New NCCN Guidelines for Vulvar Cancer

Presented by Benjamin E. Greer, MD, and Wui-Jin Koh, MD

Abstract

For the first time, NCCN Guidelines are available for vulvar cancer, a rare gynecologic cancer. Early-stage cancers can be managed by surgery and observation, and many of these patients can be cured. Lymph node status drives treatment and correlates with survival. Positive groinal nodes require additional therapy, including radiation plus chemotherapy, depending on stage. Sentinel lymph node biopsy is recommended in selected patients.

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Vulvar cancer is rare. There are about 6,000 cases of vulvar cancer a year and 1,110 deaths," said Benjamin E. Greer, MD, Professor at Fred Hutchinson Cancer Research Center and Co-Chair of the new NCCN Guidelines Panel for Vulvar Cancer. Dr. Greer presented information on the new guidelines at the recent NCCN 21st Annual Conference.

Based on 2 published randomized trials and a number of observational studies, the guidelines incorporate TNM staging based on tumor size, nodal status, extent of positive nodes, and International Federation of Gynecology and Obstetrics (FIGO) staging.

"Survival depends on nodal status," Dr. Greer continued. He said that estimated survival is 70% to 80% with negative lymph nodes and 30% to 40% with positive lymph nodes in the groin. Over the years, treatment modifications have reduced morbidity and improved quality of life for patients with vulvar cancer. Modifications include regional lymph node management for unilateral cancers, radical local excision, separate groin incision, lymphatic mapping, radiation, chemotherapy, and exenteration.

Presented by Benjamin E. Greer, MD, and Wui-Jin Koh, MD, University of Washington/Seattle Cancer Care Alliance, Seattle, Washington.

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Correspondence: Benjamin E. Greer, MD, University of Washington/Seattle Cancer Care Alliance, 4405 50th Avenue NE, Seattle, WA 98105. E-mail: bengreer@u.washington.edu

Wui-Jin Koh, MD, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, 825 Eastlake Avenue E, G1-101, Seattle, WA 98109. E-mail: wkoh@u.washington.edu

Surgery

The goal of primary surgery is to obtain an adequate negative margin of 1 to 2 cm, Dr. Greer told the audience. Early-stage tumors (T1, smaller T2) are biopsied and treated according to size. "Early-stage disease is often cured by surgery alone," Dr. Greer continued.

Microinvasion, defined as tumors smaller than 1 mm, should be treated with wide local resection and observation. Tumors larger than 1 mm are treated according to site. Both vulvar midline lesions and lateral lesions (>2 cm from vulvar midline) are treated with lateral local resection or modified radical vulvectomy; vulvar midline lesions require bilateral inguinofemoral node evaluation and sentinel lymph node biopsy (SLNB) or bilateral inguinofemoral lymph node dissection (LND). Lateral lesions should have ipsilateral groin node evaluation plus SLNB or ispsilateral groin LND. LND is performed through a separate incision, Dr. Greer noted.

SLNB is advisable only in selected patients. Criteria for patient selection include unifocal tumor less than 4 cm, clinically nonsuspicious nodes in the groin, no previous vulvar surgery, and adequate surgical experience and resources for the physician to perform the procedure properly.

Primary Treatment

The primary tumor is assessed after surgery, and nodal surgical pathology drives treatment. Postoperative radiation is given to patients with node-positive disease. Radiation with concurrent chemotherapy is advised for

patients with inoperable carcinomas. Chemotherapy agents used concurrently with radiation include cisplatin, 5-FU and cisplatin, and 5-FU plus mitomycin C. For advanced, recurrent, or metastatic disease, chemotherapy should include cisplatin, cisplatin/vinorelbine, or cisplatin/paclitaxel.

"The site of the cancer matters," said Wui-Jin Koh, MD, Professor at Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance and Co-Chair of the NCCN Vulvar Cancer Panel. "Primary site and groin sites are considered separately. Metachronous groin failure occurs early and these are rarely curable, while local vulvar failures occur later and are often cured with additional surgery."

"Studies have shown that not all groin failures are fatal. The vast majority of experts believe you need to control groin disease," he said.

For early-stage tumors, adjuvant radiation is an effective treatment modality that significantly decreases recurrence in surgically resected groins with positive lymph nodes, leading to improved relapse-free and overall survivals, Dr. Koh said. Nodal involvement at presentation is the strongest independent predictor of relapse.

"Chemotherapy given concurrently with radiation may provide additional benefit, especially in advanced, unresectable disease and patients with multiple positive lymph nodes. However, the role of chemotherapy in addition to radiation given concurrently remains unclear," Dr. Koh continued.

The randomized GOG 37 trial, conducted in the late 1980s, included patients with fairly advanced lymph node–positive vulvar cancers who were randomized to undergo bilateral pelvic node dissection versus bilateral groin/pelvic radiation.[1] An interim analysis showed that the 2-year survival rate was 68% in women treated with radiation versus 54% for those treated with pelvic LND. This was a significant advantage (P=.03) manifest primarily as groin control.

Posthoc analysis of that trial and a longer-term follow-up of 74 months[2] suggested that patients who derived the most benefit from radiation had more than 2 positive nodes or N2 (palpable suspicious lesion)/N3 (fixed ulcerated node), Dr. Koh said. Today's staging (Figure 1) considers N3 as extracapsular extension and N2 as gross disease, Dr. Koh noted. He stated that selecting patients for adjuvant therapy is challenging. Rather than look at the total number of nodes, he suggested using a ratio of the number of positive nodes per side divided by the number of resected nodes. "This may allow for better selection for adjuvant radiation," he finished.

If the SLNB is negative, observation is the standard of care. If the SLNB is positive, radiation is given for sentinel lymph nodes less than 2 mm; for sentinel lymph nodes larger than 2 mm, more aggressive treatment, including chemotherapy, can be considered.

Nodes larger than 2 mm have a poor prognosis. Microscopic staging and size of 2 mm are useful cutoffs for decision-making, Dr. Koh said.

Dr. Koh explained that in older trials, radiation treatment was given to a depth of 3 cm, which is inadequate. "Very few groin nodes lie within 3 cm of the skin," he noted. In today's environment, the standard of care is to use CT-based treatment planning to determine radiation field and dose. Predictors of vulvar relapse are a tumor-free margin less than 8 mm, tumor thickness and depth of invasion greater than 10 mm, spray pattern histology, and vascular space invasion.

"In my practice, I don't radiate the vulva," Dr. Koh said. "Radiation to the vulva can cause significant morbidity. I use adjuvant radiation at the primary site if the patient is not a candidate for further surgery." There is no phase III data on whether chemotherapy is of benefit for groin lymph node disease. "These patients have a poor outcome, with 2-year survival of 23%, and tend to be elderly with significant medical comorbidities," he said.

Locally Advanced Disease

Dr. Koh also discussed treatment for locally advanced disease. For locally advanced disease, neoadjuvant radiation typically given with chemotherapy results in significant clinical and pathologic responses, allowing for reduced scope, nonexenterative surgery.

Patients with locally advanced disease should not be treated with organ-sparing surgery up front. Preoperative chemoradiation can convert unresectable tumors to resectable, Dr. Koh said. He further noted that inguinal/femoral LND is included in the NCCN Guidelines for locally advanced disease.

"Treatment of vulvar cancer requires large volumes of radiation. There is a tendency to want to use IMRT [intensity-modulated radiation therapy], but I advise physicians to be cautious about using small volumes," Dr. Koh continued.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016 Staging Vulvar Cancer (Squamous Cell Carcinoma)

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Discussion

Table 1 **AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Vulva**

Primary Tumor (T)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1a	A	Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less**
T1b	IB	Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2***	II	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T3****	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

*Note: FIGO no longer includes Stage 0 (Tis).
**Note: The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
***FIGO uses the classification T2/T3. This is defined as T2 in TNM.
****FIGO uses the classification T4. This is defined as T3 in TNM.

Regional Lymph Nodes (N)

TNM Categories	FIGO Stages	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph nodes with the following features
N1a	IIIA	1 or 2 lymph node metastases each 5 mm or less
N1b	IIIA	One lymph node metastasis 5 mm or greater
N2	IIIB	Regional lymph node metastasis with the following features
N2a	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases 5 mm or greater
N2c	IIIC	Lymph node metastasis with extra-capsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis

Distant Metastasis (M)

TNM Categories	FIGO Stages	
M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

ST-1

Figure 1. AJCC and International Federation of Gynecology and Obstetrics staging used in the new NCCN Guidelines for Vulvar Cancer.

"There is a debate in the guidelines about whether you should go straight to radiation for locally advanced disease. Today's standard of care is probably weekly platinum with concurrent radiotherapy for positive lymph nodes," Dr. Koh said.

A biopsy of the tumor bed should be considered to confirm pathologic complete response for patients who are clinically negative for residual tumor at the primary site and nodes.

"Full nodal dissection is a contentious issue," Dr. Koh commented. "My preference is upfront chemoradiation and then dissect the nodes later. The guidelines give you both options."

References

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