

Failure of sentinel node identification following neo-adjuvant chemo-radiotherapy for locally advanced squamous cell carcinoma of the vulva

H. Levavi¹, M.D.; G. Sabah¹, M.D.; R. Hardoff², M.D., DSc.; C. Koren³, M.D.; H. Gutman⁴, M.D.

¹Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, ²Department of Nuclear Medicine,

³Institution of Oncology, ⁴Department of General Surgery "B", Rabin Medical Center, Petah Tiqva, Israel.

Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv (Israel)

Summary

A case of a 70-year-old patient with advanced local vulvar cancer is presented. Treatment with neo-adjuvant chemo-radiotherapy for two courses was administered and two weeks after completion of treatment the patient underwent wide local excision with bilateral inguino-femoral lymph node dissection through three separate incisions. Two methods for the evaluation of sentinel nodes-lymphoscintigraphy and intraoperative gamma hand-held probe and blue dye injection, did not detect any sentinel node on either side. Groin-node dissection revealed 23 negative nodes. It is our hypothesis that the non-visualization of sentinel nodes in this patient was due to post-irradiation damage to the lymph channels.

Key words: Vulvar cancer; Sentinel node; Lymphoscintigraphy.

Introduction

Vulvar cancer represents about 4% of all female genital malignancies and is predominantly (90%) of squamous cell origin [1]. The majority of the cases are diagnosed at an early stage, when the tumor is small and usually unilateral. Some of the patients present late with advanced cancer extending to adjacent organs like the rectum, urinary bladder, urethra, and even rarer are vulvar cancers with distant metastases. Significant advances in the management have been made with the trend towards individualization of treatment by tailoring to the least radical treatment as possible, without compromising the quality of life and the survival rate achieved.

Recently, several studies have reported on the results of groin sentinel node identification with blue dye or lymphoscintigraphy mapping. The aim of these techniques is to omit complete lymphadenectomy in cases where nodes have been found to be without malignant cells.

Case Report

A 70-year-old patient presented with a partially necrotic, firm squamous cell cancer mass, 6 cm in diameter, occupying the fourchette, extending to the anal margin with a 5 cm fine needle aspiration positive inguinal node in the left groin. Since a surgical procedure with good lateral free margins was impossible, she was treated with induction chemo-radiotherapy including mitomycin C 10 mg/m² on day 1 + 5-fluorouracil 1000 mg/m² on days 1-4, concomitant with external irradiation to the vulva, groin and pelvis to 3600 cGy (divided to 20 fractions of 180 cGy each day) for two courses, and then a further course of cisplatin 100 mg/m² on day 1 + 5-fluorouracil 800 mg/m² on days 2-5, with boost irradiation of 2340 cGy to the vulva and the groin area (in 13 fractions). On completion of this treatment a

significant response was achieved – a small 2 cm flat and indurated area remained on the perineal site and the left inguinal node decreased to 1.5 cm in size, and surgery was planned. The patient consented to participate in our on-going evaluation of sentinel node detection using a combination of both methods – lymphoscintigraphy and intraoperative gamma hand held probe and blue dye injection. Two weeks following completion of chemo-radiotherapy and 24 hours prior to surgery the patient was injected intradermally in four perilesional sites with a ^{99m}Tc-albumin nanocolloid (Nycomed Amersham Sorin S.r.l., Saluggia, Italy), particle size less than 100 nm, to a total of 2 mCi. Images were obtained in the anterior view using a large field of view gamma camera (SP-6, Elscint, Ltd.), in the dynamic mode for 30 minutes (60 sec/frame), and then at 1, 2, and 24 hours. There was no visualization of lymph nodes outside the injected site throughout the entire follow-up.

About ten minutes before surgical incision, Patent Blue V (2.5% in aqueous solution containing 0.6% sodium chloride and 0.05% disodium hydrogen phosphate; Laboratoire Guerbet, Aulney-Sous-Bois, France) was injected in the same four sites. Exploration of the left and then the right groin, using a hand-held collimated and uncollimated gamma probe (Neoprobe 2000, USA) did not reveal any sentinel node. No visible blue nodes were found. A complete groin-node dissection was carried out. Ex-vivo readings of 23 nodes retrieved were also negative. All nodes showed fibrosis with marked granulomatous giant cell foreign body reaction with cholesterol crystals and calcified keratin pearls. Wide local excision of the vulvar and perineal area did not reveal residual tumoral tissue. No further treatment was given, and the patient is now 11 months after completion of treatment with no evidence of disease.

Discussion

The standard treatment for early squamous cell cancer of the vulva is by radical vulvectomy or wide local excision combined with uni – or bilateral inguino-femoral node-dissection, usually through separate incisions [2].

Revised manuscript accepted for publication January 21, 2003

However, the treatment of advanced vulvar cancer is controversial and several modalities have been evaluated. Advanced local disease may be treated by radical surgery, including exenterative procedures, with significant morbidity and mortality [3]. Chemo-radiation has been used as an alternative initial treatment, which may serve as definitive management for some patients, or may reduce the complication sequelae of subsequent surgery in others. Various single and combination chemotherapy regimes have been evaluated [4-6].

Lupi *et al.*, [7] reported on the results of a pilot study on concurrent chemo-radiotherapy followed by radical surgery for patients with locally advanced squamous cell carcinomas of the vulva. They treated 31 patients with two courses of combination chemotherapy including mitomycin C, 15 mg/m² intravenously on day 1, and 5-fluorouracil, 750 mg/m² I.V., in continuous 24-hour infusion on days 1 to 5. Concurrent irradiation of the inguinal and pelvic lymph nodes and the vulva to a total dose of 36 Gy was applied. Two weeks later, a second course of chemo-radiotherapy was given (18 Gy on the vulvar region only). After a further two weeks, patients underwent radical surgery. Results showed objective response in 22 of 24 primary cases (91.6%) and in seven of seven recurrent cases. Five of nine patients (55%) with biopsy-proven inguinal lymph node metastases showed complete pathological response.

Since the study of Parry-Jones in 1963, who injected patent blue and followed its uptake, the lymphatics of the vulva have been a subject of vast interest by many researchers [8, 9].

Continued efforts to detect sentinel nodes draining to the vulvar area have been attempted using various methods. Several authors have reported that the intraoperative injection of blue dye to the tumor margins is feasible in patients with vulvar cancer [10]. Others used lymphoscintigraphy and an intraoperative gamma probe with somewhat better results [11, 12], and recently both methods have been used resulting in very successful detection rates [13, 14].

So far, studies on sentinel node detection have focused on patients with primary early vulvar cancer. de Hullu *et al.*, [15] presented a case of a locally recurrent vulvar cancer, four years after radical vulvectomy, right-side groin node-dissection and irradiation to both groins to a total of 45 Gy. Using lymphoscintigraphy, one sentinel node and one second echelon node were detected on the left side.

On the right side, slow flow to pelvic sentinel nodes via lymphatic channels in the groin was demonstrable. Blue dye injected at surgery identified the left-side sentinel node and two external iliac sentinel nodes on the right side. All nodes removed were negative. These authors claimed that their findings are suggestive of the formation of new lymphatic channels via the previously operated and irradiated groin.

In our case, which represents a locally advanced primary vulvar cancer, chemo-radiotherapy induced complete obliteration or occlusion of all the lymphatic channels draining the tumor area, thus causing the failure of both lymph-mapping modalities to detect any sentinel node.

Unlike de Hullu *et al.*, [15] we could not demonstrate any sentinel node or lymphatic flow. One may argue that the short time elapsing from radiotherapy (two weeks) was not enough for lymphangiogenesis to occur.

Conclusions

The failure, in our case, to demonstrate any nodes or channels with either mapping method, is, to our understanding, suggestive of recent radiation damage on both groin sides, precluding the radioactive colloids or the dye from flowing in the lymph channels and reaching the nodes.

We suggest that further studies with sentinel node detection in advanced vulvar cancer should be performed to confirm the observation of recent damage by irradiation as a cause for failure of the method.

References

- [1] Hacker N. F.: "Vulvar cancer". In Berek J. S., Hacker N. F. (eds): "Practical Gynecologic Oncology". Baltimore, Williams & Wilkins, 1989.
- [2] Flannelly G. M., Foley M. E., Lenehan P. M. *et al.*: "En bloc radical vulvectomy and lymphadenectomy with modifications of separate groin incisions". *Obstet. Gynecol.*, 1992, 79, 307.
- [3] Cavanagh D., Shepherd J. H.: "The place of pelvic exenteration in the primary management of advanced carcinoma of the vulva". *Gynecol. Oncol.*, 1982, 13, 318.
- [4] Muss H. B., Bundy B. N., Christopherson W. A.: "Mitoxantrone in the treatment of advanced vulvar and vaginal carcinoma. A gynecologic oncology group study". *Am. J. Clin. Oncol.*, 1989, 12, 142.
- [5] Eifel P. J., Morris M., Burke T. W., Levenback C., Gershenson D. M.: "Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva". *Gynecol. Oncol.*, 1995, 59, 51.
- [6] Thomas G., Dembo A., DePetrillo A., Pringle J., Ackerman I., Bryson P. *et al.*: "Concurrent radiation and chemotherapy in vulvar carcinoma". *Gynecol. Oncol.*, 1989, 34, 263.
- [7] Lupi G., Raspagliesi F., Zucali R., Fontanelli R., Paladini D., Kenda R. *et al.*: "Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study". *Cancer*, 1996, 77, 1472.
- [8] Parry-Jones E.: "Lymphatics of the vulva". *J. Obstet. Gynaecol. Br. Commonw.*, 1963, 70, 751.
- [9] Iversen T., Aas M.: "Lymph drainage from the vulva". *Gynecol. Oncol.*, 1983, 16, 179.
- [10] Levenback C., Burke T. W., Gershenson D. M., Morris M., Malpica, A., Ross M.: "I. Intraoperative lymphatic mapping for vulvar cancer". *Obstet. Gynecol.*, 1994, 84, 163.
- [11] Decesare S. L., Fiorica J. V., Roberts W. S., Reintgen D., Arango H., Hoffman M. S. *et al.*: "A pilot study utilizing intraoperative lymphoscintigraphy for identification of the sentinel lymph nodes in vulvar cancer". *Gynecol. Oncol.*, 1997, 66, 425.
- [12] De Cicco C., Sideri M., Bartolomei M., Grana C., Cremonesi M., Fiorenza M. *et al.*: "Sentinel node biopsy in early vulvar cancer". *Br. J. Cancer*, 2000, 82, 295.
- [13] de Hullu J. A., Hollema H., Piers D. A., Verheijen R. H., van Diest P. J., Mourits M. J. *et al.*: "Sentinel lymph node procedure is highly accurate in squamous cell carcinoma of the vulva". *J. Clin. Oncol.*, 2000, 18, 2811.
- [14] Terada K. Y., Coel M. N., Ko P., Wong J. H.: "Combined use of intraoperative lymphatic mapping and lymphoscintigraphy in the management of squamous cell cancer of the vulva". *Gynecol. Oncol.*, 1998, 70, 65.
- [15] de Hullu J. A., Piers D. A., Hollema H., Aalders J. G., van der Zee A. G. J.: "Sentinel lymph node detection in locally recurrent carcinoma of the vulva". *Br. J. Obstet. Gynaecol.*, 2000, 108, 766.

Address reprint requests to:

H. LEVAVI, M.D.

Division of Gynecologic Oncology

Rabin Medical Center

Petah Tiqva (Israel)