Sentinel Nodes in Vulvar Cancer

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Clearly, there is complexity to understanding the gene mutations involved in cancer. Stepping beyond initial BRCA testing may be problematic for the primary clinician. A practical algorithm incorporating recommendations for testing of a second set of mutations is needed for clinical management.—LVL)

Sentinel Nodes in Vulvar Cancer: Long-Term Follow-up of the Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V) I

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ABSTRACT

Treatment for early-stage vulvar cancer used to consist of wide local excision of the tumor combined with an inguinofemoral lymphadenectomy. This treatment is effective but has a high morbidity rate. The sentinel node (SN) procedure has been evaluated as an alternative approach for early-stage vulvar cancer. A sentinel lymph node (SLN) biopsy can determine whether vulvar cancer has spread. Sentinel node is a less-invasive procedure than an inguinofemoral lymphadenectomy and allows the surgeon to remove only 1 to 3 nodes.

Two large trials published in the last 8 years, the GROINSS-V-I (Groningen International Study on Sentinel nodes in Vulvar Cancer) and the Gynecologic Oncology Group 173 study, have shown that the SN procedure is safe in patients with early-stage unifocal tumors smaller than 4 cm who have no clinical suspicious groin lymph nodes. The SN procedure combined with local excision of the tumor is now part of the standard treatment in these patients. No long-term follow-up data, however, are available for the GROINSS-V-I study.

The aim of this multicenter study was to provide long-term follow-up data of GROINSS-V-I patients regarding recurrences and survival. GROINSS-V-I included 377 patients from 2000 until 2006 with unifocal squamous cell carcinoma of the vulva (T1, < 4 cm) who underwent the SN procedure. Follow-up was completed in March 2015. An inguinofemoral lymphadenectomy was performed only in patients with SN metastases. Data were analyzed for all patients and those who were SN negative and SN positive.

Median follow-up time was 105 months (range, 0–179 months). For all patients, the local recurrence rate at 5 and 10 years after primary treatment was 27.2% and 39.5%, respectively. For SN-negative patients, local recurrence rate was 24.6% at 5 years and 36.4% at 10 years, whereas in SN-positive patients, local recurrence rate was 33.2% at 5 years and 46.4% after 10 years ($P = 0.03$). An inguinofemoral lymphadenectomy was performed as part of the treatment for a local recurrence in

15.4% (39/253) of SN-negative patients. Isolated groin recurrence rate at 5 years was 2.5% in SN-negative patients and 8.0% in SN-positive patients. Ten-year disease-specific survival was significantly worse in SN-positive patients: 65%, SN positive versus 91%, SN negative, $P < 0.0001$. Ten-year disease-specific survival for all patients decreased from 90% for patients without a local recurrence to 69% for patients with a local recurrence ($P < 0.0001$).

Although survival is very good for SN-negative patients with early-stage vulvar cancer, local recurrence will occur in 36% of these patients, as well as 46% of SN-positive patients. Disease-specific survival decreases significantly when a local recurrence occurs both in SN-positive and SN-negative patients.

EDITORIAL COMMENT

(Previous to 1988, vulvar cancer staging was based on clinical examination. However, clinical examination was found to be inaccurate. Given the prognostic implications of finding metastatic disease to the groin, International Federation of Gynecology and Obstetrics changed vulvar cancer staging to a surgical approach. In that era, surgical lymph node assessment was performed by inguinal femoral lymphadenectomy. This was associated with a 30% to 70% incidence of lymphedema, and 20% to 40% incidence of wound breakdown. Modern management of surgical groin node assessment now includes SLN biopsy. The SLN receives direct drainage from the tumor and is the first lymph node to receive potential lymphatic metastases from the vulva. Utilizing SLN allows for a smaller area of dissection and less postoperative morbidity. Several studies have shown this approach to be effective and accurate for detection of lymph node metastases.

One of the initial studies of the SLN approach for vulvar cancer is the 2008 GROINSS-V-I study, the largest study to date. This was an observational study of 403 women with early-stage vulvar cancer followed for a median of 35 months. Patients underwent SLN, and if metastatic disease was found, inguinofemoral lymphadenectomy was performed. The groin recurrence rate was 2.3%. Surgical complications were much lower with an incidence of wound breakdown of 11.7%, cellulitis of 4.5%, recurrent wound infection of 0.4%, and lymphedema incidence of 1.9%. A second large prospective trial from the United States, GOG 173, included 452 patients with early-stage vulvar cancer who underwent SLN with similar results.

In the current study, Dr Grootenhuis and colleagues present long-term follow-up of their 2008 GROINSS-V-I study. In this follow-up with a median of 105 months, groin recurrences again were uncommon (2.5%) for SLN-negative patients. Ten-year survival was 91% for SLN-negative patients compared with 65% for SLN-positive patients. Local recurrences continued to be high (34.6% SLN-negative patients, 46.4% SLN-positive patients). It was notable that in patients with a negative sentinel node dissection, all recurrences occurred in the first 16 months after treatment. This study is the largest prospective study of sentinel node groin dissection and concludes that this is a safe approach and was associated with low groin recurrences in biopsy-negative patients and good survival rates. The authors emphasize that “strict patient selection” is important, and that this approach should be offered to patients with unifocal tumors measuring less than 4 cm, and that it is paramount that the sentinel node dissection be performed by experienced surgeons.

Two large prospective studies have now concluded that SLN is a safe and accurate approach for groin assessment of vulvar cancers. A negative SLN result is associated with low groin recurrence, and now this study, offering 8-year follow-up, confirms this. Cost-effective analysis by McCann and Erickson indicate that SLN biopsy is a cost-effective approach for treatment of early-stage vulvar cancer. So why is SLN dissection not the standard of care? In an editorial by Ramirez and Levanbach, several important obstacles to implementation of SLN are discussed. In particular, surgeon experience with SLN seems to be of critical for the success of accurately performing this procedure. Sentinel lymph node is commonly performed for breast cancer patients, and this procedure is incorporated in fellowship training. However, unlike breast cancer for which there are upwards of 200,000 cases annually in the United States, vulvar cancer is uncommon and rare. Thus, the opportunity to “practice” and learn the SLN biopsy requires diligence and patience.

It could possibly take a year or 2 to accumulate 10 cases of SLN biopsy procedures given the uncommon occurrence of early-stage vulvar cancer meeting criteria for SLN (<4 cm, unifocal disease). One option is to perform these procedures with assistance from breast oncologists trained in SLN biopsy. With this approach, one could implement the SLN biopsy for groin assessment… tomorrow! It would be interesting to note how many institutions commonly use the SLN approach in the United States. If this is indeed a low number, a detailed analysis of barriers to implementation in the United States would be important and recommendations to improve acceptance. Given the findings of GROINSS-V-I, it seems that SLN biopsy is effective, safe, and associated with lower morbidity overall for management of early vulvar cancers in experienced hands.—LVL)

Rescue of Failed Oocyte Activation After ICSI in a Mouse Model of Male Factor Infertility by Recombinant Phospholipase Cζ

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ABSTRACT

Intracytoplasmic sperm injection (ICSI) is a widely used treatment option for treating many cases of male factor infertility. It is substantially more successful than conventional in vitro fertilization (IVF) treatments. In 1% to 5% of all ICSI treatment cycles, all of the available oocytes from a given collection fail to fertilize. The main cause of ICSI failure in such cases has been shown to be the lack of oocyte activation. Ca^{2+} oscillations observed in human and mouse oocytes after IVF and ICSI are both necessary and sufficient for oocyte activation and may influence subsequent embryo development.

A mouse model system has been used to directly test the ability of human sperm to cause oocyte activation or Ca^{2+} oscillations after cross-species ICSI. Several studies have suggested that in cases of human ICSI failure there may be either a deficiency or relative lack of Ca^{2+} oscillations. The only available treatment option in cases of failed or poor rates of fertilization after ICSI has been the use of artificial oocyte activation agents. When poor ICSI oocyte activation rates are observed in clinical cases, the most common treatment option is the use of Ca^{2+} ionophores, which provide an artificial stimulus and have been successfully used in many cases to overcome fertilization failure. However, the efficiency of activation with the Ca^{2+} ionophore protocol compared with a physiological stimulus has not been critically examined. Ca^{2+} ionophores as used in most clinics produce a single large cytosolic Ca^{2+} increase and do not mimic the series of Ca^{2+} oscillations seen at fertilization. A more effective means of activating mammalian oocytes is use of stimuli that elicit multiple Ca^{2+} transients. Accumulating scientific and clinical evidence has shown that multiple Ca^{2+} oscillations triggered after sperm oocyte membrane fusion allow the entry of a sperm-specific recombinant phospholipase Cζ isoform (termed PLCζ) into the oocyte cytoplasm. PLCζ causes Ca^{2+} oscillations indistinguishable from those occurring during fertilization but is untested for its efficacy in cases of ICSI fertilization failure.

The aim of this study was to investigate whether recombinant human PLCζ protein can rescue cases of failed fertilization or to improve poor development rates after ICSI. PLCζ was compared with Ca^{2+} ionophores in a mouse model of failed oocyte activation after ICSI that mimics poor fertilization after ICSI. Increasing periods of exposure of sperm to 56°C produce a progressive loss of Ca^{2+} oscillations after ICSI in this model system and reduces oocyte activation and embryo development to the blastocyst stage. Mouse sperm exposed to mild heat were injected into mouse oocytes.

Heat-treated oocytes that failed to activate after ICSI were treated with either Ca^{2+} ionophores or with Sr^{2+} media (which causes Ca^{2+} oscillations) or were injected with recombinant human PLCζ. All these treatments rescued oocyte activation and led to development to the blastocyst stage, but Sr^{2+} and PLCζ were more effective than Ca^{+2} ionophores. Recombinant PLCζ given to oocytes previously injected with control sperm developed normally to the blastocyst stage at rates similar to that after control ICSI.