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Cancer Australia

The role of sentinel lymph node biopsy in the treatment of women with early vulval cancer: A summary of the evidence

Early-stage cancer of the vulva

The International Federation of Gynaecology and Obstetrics (FIGO) categorises cancer of the vulva into stages, with early-stage (1A or 1B) defined as being confined to the vulva or perineum, with stromal invasion, and negative inguino-femoral lymph nodes.[1] In Australia, vulval cancer represents 6.2 % of all gynaecological cancers, with 83% cases of vulval cancer having squamous cell histology.[2] In 2008, vulval cancer was the fourth most commonly diagnosed gynaecological cancer with 282 new cases in Australia.[2] Between 2006 and 2010, five-year relative survival was 71.3% for vulval cancer in Australia.[2]

In Australia vulval cancer is usually treated with radical vulvectomy and unilateral or bilateral node dissection, depending on tumour factors. Complete inguino-femoral lymph node dissection (IFLND) is associated with a high frequency of early and late complications, specifically wound infection, wound breakdown, lymphocyst and lymphoedema of the leg. [3] Sentinel lymph node biopsy (SLNB) is a procedure used to identify the first lymph node(s) to which a carcinoma drains.[4, 5] Identifying sentinel lymph nodes (SLN) allows for the resection of limited nodal tissue without removal of the entire lymph node chain. The goal of this procedure is to minimise morbidity, without compromising survival.[4, 5] Sentinel node dissection has been evaluated and is used in the management of breast cancer, and has been investigated as a way to minimise the morbidity associated with groin node dissection in the management of vulval cancer.

Sentinel lymph node identification

The performance of SLNB (expressed as the identification rate and the false negative rate) will be influenced by appropriate patient selection (i.e. early clinical stage disease), operator experience and histopathological assessment of dissected nodes. The false negative rate associated with SLNB is of key importance, as the failure to identify positive sentinel lymph nodes is expected to be associated with higher rates of groin recurrence and poorer survival outcomes.

Operator experience

Operator experience is inconsistently defined in studies of SLNB. Little information is provided regarding who performed the peri-tumoural injection or the experience of the operator. One study calculated that the rate of SLN detection was worse in the first two years of the study (failure rate of 16% versus 7% per patient).[6] Other studies have suggested surgeons perform at least ten successful SLNB procedures followed by completed IFLND without any false-negative results, before performing SLNB alone [5]

False negative rate

In 22 studies that used blue dye, radio-isotope (R-I), or both together, the false negative rate for SLNB ranges from 0% to 14%, with a pooled false negative rate of 4.8%.[8] A recently published meta-analysis reported the pooled false negative rate with SLNB of 10.4% for R-I alone, 9.3% for blue dye alone, and 6.6% for both combined.[9] Ten studies report subgroup analyses for lateral versus midline tumours, and the pooled false negative rate across these studies was similar to the rate observed across all studies. [8]

Identification rate

Lymphatic mapping using a combination of radio-isotope and blue dye was associated with a higher rate of sentinel node detection (35.4-100%) compared to blue dye alone (2.2-94%).[8] In eight studies that compared blue dye alone versus blue dye plus R-I, six studies found higher identification rates of positive nodes for the combined labelling technique (with an additional absolute identification rate of 29-71%), and two studies found equivalent identification rates with the two techniques. In a recently published meta-analysis mean SLN detection rates were calculated as 94% for R-I, 68.7% for blue dye, and 97.7% for R-I and blue dye together.[7] Limited evidence suggests that the rates of SLN identification are 93% versus 100% when the prior vulval surgery is incisional or excisional, respectively.[8]

Histopathological assessment

If sentinel node dissection is being performed, it is imperative to reduce the possibility of missing positive nodes. Standard staining by haematoxylin–eosin (H&E) may miss small volume or isolated tumour cells in the lymph node, giving a false negative result. The use of both ultrasectioning and immunohistochemistry increases the positive node identification rate (by 9-11%) as compared to routine H&E processing.[8] Consensus standards for histopathological examination and reporting are needed.

Patient Outcomes

Survival

In order to consider SLNB as an alternative to complete IFLND, there must be confidence in the performance of the procedure to identify affected nodes so that the survival of women undergoing SLNB is not compromised. In the Cancer Australia systematic review only two out of the 29 included studies of SLNB reported survival results.[8] Neither of these studies was comparative. The larger, prospective study in 259 patients reported a 3-year survival rate of 97% (95% CI, 91 – 99%) for SLNB in patients with unifocal vulval disease and a negative sentinel node.[10]

Recurrence

Whilst overall survival is the oncological outcome of most relevance to patients, the majority of SLNB studies only report local-regional recurrence in the groin. A recent meta-analysis has reported a pooled recurrence rate after SLNB of 2.8% (95% CI, 1.5 - 4.4) compared with a pooled recurrence rate after complete IFLND of 1.4% (95% CI 0.5 - 2.6).[9] These pooled rates were not statistically significantly different. However, it should be noted that this meta-

analysis is limited by the fact that it included studies of heterogeneous vulval cancers (including melanoma and adenocarcinoma).

An earlier systematic review with a sub-analysis limited to studies of clearly defined early vulval cancer reported a groin recurrence rate for SLNB of 2.04% (range 0 – 2.3%).[5] A different analysis from the same systematic review found that studies specifically reporting superficial lymphadenectomy had a recurrence rate of 5.7%, while studies reporting complete lymphadenectomy had a recurrence rate of 1.3%. [5]

In addition, there is evidence from a large, prospective, multi-centre observational study (GROINSS-V) of higher recurrence rates after SLNB in women with multifocal disease compared to women with unifocal disease: 11.8% versus 2.3%.[10]

Complications

Potential adverse effects of inguinal femoral lymph node dissection include cellulitis and wound complications, lymphocyst formation, and lymphoedema. Acute complications were less frequent among patients undergoing SLNB compared to those having complete IFLND.[7] For example, in the GROINSS-V study the incidence of acute complications for SLNB versus IFLND was 11.7% versus 34% for groin wound breakdown, and 4.5% versus 21.3% for wound cellulitis.[10]

The frequency of longer term adverse effects such as lymphoedema and recurrent cellulitis has been poorly documented but appears to be much lower for patients who had SLNB compared to patients who had complete node dissection. In the GROINSS-V study the incidence of longer term complications with SLNB versus IFLND was 1.9% versus 25.2% for lymphoedema of the legs, and 0.4% versus 16.2% for recurrent erysipelas.[10]

Quality of Life

Whilst lymphoedema in the legs can be associated with pain, discomfort and reduced sexual activity, there are few studies addressing quality of life (QOL) in vulval cancer patients managed by surgery alone. One study reported no statistically significant differences in overall quality of life (as measured with the EORTC QLQ-C30) for women undergoing SLNB when compared to women undergoing complete IFLND) .[11] These results should be interpreted with caution as the sample size of this study (N=62) is unlikely to have been sufficient to detect a difference. The same study did find statistically significantly better results for women undergoing SLNB compared to IFLND for the contentment functional scale, and the oedema symptom scale (measured by the FACT-V questionnaire).

A recent non-comparative study measured the quality of life (using the validated Utility-Based-Questionnaire-Cancer) in women after complete lymphadenectomy for cancer of the vulva[12],. The study found that even though the quality of life was reduced in women who underwent complete IFLND, 80% would choose this surgery over SLNB if the risk of missing a positive lymph node was higher than 1 in 100.[12]

Summary

- **The role of sentinel lymph node identification and biopsy in the management of clinical early stage squamous cell cancer of the vulva is unclear.**

- **From the available evidence*, the use of SLNB is associated with lower rates of lymphoedema and other surgical complications, and a non-statistically significant difference in risk of groin recurrence when compared to IFLND**.
- **The use of radio-isotope in combination with blue dye enhances the rate of sentinel lymph node identification and reduces the false negative rate**
- **The addition of both ultrasectioning and immuno-histochemistry evaluation of sentinel lymph nodes found to be negative on routine sections, increases the rate of positive SLN identification in squamous cell cancer of the vulva.**
- **It is important that women with early stage vulval cancer who are offered SLNB as an alternative to IFLND be advised of the likely reduction in morbidity in the context of limited evidence around long term outcomes.**
- **More research and longer term follow-up is needed to further evaluate the place of SLNB in the management of women with early vulval cancer.**

*It should be noted that there are limitations with the evidence. Many studies included small patient numbers, with heterogeneous patient populations, and the variables that may influence the detection of the sentinel node, such as size of lesion, clinically suspicious lymph nodes, prior vulval or inguinal surgery and operator experience, are inconsistently defined across studies.

References

1.FIGO. Fedreation Internationale de Gynecologie et d'Obstetrique. Committee on Gynecology Oncolgoy. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Int J Gynecol Obstet. 2009;105:103-104

2.AIHW and Cancer Australia. Gynaecological cancers in Australia: an overview. Australian Institute of Health and Welfare. 2012;Cancer series no. 70. Cat. no. CAN 66. Canberra: AIHW

3.Ryan M, Stainton MC, Slaytor EK, et al. Aetiology and prevalence of lower limb lymphoedema following treatment for gynaecological cancer. Aust N Z J Obstet Gynaecol. 2003;43(2):148-51

4.Vakselj A and Bebar S. The role of sentinel lymph node detection in vulvar carcinoma and the experiences at the Institute of Oncology Ljubljana. Radiology and Oncology. 2007;41(4):167-173

5.Reade CJ, Jimenez W, O'Reilly D and Covens A. Sentinel lymph node biopsy in vulvar cancer: a health technology assessment for the Canadian health care context. J Obstet Gynaecol Can. 2012;34(11):1053-65

6.Levenback C, Coleman RL, Burke TW, et al. Intraoperative lymphatic mapping and sentinel node identification with blue dye in patients with vulvar cancer. Gynecol Oncol. 2001;83(2):276-81

7.Meads C, Sutton AJ, Rosenthal AN, et al. Sentinel lymph node biopsy in vulval cancer: a systematic review and meta-analysis. BJC. 2014;110:2837-2846

8.Cancer Australia. The role of sentinel lymph node biopsy in the management of women with early stage vulval cancer: A systematic review. Sydney, 2014

9.Covens A, Vella ET, Kennedy EB, et al. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. Gynecol Oncol. 2015;137(2):351-361

10.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

11.Oonk MH, van Os MA, de Bock GH, et al. A comparison of quality of life between vulvar cancer patients after sentinel lymph node procedure only and inguinofemoral lymphadenectomy. Gynecol Oncol. 2009;113(3):301-5

12.Farrell R, Gebski V and Hacker NF. Quality of life after complete lymphadenectomy for vulvar cancer: do women prefer sentinel lymph node biopsy? . Int. J. Gynecol. Cancer. 2014;24(4):813–819