

Does the count after inguinofemoral lymphadenectomy in vulvar cancer correlate with outcome?

G. Baiocchi^{a,*}, F.M. Silva Cestari^a, R.M. Rocha^b, C.C. Faloppa^a, L.Y. Kumagai^a,
E.M. Fukazawa^a, L. Badiglian-Filho^a, L.A. Cestari^a, I. Sant'Ana Rodrigues^b,
A. Lavorato-Rocha^b, B.M. Maia^b, F.A. Soares^b

^aDepartment of Gynecologic Oncology, AC Camargo Cancer Hospital, Rua Antonio Prudente, 211, 01509-010, São Paulo, Brazil

^bDepartment of Pathology, AC Camargo Cancer Hospital, Sao Paulo, Brazil

Accepted 1 February 2013

Available online 17 February 2013

Abstract

Background: Inguinal lymph node (LN) metastasis is an important prognostic factor in vulvar cancer. Our aim was to determine the prognostic value of the number of resected LNs in inguinofemoral lymphadenectomy.

Methods: A retrospective analysis was performed in a series of 158 individuals who underwent bilateral inguinofemoral lymphadenectomy for vulvar squamous cell carcinoma from January 1980 to February 2010.

Results: The mean age was 67 years (range: 15–90). Median tumor size was 5 cm (range: 1–18). A median of 22.5 inguinal LNs (range: 2–57) was resected. Thirteen (8.2%) patients had <12 LNs resected, and 145 (91.8%) had ≥12 LNs resected. Eighty (50.6%) patients had LN metastasis, with a median of 2 positive LNs (range: 1–16). Of those with positive LNs, 19 (23.8%), 23 (28.8%), and 38 (47.5%) patients had 1, 2, and 3 or more positive LNs, respectively. Thirty-three (41.2%) patients had bilateral LN metastasis. For patients without LN involvement, we failed to observe any significant difference between patients with <12 LNs and ≥12 LNs that were resected with regard to risk of recurrence ($p = 0.97$) and death from cancer ($p = 0.43$) in 5 years. However, resection of <12 LNs in patients with positive LNs negatively impacted the risk of recurrence ($p = 0.003$) and death from cancer ($p = 0.043$).

Conclusions: Resection of fewer than 12 LNs in vulvar cancer has a negative impact on outcome for patients with positive inguinal LNs. © 2013 Elsevier Ltd. All rights reserved.

Keywords: Vulvar cancer; Lymph node metastasis; Lymphadenectomy; Prognosis; Tumor staging

Introduction

Vulvar cancer accounts for approximately 3–5% of all gynecological malignancies.¹ It usually affects women, with a median age of 65–70 years,² and the majority of cases (~90%) are squamous cell carcinoma (SCC).^{1,2}

The prognosis is linked to inguinal lymph node (LN) involvement, and hematogenic metastasis is a rare event, even in the presence of LN metastasis.^{1,2} Thus, LN status is an important prognostic factor – 5-year survival rates

range from 90% for patients without LN metastasis to 24% when 5 or 6 LNs are involved.³

In 2009, the FIGO staging system was revised,⁴ and in its surgical–pathological classification, only patients with positive nodes are classified as stage III. Moreover, the number of involved LNs, the size of LN metastasis, and the presence of extracapsular spread are taken into account. However, the prognostic impact of the number of LNs that are removed is unknown.

Systematic inguinofemoral lymphadenectomy comprises the resection of both superficial inguinal LNs (above the cribriform fascia) and deep inguinal (femoral) LNs.⁵ Appropriate management of groin LNs correlates to a lower recurrence rate and better outcome.¹ When indicated, systematic inguinofemoral lymphadenectomy has an important role in vulvar cancer – higher groin recurrence rates have been reported

* Corresponding author. Tel.: +55 11 2189 5110; fax: +55 11 2114 6072.

E-mail addresses: glbaiocchi@me.com, glbaiocchi@yahoo.com.br (G. Baiocchi).

after superficial inguinal lymphadenectomy.^{6–9} Moreover, recurrences in an undissected groin correlate with a high mortality rate.¹

Only 2 studies have suggested that a high number of removed LNs is associated with better outcomes.^{10,11} Our aim was to analyze the prognostic value of lymphadenectomy in vulvar SCC, considering the number of LNs that are resected, for patients with negative and positive LNs.

Patients and methods

This retrospective analysis included 158 individuals with vulvar SCC who underwent surgical treatment, including bilateral inguinofemoral lymphadenectomy, at the Department of Gynecologic Oncology, AC Camargo Cancer Hospital, from January 1980 to February 2010. The Institutional Review Board approved the study.

The clinical features that we analyzed were age, type of vulvar surgery (wide local excision or radical vulvectomy), and pattern of recurrence. The pathology data included tumor size, the depth of invasion, the number of resected LNs, and the presence of LN metastasis. The 10th percentile of the number of LNs that were resected was 12, and resection of at least 12 LNs in both groins was considered an adequate lymphadenectomy. Further, the number of LNs that were resected was categorized into 2 groups: <12 LNs and ≥12 LNs.

Follow-up time spanned the date of surgery to the last date for which information was available. Progression-free survival (PFS) was the time from surgery to the date of recurrence or last follow-up. Overall survival (OS) was defined as the time from surgery to the date of death or last follow-up. Disease-specific survival (DSS) was the time from surgery to the date of death due to vulvar cancer or last follow-up. The database was generated in SPSS, version 16.0 (SPSS, Inc., Chicago, IL) for Mac. The association between parametric variables was assessed by chi-square or Fischer's exact test. Survival curves were constructed by Kaplan–Meier life table analysis. For all tests, an alpha error of up to 5% ($p < 0.05$) was considered significant.

Results

Clinical and pathological data

The mean age was 67 years (range: 15–90). Median tumor size was 5 cm (range: 1–18). Fifty-four (34.2%) patients had the depth of invasion analyzed, with a median of 10 mm (range: 2–30 mm). One hundred fifty-four patients (97.5%) had radical vulvectomies, and 4 (2.5%) had wide local excision. All patients underwent bilateral inguinal lymphadenectomy. Twelve (7.6%) patients received adjuvant radiotherapy.

A median of 22.5 LNs (range: 2–57) was resected. Thirteen (8.2%) patients had <12 LNs resected, vs. 145 (91.8%) with ≥12 LNs resected. Eighty (50.6%) patients had LN metastasis, with a median of 2 positive LNs (range: 1–16). Of those with positive LNs, 19 (23.8%), 23

(28.8%), and 38 (47.5%) patients had 1, 2, and 3 or more positive LNs, respectively. Thirty-three (41.2%) patients had bilateral LN metastasis.

We hypothesized that the number of resected LNs correlated with LN involvement, but we did not observe a significant difference – patients with <12 LNs and ≥12 LNs resected had 46.2% and 51% of LN involvement, respectively ($p = 0.73$). Notably, only 6 patients with <12 LNs resected had positive LNs, 3 of whom (50%) had ≥2 positive LNs. Conversely, 58/74 (78.4%) of patients with ≥12 LNs had ≥2 positive LNs ($p = 0.14$).

We also examined whether the number of resected LNs was associated with a tumor size of more than 4 cm or a depth of invasion of more than 10 mm. There was no statistically difference between groups with regard to tumor size ($p = 0.36$) or depth of invasion ($p = 1.0$).

Sixty-nine (43.7%) patients experienced a recurrence – 35 (51.5%) had only local recurrence, 16 (23.5%) had groin only, 7 (10.3%) had distant only, and 10 (14.7%) had both locoregional and distant recurrence. Notably, there was no difference in exclusive groin recurrence in patients with <12 LNs (28.6% of recurrences) vs. ≥12 LNs (23% of recurrences) ($p = 0.74$).

Median follow-up time was 34 months (range: 1–301.5). At the end of the follow-up, 57 patients (36.1%) were alive with no evidence of disease, 67 (42.4%) had died due to cancer, 28 (17.7%) died of other causes, and 6 (3.8%) were alive with evidence of disease.

Recurrence and survival

The 5-year PFS, OS, and DSS rates were 55.9%, 48.2%, and 60.4%, respectively. The 10-year PFS, OS, and DSS rates were 48.8%, 35.8%, and 50.8%, respectively.

As expected, the presence of LN metastasis negatively impacted the risk of recurrence (70.8% vs. 42.2%; $p = 0.005$), death (60.2% vs. 37.1%; $p = 0.028$), and death from cancer (78.1% vs. 44.6%; $p = 0.004$) at 5 years.

We initially stratified patients into categories per the FIGO staging system and analyzed patients without LN involvement (grouped stages I and II) and those with positive LNs (stage III) separately. In patients without LN involvement, we failed to observe any significant difference between patients that had <12 LNs or ≥12 LNs resected with regard to PFS (60% vs. 71.5%; $p = 0.97$), DSS (66.7% vs. 76.2%; $p = 0.43$), or OS (66.7% vs. 57.4%; $p = 0.42$) at 5 years (Fig. 1).

Further, we analyzed patients with positive LNs (stage III) and noted a significant correlation between the number of LNs resected and outcome. Two-year PFS was 20.8% for those with <12 LNs resected and 52.8% for ≥12 LNs resected ($p = 0.003$) (Fig. 2). Three-year DSS was 20.8% for those with <12 LNs resected vs. 78.6% for ≥12 LNs resected ($p = 0.043$) (Fig. 3). Three-year OS was also worse for those with <12 LNs resected (20.8%), compared with ≥12 LNs resected (48%) ($p = 0.084$).

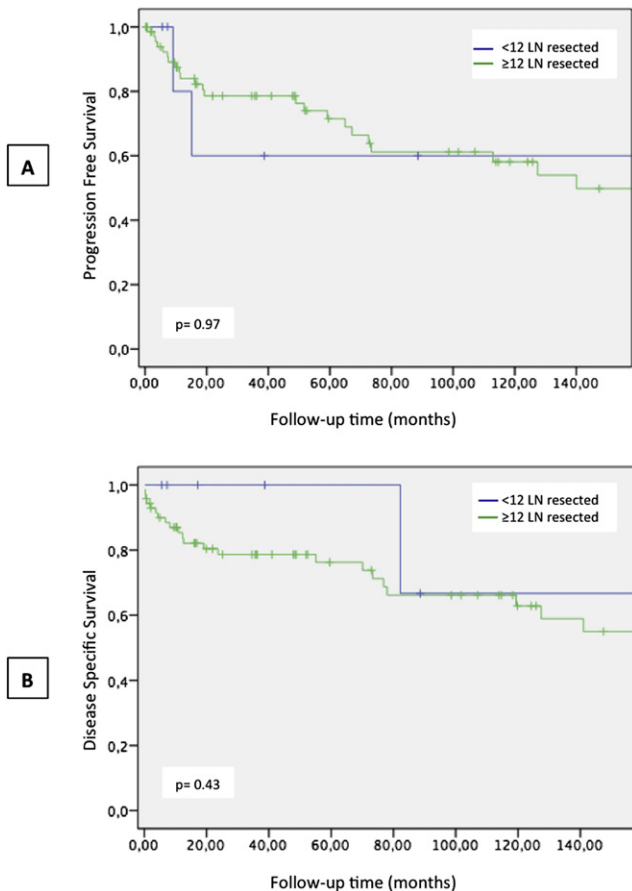


Fig. 1. (A) Progression-free survival curves for patients with <12 lymph nodes (LN) or ≥ 12 LNs resected and negative inguinal LNs ($p = 0.97$). (B) Disease-specific survival curves for patients with <12 or ≥ 12 LNs resected and negative inguinal LNs ($p = 0.43$).

Further, after analyzing only patients with positive LNs, adjuvant radiotherapy did not affect PFS ($p = 0.51$) or DSS ($p = 0.98$) (Fig. 4).

Discussion

The current management of vulvar cancer includes radical vulvectomy with safety margin and bilateral inguofemoral lymphadenectomy.¹² For locally advanced tumors, where resection might include pelvic exenteration, the primary treatment is currently neoadjuvant chemo-radiation followed by tailored surgery.¹³ If LN metastasis is found, the standard post-operative therapy is inguinal and pelvic radiation. Nevertheless, other strategies as adjuvant chemotherapy have been reported.¹⁴

Although some biologic markers have been suggested as prognostic factors,^{15,16} LN involvement remains as the most important prognostic factor in vulvar cancer.^{1,2} Regarding LN-related parameters, the number of positive LNs,^{3,17–20} percentage of nodal replacement,^{19,21} and size of LN metastasis²² have been reported as significant prognostic factors. However, few studies have addressed the prognostic value of the number of LNs that have been resected.^{10,11}

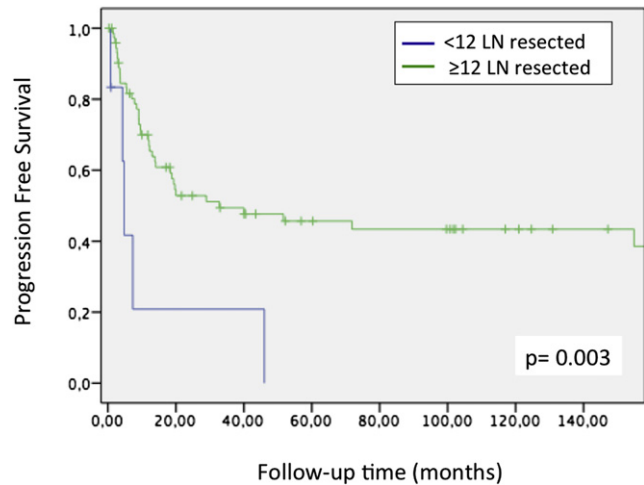


Fig. 2. Progression-free survival curves for patients with <12 or ≥ 12 LNs resected and positive inguinal LNs ($p = 0.003$).

After inguofemoral lymphadenectomy, recurrence in the groin as the initial site is an unusual event. In the GOG study, Homesley et al.²³ reported only 1 recurrence in 388 patients and a 3.7% overall recurrence rate (22/588). In De Hullu et al.,²⁴ the overall rate of groin recurrence was 3.5% (3/85) after inguofemoral lymphadenectomy through separate incisions.

However, in an attempt to decrease the morbidity of groin dissection, some studies suggested new technique strategies^{25,26} and others evaluated the outcome only after superficial lymphadenectomy. Gordinier et al.⁸ reviewed 104 patients with negative LNs who were treated by wide radical excision and superficial inguinal lymphadenectomy. Nine (8.6%) patients had groin recurrences. The recurrence developed in residual LNs in 6 of 8 patients who underwent groin re-exploration, suggesting that those recurrences were due to unresected positive LNs. In addition, the authors did not observe any further micrometastasis after reviewing all negative LNs. These data strongly suggest that groin

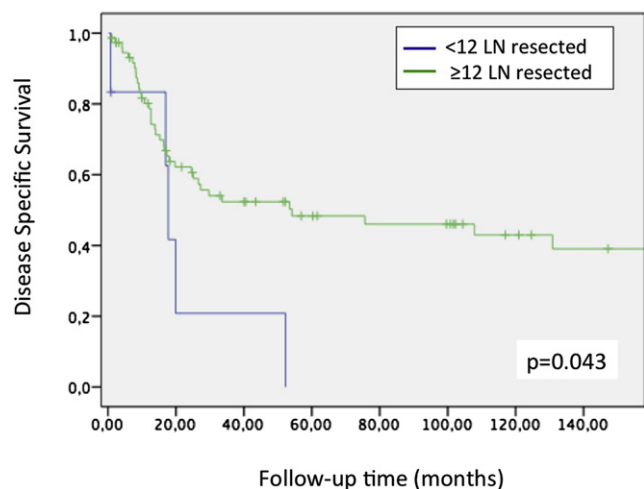


Fig. 3. Disease-specific survival curves for patients with <12 or ≥ 12 LNs resected and positive inguinal LNs ($p = 0.043$).

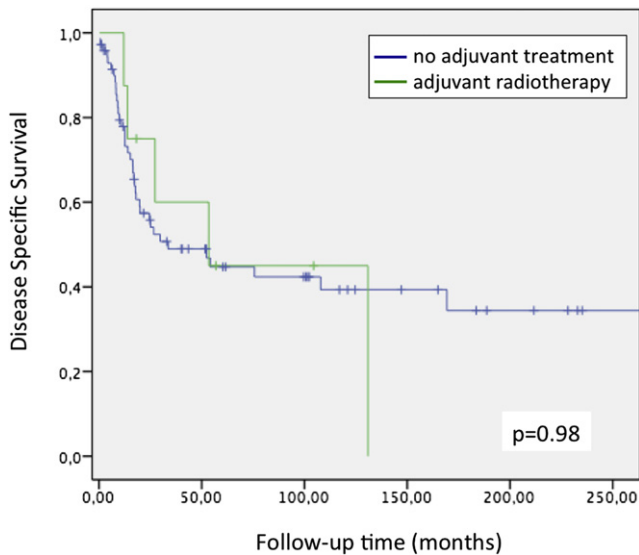


Fig. 4. Disease-specific survival curves for patients with positive inguinal lymph nodes and no adjuvant treatment or adjuvant radiotherapy ($p = 0.98$).

relapse is due to metastatic disease in LNs that remain after superficial lymphadenectomy.

Other groups have also described groin recurrence rates after superficial inguinal lymphadenectomy of up to 4.6%.^{6,7,9} Considering all of these studies, the overall expected recurrence rate after superficial lymphadenectomy is 5.3%.^{6–9} Moreover, in a series of 113 patients, Stehman et al.²⁷ were unable to correlate a low LN count after superficial groin dissection to first recurrence in the groin. Nine patients experienced a first recurrence in the groin (4 in the undissected contralateral groin). However, the study conclusions were limited due to the small number of patients with groin recurrence.

Nevertheless, inguinal LN metastases are expected in approximately 25–30% of vulvar cancer patients, and consequently, the majority of patients may be overtreated by radical groin lymphadenectomy.⁵ Thus, sentinel node dissection has emerged as the preferred approach for patients with clinically negative nodes. Based on the results from a large prospective trial, GROINSS-V,²⁸ this procedure should be offered to patients with tumors that are up to 4 cm and unifocal with clinically negative groins.

However, the clinical significance of isolated tumor cells and micrometastases in the LN remains unknown. Oonk et al.²⁹ demonstrated that even when only isolated cells are found in the sentinel node, the rate of non-sentinel node metastasis is 4.1% (1/24 cases), and in cases of metastasis of less than 5 mm, 11.7% (4/34 cases) also had non-sentinel node metastasis. Thus, inguinofemoral lymphadenectomy should be recommended when disease of any size is detected in the sentinel nodes.

Further, the optimal number of LNs that should be expected after an inguinal lymphadenectomy is unknown. The node count varies widely, from 1 to 36 per groin.^{9,10,26,27,30–33}

This finding reflects not only the variation in individual anatomy but also differences in surgical techniques and skills and pathologists' efforts to identify and analyze the LNs within the surgical specimen.^{27,31}

Only 2 studies have examined the prognostic value of the number of resected inguinal LNs in vulvar cancer. In 2007, Le et al.¹¹ reported a series of 58 patients, 21% of whom had positive LNs. They concluded that a total node count of less than 10 LNs after bilateral lymphadenectomy negatively impacted the risk of recurrence and death and suggested that optimal bilateral lymphadenectomy should be defined as resection of ≥ 10 LNs. In contrast to our study, due to the small number of patients, they could not stratify patients into groups with or without positive LNs.

The other study was a large population database analysis that was recently published by Courtney-Brooks et al.,¹⁰ who evaluated the impact of LN count on survival in 1030 patients with vulvar cancer and negative LNs. In their study, resection of ≥ 10 nodes correlated significantly with better DSS and OS in former stage III node-negative vulvar cancer patients. No difference in survival was observed among stage I patients. The group suggested that radical inguinofemoral lymphadenectomy should be performed in patients with node-negative, locally advanced vulvar cancer and that the survival benefit from radical lymphadenectomy for these patients is attributed to resection of LNs with undetected micrometastases.

The latter hypothesis is not corroborated by Gordinier et al.,⁸ who failed to note any LN micrometastases in LNs that were resected in 104 patients with negative groins. Further, the group did not describe whether the lymphadenectomy was unilateral or bilateral. Because patients with only 1 resected LN and a low median of resected LNs were included, we conclude that patients with unilateral lymphadenectomy were part of the study group. They also stratified patients by the old FIGO staging system, in which stage III included tumors of any size with adjacent spread to the lower urethra, vagina, or anus. Patients with locally advanced disease and negative lymph nodes have a better prognosis than those with positive (unilateral) lymph nodes^{20,34} and are now considered to have stage II disease.⁴

Our cohort included patients with both negative and positive LNs. In contrast to Courtney-Brooks et al.,¹⁰ we did not find any benefit in resecting more LNs in patients with negative nodes. Moreover, we included only patients with bilateral LN dissections and more locally advanced tumors with regard to size and depth of invasion; thus, we had a higher rate of LN metastasis (50.6%). Further, there was no difference between the groups (< 12 LNs and ≥ 12 LNs resected) in tumor size or depth of invasion. Nevertheless, we deduce that patients with locally advanced tumors have better outcomes after an appropriate lymphadenectomy.

We anticipated observing a higher prevalence of exclusive inguinal recurrences for patients with < 12 LNs resected, but our findings did not corroborate this hypothesis. Conversely, we observed that resection of < 12 LNs had a significantly negative impact on not only DSS but also PFS.

Because adjuvant radiotherapy was performed in only 7.6% of patients, we believe that there is a therapeutic effect of lymphadenectomy. Most patients who received radiotherapy were treated in last decade after an institutional paradigm shift, in which we began to indicate adjuvant radiotherapy for patients with 2 metastases that were below 5 mm, LN metastases that were larger than 5 mm, and extracapsular invasion. Nevertheless, in our series, adjuvant radiotherapy had no impact on outcomes in patients with positive LNs, which we attribute to the small number of patients who received adjuvant radiotherapy.

Overall, we present a large, uni-institutional series on a rare disease that contributes valuable data. Unfortunately, in a retrospective setting that spanned nearly 3 decades, it suffers from institutional bias.

In conclusion, our data suggest that regarding outcomes, resection of <12 LNs in bilateral lymphadenectomy for patients with vulvar cancer and positive inguinal LNs have a negative impact on recurrence and death from cancer. Resection of at least 12 LNs should be considered the goal for patients with vulvar cancer that requires bilateral lymphadenectomy.

Conflict of interest

All authors declare that there is no conflict of interest.

References

- Hacker NF. Vulvar cancer. In: Berek JS, Hacker NF, editors. *Berek and Hacker's gynecologic oncology*. 5th ed. Philadelphia: Williams and Wilkins; 2010, p. 576–92.
- de Hullu JA, van der Zee AG. Surgery and radiotherapy in vulvar cancer. *Crit Rev Oncol Hematol* 2006;**60**(1):38–58.
- 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* 1991;**164**:997–1004.
- Hacker NF. Revised FIGO staging for carcinoma of the vulva. *Int J Gynaecol Obstet* 2009;**105**(2):105–6.
- Woelber L, Kock L, Gieseking F, et al. Clinical management of primary vulvar cancer. *Eur J Cancer* 2011;**47**(15):2315–21.
- Berman ML, Soper JT, Creasman WT, et al. Conservative surgical management of superficially invasive stage I vulvar carcinoma. *Gynecol Oncol* 1989;**35**:352–7.
- Stehman FB, Bundy BN, Dvoretzky PM, et al. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the Gynecologic Oncology Group. *Obstet Gynecol* 1992;**79**:490–7.
- Gordinier ME, Malpica A, Burke TW, et al. Groin recurrence in patients treated with negative nodes on superficial inguinal lymphadenectomy. *Gynecol Oncol* 2003;**90**:625–8.
- Kirby TO, Rocconi RP, Numnum TM, et al. Outcomes of stage I/II vulvar cancer patients after negative superficial inguinal lymphadenectomy. *Gynecol Oncol* 2005;**98**:309–12.
- Courtney-Brooks M, Sukumvanich P, Beriwal S, et al. Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease? *Gynecol Oncol* 2010;**117**(2):308–11.
- Le T, Elsugi R, Hopkins L, et al. The definition of optimal inguinal femoral nodal dissection in the management of vulva squamous cell carcinoma. *Ann Surg Oncol* 2007;**14**(7):2128–32.
- Palaia I, Bellati F, Calcagno M, et al. Invasive vulvar carcinoma and the question of the surgical margin. *Int J Gynaecol Obstet* 2011 Aug;**114**(2):120–3.
- Tomao F, Di Tucci C, Marchetti C, et al. Role of chemotherapy in the management of vulvar carcinoma. *Crit Rev Oncol Hematol* 2012 Apr;**82**(1):25–39.
- Bellati F, Angioli R, Manci N, et al. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. *Gynecol Oncol* 2005 Jan;**96**(1):227–31.
- Bellati F, Napoletano C, Tarquini E, et al. Cancer testis antigen expression in primary and recurrent vulvar cancer: association with prognostic factors. *Eur J Cancer* 2007 Nov;**43**(17):2621–7.
- Lavorato-Rocha AM, de Melo Maia B, Rodrigues IS, et al. Prognostication of vulvar cancer based on p14(ARF) status: molecular assessment of transcript and protein. *Ann Surg Oncol* 2013 Jan;**20**(1):31–9.
- Fons G, Hyde SE, Buist MR, et al. Prognostic value of bilateral positive nodes in squamous cell cancer of the vulva. *Int J Gynecol Cancer* 2009;**19**(7):1276–80.
- Hacker NF, Berek JS, Lagasse LD, et al. Management of regional lymph nodes and their prognostic influence in vulvar cancer. *Obstet Gynecol* 1983;**61**(4):408–12.
- van der Velden J, van Lindert ACM, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. *Cancer* 1995;**75**:2885–90.
- van der Steen S, de Nieuwenhof HP, Massuger L, et al. New FIGO staging system of vulvar cancer indeed provides a better reflection of prognosis. *Gynecol Oncol* 2010;**119**(3):520–5.
- Raspagliesi F, Hanozet F, Ditto A, et al. Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. *Gynecol Oncol* 2006;**102**(2):333–7.
- Paladini D, Cross P, Lopes A, et al. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. *Cancer* 1994;**74**:2491–6.
- 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). *Gynecol Oncol* 1993;**49**:279–83.
- De Hullu JA, Hollema H, Lolkema S, et al. Vulvar carcinoma. The price of less radical surgery. *Cancer* 2002;**95**:2331–8.
- Manci N, Marchetti C, Esposito F, et al. Inguinofemoral lymphadenectomy: randomized trial comparing inguinal skin access above or below the inguinal ligament. *Ann Surg Oncol* 2009;**16**(3):721–8.
- Rouzier R, Haddad B, Dubernard G, et al. Inguinofemoral dissection for carcinoma of the vulva: effect of modifications of extent and technique on morbidity and survival. *J Am Coll Surg* 2003;**196**:442–50.
- Stehman FB, Ali S, DiSaia PJ. Node count and groin recurrence in early vulvar cancer: a gynecologic oncology group study. *Gynecol Oncol* 2009;**113**(1):52–6.
- 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):884–9.
- 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):646–52.
- Borgno G, Micheletti L, Barbero M, et al. Topographic distribution of groin lymph nodes: a study of 50 female cadavers. *J Reprod Med* 1990;**35**:1127–9.
- Bell JG, Lea JS, Reid GC. Complete groin lymphadenectomy with preservation of the fascia lata in the treatment of vulvar carcinoma. *Gynecol Oncol* 2000;**77**:314–8.
- Gaarenstroom KN, Kenter GG, Trimbos JB, et al. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate incisions. *Int J Gynecol Cancer* 2003;**13**:522–7.
- Gould N, Kamelle S, Tillmanns T, et al. Predictors of complications after inguinal lymphadenectomy. *Gynecol Oncol* 2001;**82**:329–32.
- Rouzier R, Preti M, Sideri M, et al. A suggested modification to FIGO stage III vulvar cancer. *Gynecol Oncol* 2008;**110**(1):83–6.