence, with a 10-mm reference value predictive of 90% nonrecurrence and 33% recurrences. Lymphovascular space invasion has a combined predictive accuracy of 81.5%. 14/21 patients with vulvar recurrence died of metastatic disease, 4 died of intercurrent disease, and 3 were alive at 32, 68, and 157 months, with 16 recurring in $< 1$ year.	3

Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
5. Mahner S, Jueckstock J, Hilpert F, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. <i>J Natl Cancer Inst.</i> 2015;107(3).	Observational-Tx	1,249 patients	To further understand the role of adjuvant therapy in node-positive disease.	447/1,249 patients (35.8%) had lymph node metastases (N+). The majority of N+ patients had one (172 [38.5%]) or 2 (102 [22.8%]) positive nodes. The 3-year PFS rate of N+ patients was 35.2%, and the OS rate 56.2% compared with 75.2% and 90.2% in node-negative patients (N-). 244 (54.6%) N+ patients had adjuvant therapy, of which 183 (40.9%) had RT directed at the groins (+/- other fields). 3-year PFS and OS rates in these patients were better compared with N+ patients without adjuvant treatment (PFS: 39.6% vs 25.9%, HR = 0.67, 95% CI, 0.51 to 0.88, P=.004; OS: 57.7% vs 51.4%, HR = 0.79, 95% CI, 0.56 to 1.11, P=.17). This effect was statistically significant in multivariable analysis adjusted for age, Eastern Cooperative Oncology Group, Union internationale contre le cancer stage, grade, invasion depth, and number of positive nodes (PFS: HR = 0.58, 95% CI, 0.43 to 0.78, P<.001; OS: HR = 0.63, 95% CI, 0.43 to 0.91, P=.01).	2
6. Faul CM, Mirmow D, Huang Q, Gerszten K, Day R, Jones MW. Adjuvant radiation for vulvar carcinoma: improved local control. <i>Int J Radiat Oncol Biol Phys.</i> 1997;38(2):381-389.	Observational-Tx	62 patients	To evaluate the impact of adjuvant vulvar radiation on local control in high risk patients and the impact of local recurrence on OS.	Local recurrence occurred in 58% of observed patients and 16% in patients treated with adjuvant RT. Adjuvant RT significantly reduced local recurrence rates in both the close margin and positive margin groups (P=0.036, P=0.0048). On both univariate and multivariate analysis adjuvant radiation and margins of excision were significant prognostic predictors for local control. Significant determinants of actuarial survival included FIGO stage, percentage of pathologically positive inguinal nodes and margins of excision. The positive margin observed group had a significantly poorer actuarial 5 year survival than the other groups (P=0.0016) and adjuvant RT significantly improved survival for this group. The 2 year actuarial survival after developing local recurrence was 25%. Local recurrence was a significant predictor for death from vulva carcinoma (risk ratio 3.54).	2

\* See Last Page for Key

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. <i>Obstet Gynecol.</i> 1986;68(6):733-740.	Experimental-Tx	114 patients	To assess patients with invasive squamous cell carcinoma of the vulva and positive groin nodes after radical vulvectomy and bilateral groin lymphadenectomy to receive either RT or pelvic node resection.	53/59 patients randomized to RT received a 4500- to 5000-rad tumor dose in 5 to 6.5 weeks bilaterally to the groins and to the midplane of the pelvis even if only unilateral positive groin nodes had been detected; no radiation was given to the central vulvar area. 53/55 patients randomized to further surgery had pelvic node resection performed on the side containing positive groin nodes either unilaterally or bilaterally. Acute and chronic morbidity was similar for both regimens. The 2 major poor prognostic factors were clinically suspicious or fixed ulcerated groin nodes and 2 or more positive groin nodes. The difference in survival for the 114 evaluable patients was significant, favoring the adjunctive RT group ( $P=.03$ ). The estimated 2-year survival rates were 68% for the RT group and 54% for pelvic node resection group.	1
8. Gaffney DK, Du Bois A, Narayan K, et al. Patterns of care for radiotherapy in vulvar cancer: a Gynecologic Cancer Intergroup study. <i>Int J Gynecol Cancer.</i> 2009;19(1):163-167.	Review/Other-Tx	32 surveys	To describe radiotherapeutic practice in the treatment of vulvar cancer in member study groups of the Gynecologic Cancer Intergroup.	32 surveys were returned from 12 different cooperative groups. The most common indications for neoadjuvant RT include unresectable disease or FIGO stage $\geq$ III. For the neoadjuvant treatment of vulvar cancer, pelvic doses were 48.2 +/- 5.0 Gy (mean +/- SD). 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 +/- SD). 16 of 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

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. 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. <i>J Clin Oncol</i> . 2012;30(31):3786-3791.	Experimental-Dx	452 patients	To determine the safety of SLN biopsy as a replacement for inguinal femoral lymphadenectomy in selected women with vulvar cancer.	In all, 452 women underwent the planned procedures, and 418 had at least 1 SLN identified. 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 SLN. The sensitivity was 91.7% (90% lower confidence bound, 86.7%) and the false-negative predictive value (1-negative predictive value) was 3.7% (90% upper confidence bound, 6.1%). In women with tumor <4 cm, the false-negative predictive value was 2.0% (90% upper confidence bound, 4.5%).	2
10. Robison K, Roque D, McCourt C, et al. Long-term follow-up of vulvar cancer patients evaluated with sentinel lymph node biopsy alone. <i>Gynecol Oncol</i> . 2014;133(3):416-420.	Observational-Tx	73 patients	To examine SLN evaluation alone in women with squamous cell carcinoma of the vulva and evaluate the inguinal recurrence and complication rates.	A total of 73 women were enrolled onto protocol with 69 patients undergoing SLN dissection. Mean age was 66.9 years (range: 29–91) with 47 stage I, 12 stage II, 9 stage III, 2 stage IV and 3 unstaged patients. SLN dissections were successful in 63 patients. Of the 111 groins evaluated with a SLN dissection 93% had a SLN identified with an average of 2 SLN per groin. There were 92 groins with negative SLN and 11 groins with positive SLN. 57 patients had negative SLN and underwent conservative management with the median follow-up of 58.3months. 3 patients experienced groin recurrences (2 unilateral, 1 bilateral) for a recurrence rate of 5.2% (3/57). The complication rate for the inguinal incisions was 17.5% (1 cellulitis, 1 abscess, 2 lymphoceles, 5 lymphedema and leg pain).	2

Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
11. Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. <i>J Clin Oncol.</i> 2008;26(6):884-889.	Observational-Tx	403 assessable patients; 623 groins	To investigate the safety and clinical utility of the sentinel node procedure in early-stage vulvar cancer patients.	From March 2000 until June 2006, a sentinel node procedure was performed in 623 groins of 403 assessable patients. In 259 patients with unifocal vulvar disease and a negative sentinel node (median follow-up time, 35 months), 6 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; $P<.0001$ ).	1
12. Han SC, Kim DH, Higgins SA, Carcangiu ML, Kacinski BM. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. <i>Int J Radiat Oncol Biol Phys.</i> 2000;47(5):1235-1244.	Observational-Tx	54 patients	To determine the impact of primary or adjuvant chemotherapy and radiation on the survival rates of patients with locally advanced vulvar carcinoma.	OS was superior in the patients treated with primary chemotherapy and radiation vs primary RT with statistical significance ( $P=0.04$ ). There was also a statistically significant improvement in disease-specific survival ( $P=0.03$ ) and RFS ( $P=0.01$ ) favoring primary chemotherapy and radiation. No statistically significant trends of improved survival rates favoring adjuvant chemotherapy and radiation over adjuvant RT were observed.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Mulayim N, Foster Silver D, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. <i>Gynecol Oncol.</i> 2004;93(3):659-666.	Observational-Tx	17 patients	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 2 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 (range: 16.2–48 Gy). 1 patient developed bowel perforation and colovaginal fistula 1.5 years after completion of chemoradiation therapy.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Homesley HD, Bundy BN, Sedlis A, et al. Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study). <i>Gynecol Oncol.</i> 1993;49(3):279-283.	Observational-Dx	637 patients	To render a thorough analysis of the entire dataset of all patients with invasive squamous carcinoma of the vulva who were entered into the large prospective staging study.	From 1977 to 1984 the Gynecologic Oncology Group (GOG) conducted a prospective clinical and surgical staging protocol of squamous cell carcinoma of the vulva (n = 637). The patients with superficial (≤5 mm) lesions were the subject of a previous report (n = 272). The subject of this report is on factors that predict groin node metastasis based on all 588 evaluable patients. Comparisons between the 2 reports are made. Almost half of this group (49.3%) had minimal tumor thickness ≤ mm). Almost one-third of patients had small vulvar lesions (≤ cm). Groin node metastasis was 18.9% for the ≤2-cm diameter tumors and 41.6% for the >2-cm diameter lesions. The inaccuracy of clinical palpation of the groin nodes (23.9% false negative) largely accounts for underestimation of extent of disease. Body weight was not related to the sensitivity of detecting positive groin nodes (P=0.26). Using the logistic model, independent predictors of positive groin nodes were identified (in order of importance): less tumor differentiation by GOG criteria (P<0.0001), suspicious or fixed/-ulcerated nodes (P<0.0001), presence of capillary-lymphatic involvement (P<0.0001), older age (P=0.0002), and greater tumor thickness (invasion) (P=0.03). Lesion size and location were not independent predictors of positive groin nodes.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Peiro V, Chiva L, Gonzalez A, et al. [Utility of the PET/CT in vulvar cancer management]. <i>Rev Esp Med Nucl Imagen Mol.</i> 2014;33(2):87-92.	Observational-Dx	13 studies (corresponding to 10 patients)	To assess the diagnostic yield of FDG-PET/CT in the management of patients with vulvar cancer and determine its possible impact on the diagnosis and treatment of these patients.	Abnormal vulvar PET/CT uptake was found in 9/13 studies and invasion of adjacent structures in 5 of them (urethra, perineal, vagina). The inguinal-femoral lymph nodes were considered as affected in 3 studies and 1 pelvic lymph node was also affected. Four of the studies had extralymphatic involvement: 3 in lung and 1 in ischiorectal fossa. The PET/CT showed a 100% sensitivity for the detection of the vulvar lesion in squamous cell carcinomas and 60% in nonsquamous cell ones. There was a false positive result for local invasion due to urine contamination. One of the studies with lung metastases was related to a synchronous breast tumor. All the pathological lymph node levels detected in the PET/CT study were confirmed in the histopathology study. No new lesions were identified by surgery. PET/CT changed the therapeutic management in 8/13 studies (61.5%).	3
16. Kamran MW, O'Toole F, Meghen K, Wahab AN, Saadeh FA, Gleeson N. Whole-body [18F]fluoro-2-deoxyglucose positron emission tomography scan as combined PET-CT staging prior to planned radical vulvectomy and inguinofemoral lymphadenectomy for squamous vulvar cancer: a correlation with groin node metastasis. <i>Eur J Gynaecol Oncol.</i> 2014;35(3):230-235.	Observational-Dx	58 patients	To determine the sensitivity, specificity, and predictive value of the modality in the detection of groin node metastases and thereby the identification of Stage III disease prior to definitive surgery for squamous vulvar cancer.	In patients with histologically proven metastases to groin nodes, comparisons between PET/CT positive (True-positive) and negative (False-negative) groups vis-a-vis histology showed a tendency towards higher FDG avidity in the vulvar lesions, more bilateral nodes, multiple metastases, larger metastases and more extra-capsular extension in the True-positive group. Calculations per patient for PET/CT yielded a sensitivity of 50% and specificity at 100%. The positive predictive value was 100% and the negative predictive value was 57.1%. The test accuracy was 70% per patient. The high positive predictive value of PET/CT can be used to advance treatment planning prior to surgical staging of patients identified with Stage III disease. The poor sensitivity makes it unsuitable as a substitute for staging lymphadenectomy.	3

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
17. Rouzier R, Haddad B, Plantier F, Dubois P, Pelisse M, Paniel BJ. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. <i>Obstet Gynecol.</i> 2002;100(6):1159-1167.	Observational-Tx	215 patients	To evaluate the risk factors for local relapse in vulvar cancer patients and its impact on survival as a function of its different patterns, which include local recurrences at the primary tumor site, recurrences remote from the primary tumor, and skin bridge recurrences.	The local RFS rate was 78.6% (+/- 7.1%) at 5 years. Multivariable analyses showed that the local relapse was increased by the factors margin status and depth of invasion. Pathologic nodal status, tumor size, margin status, and depth of invasion were predictors of cancer-related death in the Cox multivariable model with fixed covariates. The contribution of local relapse for disease-specific survival at the site of the primary tumor (RR 6.35; 95% CI, 2.07, 15.76) or skin bridge recurrence (RR 6.48; 95% CI, 2.54, 16.49) was highly significant, whereas the contribution of local relapse at the other sites was not (RR 2.29; 95% CI, 0.53, 9.91). In this model, margin status was not significant. The risk of cancer-related death after local relapse was 58.4% (+/- 18.3%) at 1 year and 70.9% (+/- 17.6%) at 3 years.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. <i>Gynecol Oncol.</i> 2007;104(3):636-641.	Observational-Tx	90 patients	To determine the importance of margin status and other prognostic factors associated with the recurrence and survival of patients with squamous cell vulvar carcinoma.	90 patients (median age: 69) were treated for vulvar carcinoma from 1984 to 2002, including 28 FIGO stage I, 20 stage II, 26 stage III and 16 with stage IV disease. 63 (70%) patients underwent complete radical vulvectomies and 27 (30%) had modified radical vulvectomies. 19 (20%) patients received adjuvant RT. 5-year disease-specific survival rates were 100%, 100%, 86% and 29% for stages I-IV, respectively. None of the 30 patients with a pathologic margin distance >8 mm had local recurrence. Of the 53 women with tumor-free pathologic margin of <8 mm, 12 (23%) had a local recurrence. Moreover, women with >2 positive groin nodes had significantly higher recurrence risk compared to those with <2 metastatic groin nodes ( $P<0.001$ ). On multivariate analysis, positive groin nodes and margin distance were important prognostic factors for recurrence. Moreover, stage, tumor size, margin distance, and depth of invasion were significant independent predictors for disease-specific survival. The median follow-up was 58 months (range: 2–188).	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Viswanathan AN, Pinto AP, Schultz D, Berkowitz R, Crum CP. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. <i>Gynecol Oncol.</i> 2013;130(3):545-549.	Observational-Tx	300 patients	To evaluate the effect of margin status and radiation dose in patients treated with RT for vulvar cancer. Clinical outcomes included vulvar recurrence, RFS and OS.	Of 205 eligible patients, 69 (34%) had negative surgical margins, 116 (56%) had close margins and 20 (10%) had positive margins. Median follow-up time was 49 months. The 4-year RFS rate was 53% and OS was 73%. Of 78 recurrences, 62 had the vulva as the first site of recurrence. The 4-year rates of freedom from vulvar recurrence were 82%, 63% and 37% for those with negative, close and positive margins, respectively ( $P$ for trend=0.005). On multivariate analysis, close margins (HR = 3.03, 95% CI, 1.46–6.26) and positive margins (HR = 7.02, 95% CI, 2.66–18.54) were associated with a significantly increased risk of vulvar relapse. Those who received a dose $\geq$ 56 Gy had a lower risk of relapse than those who received $\leq$ 50.4 Gy ( $P$ <0.05). Though recurrences were noted with margins up to 9 mm, the highest risk of vulvar recurrence was associated with margins $\leq$ 5 mm ( $P$ =0.002).	2
20. Fons G, Groenen SM, Oonk MH, et al. Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. <i>Gynecol Oncol.</i> 2009;114(2):343-345.	Observational-Tx	75 patients	To analyze the benefit from adjuvant RT in patients with vulvar cancer and a single positive node without extracapsular spread.	Out of 75 patients, 31 (41%) were treated with adjuvant RT. Both DFS and disease-specific survival were comparable between the groups who did and who did not receive adjuvant RT (HR 0.98, 95% CI, 0.45–2.14, $P$ =0.97 and HR=1.02, 95% CI, 0.42–2.47, $P$ =0.96).	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
21. Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. <i>Gynecol Oncol.</i> 2006;103(3):1095-1099.	Observational-Tx	490 patients	To determine if adjuvant RT improves the survival of women with invasive squamous cell carcinoma of the vulva involving 1 inguinal node.	Of the 490 patients with stage III, node-positive vulvar cancers, 208 had a single positive inguinal node. The median age of this group was 71 years (range: 29–100). 82.2% of patients were White, 7.2% were Hispanic, 7.7% were Black, 1.4% were Asian, and 1.4% were Others. 91.8% of patients underwent a radical vulvectomy with a unilateral or bilateral inguinal lymphadenectomy. The median number of lymph nodes resected was 13 (range: 1–34). 102 women underwent adjuvant RT, while 106 did not receive any radiation treatment. Women who received adjuvant RT had a 5-year disease-specific survival of 77.0% compared to 61.2% in those without RT ( $P=0.02$ ). After stratifying the study group based on the extent of lymphadenectomy, we found that radiation treatment improved the survival of those with $\leq 12$ lymph nodes removed (76.6% vs 55.1%, $P=0.035$ ). In those with more than 12 nodes resected, RT increased the survival from 66.7% to 77.3%, though this difference was not statistically significant ( $P=0.23$ ). In multivariate analysis, younger age ( $P=0.01$ ) remained as a significant prognostic factor for improved survival; however, adjuvant RT had a borderline significance ( $P=0.06$ ).	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Woelber L, Eulenburg C, Choschzick M, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. <i>Int J Gynecol Cancer</i> . 2012;22(3):503-508.	Observational-Tx	157 patients	To assess lymph node metastases as the prognostic factor for recurrence and survival in vulvar cancer.	Median age was 61 years; 49 patients (31%) had lymph node metastases; 21 patients had 1, 13 had 2, and 15 had more than 2 positive lymph nodes. 32% of the patients received adjuvant RT. The risk of lymph node metastases increased with age, greater tumor size, deeper invasion, and higher tumor grade. Median follow-up was 36 months; 23 patients (14.6%) developed disease recurrence (61% vulva, 35% groins, and 4% both). Compared with node-negative patients, survival in all node-positive patients was significantly impaired ( $P<0.001$ ; disease-free patients after 2 years: 88% in node-negative patients; 60%, 43%, and 29% in patients with 1, 2, and >2 affected nodes, respectively), whereas no significant difference between the node-positive subgroups could be demonstrated regarding DFS. In multivariate analysis, lymph node status remained the most important prognostic factor regarding DFS, but the effect of positive nodes differed significantly dependent on adjuvant treatment ( $P=0.001$ ). In patients without adjuvant RT to the groins/pelvis, the number of metastatic nodes was highly relevant for prognosis (HR, 1.752; $P<0.001$ ), whereas this effect disappeared in patients who were treated with adjuvant RT (HR, 0.972; $P=0.828$ ).	2
23. van der Velden J, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. <i>Cancer</i> . 1995;75(12):2885-2890.	Observational-Tx	71 patients	To determine the influence of several clinicopathologic parameters on the pattern of recurrence and survival.	Using the Mantel-Cox test, extracapsular growth of lymph node metastases ( $P=0.00$ ), 2 or more positive lymph nodes ( $P=0.02$ ), and greater than 50% replacement of lymph nodes by tumor ( $P=0.03$ ) were predictors of poor survival. No difference was found between the groups with 2 positive lymph nodes and those with 3 or more. Extracapsular growth of lymph node metastases was the most significant independent predictor for survival. Distant metastases occurred in 7/15 patients (48%) who had a combination of extranodal spread, lymph node replacement greater than 50%, and 3 or more positive lymph nodes.	2

\* See Last Page for Key

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. <i>Obstet Gynecol.</i> 2009;114(3):537-546.	Experimental-Tx	114 patients	To report long-term survival and toxicity of radiation compared with pelvic node resection for patients with groin node-positive vulvar cancer.	Median age was 70 years. Median survivor follow-up was 74 months. The RR of progression was 39% in radiation patients (95% CI, 0.17–0.88, $P=.02$ ). 14 intercurrent deaths occurred after radiation as compared with only 2 after pelvic node resection, narrowing 6-year OS (51% compared with 41%, HR 0.61 [95% CI, 0.30–1.3], $P=.18$ ). However, the cancer-related death rate was significantly higher for pelvic node resection compared with radiation (51% compared with 29% at 6 years, HR 0.49 [95% CI, 0.28–0.87], $P=.015$ ). 6-year OS benefit for radiation in patients with clinically suspected or fixed ulcerated groin nodes ( $P=.004$ ) and 2 or more positive groin nodes ( $P<.001$ ) persisted. A ratio of more than 20% positive ipsilateral groin nodes (number positive/number resected) was significantly associated with contralateral lymph node metastasis, relapse, and cancer-related death. Late chronic lymphedema (16% compared with 22%) and cutaneous desquamation (19% compared with 15%) were balanced after radiation and pelvic node resection.	1
25. Stehman FB, Bundy BN, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. <i>Int J Radiat Oncol Biol Phys.</i> 1992;24(2):389-396.	Experimental-Tx	58 patients	To determine if groin radiation was superior to and less morbid than groin dissection.	The study was closed prematurely when interim monitoring revealed an excessive number of groin relapses on the groin radiation regimen. Metastatic involvement of the groin nodes was projected to occur in 24% of patients based on this Group's previous experience. On the groin dissection regimen, there were 5/25 (20.0%) patients with positive groin nodes. These patients received post-operative radiation. There were 5 groin relapses among the 27 (18.5%) patients on the groin radiation regimen and none on the groin dissection regimen. The groin dissection regimen had significantly better progression-free interval ( $P=0.03$ ) and survival ( $P=0.04$ ).	1

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
26. Koh WJ, Chiu M, Stelzer KJ, et al. Femoral vessel depth and the implications for groin node radiation. <i>Int J Radiat Oncol Biol Phys.</i> 1993;27(4):969-974.	Observational-Tx	50 patients	To quantify, based on pretreatment CT measurements, potential groin node depths, which will aid in optimal treatment planning for patients requiring groin node radiation.	Individual femoral vessel depths ranged from 2.0 to 18.5 cm. When the depths of all 4 femoral vessels were averaged in each patient, the mean "4-vessel average" depth for this patient population was 6.1 cm. The median Quetelet index for the group was 25.6, and there was a strong correlation between femoral vessel depth and patient Quetelet index. Recalculation of doses provided to the 5 patients failing prophylactic groin radiation in the GOG study showed that all had received potential tumor doses <4700 cGy, with 3 patients being underdosed by >30%.	3
27. Hallak S, Ladi L, Sorbe B. Prophylactic inguinal-femoral irradiation as an alternative to primary lymphadenectomy in treatment of vulvar carcinoma. <i>Int J Oncol.</i> 2007;31(5):1077-1085.	Observational-Tx	294 cases	To determine whether primary RT with an adequate radiation dose and technique is a safe treatment of the groin in a selection of patients with early stage vulvar cancer.	Inguinal lymph node dissection was performed in only 27 cases (9%) and was not part of the standard surgery. The histology was squamous cell carcinoma in 269 cases (92%). The primary surgery was total vulvectomy, partial vulvectomy, or local resection of the tumor. The main type of RT was adjuvant inguinal irradiation. 2 separate, symmetrical and rectangular inguinal fields were irradiated with combined photon and electron beams. In the complete series 127 recurrences (43%) were recorded. Local (24%) and regional recurrences (19%) were most frequent. Type of surgery was not associated with the risk of tumor recurrence. The 5-year OS rate was 53% and the RFS rate was 55%. Tumor grade was significantly ( $P=0.007$ ) associated with the RFS. The inguinal RFS rate was 75% both for patients treated with adjuvant inguinal irradiation without lymphadenectomy and patients treated with primary lymph adenectomy +/- inguinal irradiation. Postoperative complications were recorded in 22%.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Petereit DG, Mehta MP, Buchler DA, Kinsella TJ. A retrospective review of nodal treatment for vulvar cancer. <i>Am J Clin Oncol.</i> 1993;16(1):38-42.	Review/Other-Tx	42 patients	A retrospective analysis reviewing treatment outcome and complications of inguofemoral dissection vs photon irradiation.	Group I (n = 24) underwent either bilateral or unilateral inguofemoral dissection; Group II (n = 18) underwent bilateral groin irradiation. The 3-year DFS was 84.5% and 79.7% for Group I and II (P=0.74). The nodal failure rate at 3 years was not significantly different. The postoperative complications in the surgically treated nodes were: 17% seromas, 46% wound infection, and 71% wound separation. Of those patients developing either an infection or wound separation, 41% required daily wound care for more than 2 weeks by a visiting nurse after discharge. Only 1 of 18 (6%) irradiated patients developed a clinically significant skin reaction. The median time for complete skin/wound healing was 8 weeks (range 4–24 weeks) in Group I and 2 weeks (range 2–6 weeks) in Group II. Late postoperative complications in the surgically treated patients included meralgia paresthetica (8%) and lymphedema (12%); 1 (6%) Group II patient developed lymphedema.	4
29. Oonk MH, van Os MA, de Bock GH, de Hullu JA, Ansink AC, van der Zee AG. A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguofemoral lymphadenectomy. <i>Gynecol Oncol.</i> 2009;113(3):301-305.	Review/Other-Tx	62 patients	To compare quality of life in vulvar cancer patients who were treated with a SLN-procedure only to those who underwent inguofemoral lymphadenectomy.	With a response rate of 85%, 35 patients after the SLN-procedure and 27 patients after inguofemoral lymphadenectomy filled out the questionnaires. No difference in overall quality of life was observed between the 2 groups. The major difference was the increase in complaints of lymphedema of the legs after inguofemoral lymphadenectomy. The majority of patients would advise the SLN-procedure to relatives. Patients after inguofemoral lymphadenectomy were more reserved concerning the acceptable false negative rate of a new diagnostic procedure.	4

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Woelber L, Kock L, Giesecking F, et al. Clinical management of primary vulvar cancer. <i>Eur J Cancer</i> . 2011;47(15):2315-2321.	Review/Other-Tx	N/A	To discuss the current literature to elaborate recommendations for the management of primary vulvar cancer in clinical routine.	Surgery of the primary tumor and the groins remain the cornerstone of treatment in vulvar cancer with a strong trend towards a less radical approach in early stage disease. Complete vulvectomy was replaced by radical local excision with plastic reconstruction and the sentinel node technique was implemented to avoid the morbidity of complete groin dissection in node negative patients. In patients with advanced primary disease, treatment decisions are still a challenge. Criteria for the indication and performance of chemo/RT of the vulva/groins/pelvis are still not fully established and vary between different countries and institutions due to the low level of evidence. Often an individualized therapeutic approach aside from guidelines is necessary to treat these patients adequately.	4

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Mak RH, Halasz LM, Tanaka CK, et al. Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3-4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva. <i>Gynecol Oncol.</i> 2011;120(1):101-107.	Observational-Tx	44 patients	To compare outcomes in patients with squamous cell carcinoma of the vulva treated with RT and concurrent weekly platinum-based or every-3-4-week regimens containing 5-FU.	The median age was 63 years (range, 44–90), 84.1% of patients had ECOG performance status 0-1, and patients had FIGO Stage II (n=6), III (n=31), or IVA (n=7) disease. Patients were treated preoperatively (n=10), postoperatively (n=10), or without surgery (n=24). The median RT dose to the vulva was 50.2 Gy (range, 22–75). Concurrent chemotherapy regimens included weekly platinum (n=16) or every 3–4 week regimens with 5-FU as the backbone (n=28). With a median follow-up of 31.5 months, there was no significant difference in 2-year OS (74.5% vs 70.0%; $P=0.65$ ), DFS (61.9% vs 56.0%; $P=0.85$ ), LRR (31.3% vs 32.9%; $p=0.93$ ), or distant metastases (6.3% vs. 10.6%; $P=0.81$ ) between the weekly platinum and every-3–4 week 5-FU regimens. 20 patients (45.4%) recurred: 16 LRR, 2 distant metastases, and 2 with both. The clinical and pathologic complete response rates were 58.8% (20/34), and 53.8% (14/26), respectively. There was a higher proportion of grade 3 or higher acute nonskin toxicities in patients receiving every-3–4 week 5-FU (46.1% vs 13.3%; $P=0.07$ ), but more grade 3 or higher skin toxicity in patients receiving weekly platinum (62.5% vs 32.0%; $P=0.01$ ).	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Dusenbery KE, Carlson JW, LaPorte RM, et al. Radical vulvectomy with postoperative irradiation for vulvar cancer: therapeutic implications of a central block. <i>Int J Radiat Oncol Biol Phys.</i> 1994;29(5):989-998.	Observational-Tx	27 patients	To report the long-term results of vulvectomy, node dissection, and postoperative nodal irradiation using a midline vulvar block in patients with node positive vulvar cancer.	Actuarial 5-year OS and DFS estimates were 40% and 35%, respectively. Recurrences developed in 63% (17/27) of the patients at a median of 9 months from surgery (range 3 months to 6 years) and 15 of these have died; 2 patients with recurrences are surviving at 24 and 96 months after further surgery and RT. Central recurrences (under the midline block) were present in 13 of these 17 patients (76%), either as central only (n = 8), central and regional (n = 4), or central and distant (n = 1). Additionally, 3 patients developed regional recurrences and 1 patient developed a concurrent regional and distant relapse. 1 patient developed a squamous cell cancer of the anus under the midline block 54 months after the initial vulvar cancer and an additional patient developed transitional cell carcinoma of the ureter (outside the radiation field) 12 months after diagnosis. Factors associated with a decreased RFS included increasing FIGO stage ( $P=0.01$ ) and invasion of the tumor into the subcutaneous fat or deep soft tissue ( $P=0.05$ ). Chronic lower extremity edema developed in 4 patients, but there have been no other complications.	2
33. Beriwal S, Heron DE, Kim H, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. <i>Int J Radiat Oncol Biol Phys.</i> 2006;64(5):1395-1400.	Observational-Tx	15 patients	To assess early clinical outcome of IMRT in the treatment of vulvar cancer and compare dosimetric parameters with 3D CRT.	The mean volume of small bowel, rectum, and bladder that received doses in excess of 30 Gy with IMRT was reduced when compared with 3D CRT. Treatment was well tolerated, and only 1 patient had acute Grade 3 small-bowel toxicity. Median follow-up was 12 months. In the preoperative group, 5 patients (71%) had clinical complete response and 3 patients (42.8%) had pathologic complete response. In the adjuvant group, 2 patients had recurrences in the treatment field. No patients had late Grade 3 toxicity. The 2-year actuarial disease-specific survival was 100%.	2

**Adjuvant Therapy in Vulvar Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Kim CH, Olson AC, Kim H, Beriwal S. Contouring inguinal and femoral nodes; how much margin is needed around the vessels? <i>Pract Radiat Oncol.</i> 2012;2(4):274-278.	Review/Other-Tx	22 patients	To determine the optimal margin needed around the femoral vessels for appropriate inguinofemoral lymph node coverage and to propose guidelines defined by anatomic boundaries for clinical target volume delineation.	There were 52 total positive inguinal nodes among 22 patients. Relative to the femoral vessels, the location of the nodes were 51.9% anteromedial, 21.2% anterior, 11.5% anterolateral, 9.6% medial, 1.9% posterior, and 3.9% lateral. To cover $\geq 90\%$ disease, the margins needed around the nearest femoral vessel were anteromedial $\geq 35$ mm, anterior $\geq 23$ mm, anterolateral $\geq 25$ mm, medial $\geq 22$ mm, posterior $\geq 9$ mm, and $\geq 32$ mm lateral. The corresponding anatomic boundaries were the following: laterally, medial border of the iliopsoas; medially, lateral border of adductor longus or medial end of pectineus; posteriorly, iliopsoas muscle laterally and anterior aspect of the pectineus muscle; medially and anteriorly, the anterior edge of the sartorius muscle. Most of the macroscopic nodes were medial or anteromedial to the femoral vessels. No patient had involved posterior or lateral nodes alone without positive nodes in the anterior or anteromedial positions.	4

## Evidence Table Key

### Study Quality Category Definitions

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

---

Dx = Diagnostic

Tx = Treatment

## Abbreviations Key

3D CRT = 3D conformal radiotherapy

5-FU = 5-fluorouracil

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

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

HR = Hazard ratio

IMRT = Intensity-modulated radiation therapy

LRR = Local-regional recurrence

OS = Overall survival

PFS = Progression-free survival

RFS = Relapse-free survival

RR = Relative risk

RT = Radiation therapy

SD = Standard deviation

SLN = Sentinel lymph node