History and Updates of the GROINSS-V Studies

Subjects: Oncology

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GROINSS-V-I showed that omitting inguinofemoral lymphadenectomy was safe in early-stage vulvar cancer patients with a negative sentinel lymph node, with an impressive reduction in treatment-related morbidity. GROINSS-V-II, a prospective multicenter phase II single-arm treatment trial (from 2005 to 2016) investigated whether radiotherapy could be a safe alternative for inguinofemoral lymphadenectomy in patients with a metastatic sentinel lymph node. This research showed that radiotherapy in patients with sentinel lymph node micrometastases (≤2 mm) was safe in terms of groin recurrence rate and with less treatment-related morbidity. These results, published in August 2021, should be implemented in (inter)national treatment guidelines for vulvar cancer. GROINSS-V-III recently started including patients. This research investigates the effectiveness and safety of chemoradiation in patients with a macrometastasis (>2 mm) in the sentinel lymph node.

vulvar cancer early-stage GROINSS-V sentinel lymph node radiotherapy

1. GROINSS V-I Study

The GROINSS-V I study showed that omitting inguinofemoral lymphadenectomy was safe in patients with early-stage vulvar cancer (unifocal tumors < 4cm and non-suspicious groin nodes) and a negative sentinel node, with an isolated groin recurrence rate after 2 years of 2.3%. In 2012, Levenback et al. published the results of the GOG-173 study [1], in which the sentinel lymph node procedure was applied in patients with early-stage vulvar cancer, followed by inguinofemoral lymphadenectomy. This research showed quite similar results compared with the GROINSS-V-I study. In patients with a vulvar tumor <4 cm, the false-negative predictive value was 2.0%. After the publication of these studies the sentinel lymph node procedure became part of standard treatment in pre-selected patients with early-stage vulvar cancer, even though at that moment no long-term follow-up data were available for large populations. In 2016, te Grootenhuis et al. published the long-term follow-up data of GROINSS-V-I [2]. The primary aim of the research was to evaluate the long-term follow-up regarding the incidence of recurrences, whereby the location of the recurrence was designated as local (vulva), groin (left or right) or distant (including pelvic recurrences), and survival.

The median follow-up time was 105 months (range 0–179). The local recurrence rate for sentinel lymph node-negative patients was 24.6% at 5 years and 36.4% at 10 years after primary treatment, and for sentinel lymph node-positive patients 33.2% and 46.4%, respectively (p = 0.03). In 15.4% of the sentinel lymph node-negative patients, inguinofemoral lymphadenectomy was performed during follow-up, as part of treatment for a macroinvasive local recurrence. The isolated groin recurrence rate was 2.5% for sentinel lymph node-negative

patients and 8.0% for sentinel lymph node-positive patients at 5 years and 10 years. Isolated distant recurrences were not observed in sentinel lymph node-negative patients and in 6.8% for sentinel lymph node-positive patients at 5 and 10 years. All groin and distant recurrences were diagnosed within 25 months after primary treatment. Sentinel lymph node-negative patients had a significantly better 5- and 10-year disease-specific survival of 93.5% and 90.8%, respectively, compared to sentinel lymph node-positive patients (75.5% and 64.5%, respectively ($p < 0.0001$)). For all patients, 10-year disease-specific survival decreased from 90% for patients without to 69% for patients with a local recurrence ($p < 0.0001$).

Local recurrences in vulvar cancer not only compromise survival; the need for an inguinofemoral lymphadenectomy means that these patients do not have the advantage of primary treatment with a sentinel lymph node procedure anymore. The advantages of a sentinel lymph node procedure for women with recurrent vulvar cancer, an impressive reduction in treatment-related morbidity, compared to a full inguinofemoral lymphadenectomy are clear. To investigate the feasibility of the repeat sentinel lymph node procedure, a prospective multicenter study is now being performed in the Netherlands, initiated by van Doorn et al (V2SLN study). The primary objective is to investigate the safety of replacing inguinofemoral lymphadenectomy by the sentinel lymph node procedure in patients with locally recurrent vulvar squamous cell carcinoma without suspicious groin lymph nodes. Patients with a first local recurrence of vulvar cancer (unifocal and <4 cm) will be included. Patients with previous ipsi- or bilateral inguinofemoral lymphadenectomy followed by radiotherapy will be excluded. Groin recurrence rate in patients with a negative sentinel lymph node will be the primary endpoint.

2. GROINSS V-II Study

Very recently, the results of the GROINSS-V-II study were published [3]. As described above in the additional analysis of the GROINSS-V-I data [4], there was no threshold for the size of sentinel lymph node metastasis below which the risk of additional metastasis was sufficiently low to safely allow for the omission of inguinofemoral lymphadenectomy. Therefore, all patients with a metastatic sentinel lymph node still have to undergo additional treatment—an inguinofemoral lymphadenectomy. In patients with more than one metastatic lymph node and/or extracapsular spread, adjuvant radiotherapy after lymphadenectomy is indicated. GROINSS-V-II was designed to find an equally effective but less morbid treatment for patients with a metastatic sentinel lymph node. The aim of the GROINSS-V-II study was to investigate the safety of inguinofemoral radiotherapy as an alternative to inguinofemoral lymphadenectomy in patients with vulvar cancer and a metastatic sentinel lymph node. Treatment-related morbidity was also taken into account.

GROINSS-V-II was a prospective multicenter phase II single-arm treatment trial, performed in patients with early-stage vulvar cancer (unifocal squamous cell cancer of the vulva, <4 cm in diameter, with a depth of invasion of more than 1 mm and nonsuspicious inguinofemoral lymph nodes by preoperative imaging) planned for surgery: wide local excision and sentinel lymph node biopsy. The primary endpoint was the isolated groin recurrence rate after two years. Secondary endpoints were short- and long-term treatment-related morbidity. Patients were included from 59 hospitals in 11 countries, from December 2005 until October 2016. In sentinel lymph node-positive patients (metastasis of any size, including isolated tumor cells), inguinofemoral radiotherapy was given

with a total dose of 50 Gy, initiated within 6 weeks after surgery. Stopping rules were defined for the occurrence of groin recurrences, based on the previously reported frequency in patients with a metastatic lymph node who underwent inguinofemoral lymphadenectomy (in GROINSS-V-I 8.1%) [5]. A major protocol amendment was made in June 2010, after the stopping rule was activated because the number of groin recurrences after a metastatic sentinel lymph node and inguinofemoral radiotherapy exceeded the upper border. Interim analysis showed that the risk of groin recurrence was especially high in patients with sentinel lymph node metastasis >2 mm and/or when extranodal tumor growth was present. Therefore, the research continued with only patients with sentinel lymph node micrometastases (≤2 mm) receiving inguinofemoral radiotherapy. Those with sentinel lymph macrometastases (>2 mm) were reverted back to standard of care and underwent inguinofemoral lymphadenectomy, with adjuvant radiotherapy if indicated.

In GROINSS-V II, a total of 322 out of 1535 (21.0%) eligible patients had sentinel lymph node metastasis. Sentinel lymph node micrometastases were found in 160 patients, and 162 had sentinel lymph node macrometastases. Among 160 patients with sentinel lymph node micrometastases, 126 received inguinofemoral radiotherapy prescribed by protocol. The ipsilateral isolated groin recurrence rate at two years was 1.6%. In 18 patients, it was decided to give no further treatment, for a variety of reasons. Despite the minimal burden of disease in the sentinel lymph node, the ipsilateral groin recurrence rate at two years was 11.8% in this group (hazard ratio 0.11; 0.015–0.76 95% CI). This points out to the importance of adjuvant treatment in the case of micrometastatic disease in the sentinel lymph node.

Among 162 patients with sentinel lymph node macrometastases, the isolated groin recurrence rate at two years was 22% in those who underwent radiotherapy only (n = 51, before activation of the stopping rule), and 6.9% in those who underwent inguinofemoral lymphadenectomy (with or without adjuvant radiotherapy, after activation of the stopping rule) (p = 0.011). After radiotherapy only, treatment-related morbidity was less frequent compared to inguinofemoral lymphadenectomy (with or without adjuvant radiotherapy). The use of concurrent chemotherapy was in GROINSS-V II at the discretion of the treating physician. Among the patients with sentinel lymph node macrometastases, only seven received radiotherapy combined with chemotherapy (13.7%). No groin recurrences were observed in these patients.

GROINSS-V-II demonstrated that, in patients with sentinel lymph node micrometastases, inguinofemoral radiotherapy resulted in a very low groin recurrence rate with acceptable treatment-related morbidity and, therefore, is a safe alternative for inguinofemoral lymphadenectomy. For patients with sentinel lymph node macrometastases, an inguinofemoral lymphadenectomy is still the standard of care.

3. GROINSS-V-III Study

The in-depth analysis of the GROINSS-V-I data showed that the risk of additional metastases in patients with sentinel lymph node macrometastases (>2 mm) is 33% [4]. As described in the GROINSS-VII study, radiotherapy (50 Gy) instead of an inguinofemoral lymphadenectomy was not safe in these patients, leading to an unacceptable high isolated groin recurrence rate [3]. The data do suggest that there is an effect of radiotherapy, but in the

absence of an inguinofemoral lymphadenectomy the dose is not enough to eradicate residual disease. The efficacy of radiotherapy can be increased by increasing the dose and/or adding chemotherapy [6]. From other (HPV-related) squamous cell carcinoma, it is well known that adding chemotherapy as a radiosensitizer during radiotherapy improves outcome on local control as well as survival. For example, in cervical cancer, several studies and meta-analyses demonstrated the beneficial effect of adding chemotherapy, both in the primary and adjuvant setting [7][8][9]. The results of several small studies in patients with locally advanced vulvar cancer treated with neoadjuvant or primary chemoradiation showed high response rates, with up to 64% complete clinical remission [10][11][12]. In a large population-based analysis, there was a significant reduction in mortality risk of 38% in patients with lymph node-positive vulvar cancer by the addition of chemotherapy to their adjuvant radiotherapy [6].

GROINSS-V-III was started to find a new treatment-strategy for patients with sentinel lymph node macrometastases. GROINSS-V III is again a prospective multicenter phase II single-arm treatment trial and recently started including patients in Europe and the United States. In this research, the researchers will investigate if chemoradiation is a safe alternative treatment for inguinofemoral lymphadenectomy in patients with early-stage vulvar cancer and a macrometastasis in their sentinel lymph node and/or extranodal tumor growth. Patients with multiple sentinel lymph node micrometastases can also be included in this study. The hypothesis is that treatment with chemoradiation is as effective as an inguinofemoral lymphadenectomy, but is associated with less treatment-related morbidity. Radiotherapy in this research is given in a dose of 48–50 Gy in 1.8 Gy daily fractions to the inguinofemoral and external iliac nodal regions, with a boost to the involved inguinal site for a total equivalent dose of 56 Gy over 5–6 weeks, preferably with the simultaneous integrated boost technique. This will be combined with weekly 40 mg/m^2 cisplatin. In the case of renal impairment (creatinine clearance between 40 and 60 mL/min), cisplatin 20 mg/m^2 or carboplatin AUC2 can be given. The primary endpoint will be groin recurrence rate in the first two years after primary treatment. Groin recurrence rate will be monitored continuously with stopping rules. Quality of life will be assessed pre-treatment, six weeks after treatment, and 6, 12 and 24 months after treatment. The research started including patients in 2021 and aims to include 157 required patients in seven years.

References

1. Levenback, C.F.; Ali, S.; Coleman, R.L.; Gold, M.A.; Fowler, J.M.; Judson, P.L.; Bell, M.C.; De Geest, K.; Spirtos, N.M.; Potkul, R.K.; 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, 30, 3786–3791.
2. Grootenhuis, N.C.T.; Van Der Zee, A.G.J.; Van Doorn, H.C.; Van Der Velden, J.; Vergote, I.; Zanagnolo, V.; Baldwin, P.J.; Gaarenstroom, K.N.; Van Dorst, E.B.; Trum, J.W.; et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol. Oncol. 2016, 140, 8–14.

3. Oonk, M.H.M.; Slomovitz, B.; Baldwin, P.J.W.; van Doorn, H.C.; van der Velden, J.; de Hullu, J.A.; Gaarenstroom, K.N.; Slangen, B.F.M.; Vergote, I.; Brännström, M.; et al. Radiotherapy Versus Inguinofemoral Lymphadenectomy as Treatment for Vulvar Cancer Patients With Micrometastases in the Sentinel Node: Results of GROINSS-V II. J. Clin. Oncol. 2021, 39, 3623–3632.
4. Oonk, M.H.; van Hemel, B.M.; Hollema, H.; de Hullu, J.A.; Ansink, A.C.; Vergote, I.; Verheijen, R.H.; Maggioni, A.; Gaarenstroom, K.N.; Baldwin, P.J.; 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, 646–652.
5. Van der Zee, A.G.; Oonk, M.H.; De Hullu, J.A.; Ansink, A.C.; Vergote, I.; Verheijen, R.H.; Maggioni, A.; Gaarenstroom, K.N.; Baldwin, P.J.; Van Dorst, E.B.; et al. Sentinel Node Dissection is Safe in the Treatment of Early-Stage Vulvar Cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2008, 26, 884–889.
6. Gill, B.S.; Bernard, M.E.; Lin, J.F.; Balasubramani, G.K.; Rajagopalan, M.S.; Sukumvanich, P.; Krivak, T.C.; Olawaiye, A.B.; Kelley, J.L.; Beriwal, S. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: A National Cancer Data Base (NCDB) analysis. Gynecol. Oncol. 2015, 137, 365–372.
7. Peters, W.A., 3rd; Liu, P.J.; Barrett, R.J.; Stock, R.J.; Monk, B.J.; Berek, J.S.; Souhami, L.; Grigsby, P.; Gordon, W., Jr.; Alberts, D.S. Concurrent Chemotherapy and Pelvic Radiation Therapy Compared with Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2000, 18, 1606–1613.
8. Green, J.; Kirwan, J.; Tierney, J.; Vale, C.L.; Symonds, P.R.; Fresco, L.L.; Williams, C.; Collingwood, M. Concomitant Chemotherapy and Radiation Therapy for Cancer of the Uterine Cervix. Cochrane Database Syst. Rev. 2001, 4, CD002225.
9. Monk, B.J.; Wang, J.; Im, S.; Stock, R.J.; Peters, W.A.; Liu, P.; Barrett, R.J.; Berek, J.S.; Souhami, L.; Grigsby, P.W.; et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: A clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol. Oncol. 2005, 96, 721–728.
10. Shylasree, T.S.; Bryant, A.; Howells, R.E. Chemoradiation for advanced primary vulval cancer. Cochrane Database Syst. Rev. 2011, 4, CD003752.
11. Moore, D.H.; Ali, S.; Koh, W.-J.; Michael, H.; Barnes, M.N.; McCourt, C.K.; Homesley, H.D.; Walker, J.L. 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, 529–533.

12. Han, S.C.; Kim, D.H.; A Higgins, S.; Carcangiu, M.-L.; Kacinski, B.M. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int. J. Radiat. Oncol. 2000, 47, 1235–1244.