ASTRO
TARGETING CANCER CARE

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Peter E. Clark, MD
Chair, NCCN Penile Cancer Guidelines (Version 2.2015)
Associate Professor of Urologic Surgery
Vanderbilt Ingram Cancer Center
Nashville, TN 37232

Dear Dr. Clark,

The American Society for Radiation Oncology is pleased to provide the results of an exhaustive review of the NCCN penile cancer guidelines. Our penile cancer experts reviewed the guidelines for gaps relative to radiation therapy (appropriate modality, dose, timing, etc.) and offer the attached recommendations supported by evidence-based rationale for your consideration when the NCCN Penile Cancer Guideline Panel convenes in October.

We are excited about the prospect of contributing to the quality of cancer care for patients undergoing treatment for penile cancer. The attached document provides a summary of the findings, recommendations and rationale from the evaluators. In the meantime, if you have any questions or concerns, please contact Nadine Eads, Director of Quality Improvement, at nadinee@astro.org.

Sincerely,

Laura Thevenot

Laura I. Thevenot
CEO

AMERICAN SOCIETY FOR RADIATION ONCOLOGY
8280 WILLOW OAKS CORPORATE DRIVE • SUITE 500 • FAIRFAX, VA 22031 • 800.962.7876 • 703.502.1550 • FAX: 703.502.7852
www.astro.org • www.rtanswers.org

Introduction
To summarize our findings, we feel strongly that data from other disease sites, vulvar cancer in particular, suggest that chemoradiation has an important role to play in the management of penile cancer. The absence of data looking at chemoradiation for penile cancer is challenging for all of us. However, pending results from the International Advanced Penile Cancer Trial (InPACT) sponsored by the International Rare Tumors Initiative, and currently under consideration at NCI , we do believe there is sufficient reason to include chemoradiation in several of the guideline algorithms, albeit labeled as level 3 evidence.

We also would like to add a general philosophical recommendation to the Overview (MS-2) that because of the rarity of the disease and the severe emotional and physical consequences of treatment, patients should be referred, and encouraged to travel, to centers of expertise for best results. The external radiation component of treatment is complicated and brachytherapy for organ-sparing requires technical expertise that is not available in the community.

Below are the findings, recommendations and rationales from the evaluators.

Finding One: *Primary Treatment T1, T2 or Greater (PN-2),* page PN-2

Recommendation: Remove 'T2 tumors only'

Rationale: T3 and T4 tumors may be treated with radiation, particularly if chemotherapy is used. Treatment of the primary tumor has not been shown to correlate with survival. Nodal disease correlates with survival. Patients who undergo radiation therapy to the primary and relapse at the primary site are almost always salvageable with penectomy.

References:
Zouhair A et al. Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis. Europ J Cancer 2001;37: 198-203

Soria JC et al. Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in a monocentric study with a conservative policy. Ann Oncol 1997;8: 1089-1098

Sarin R et al. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 1997;38: 719-722

Finding Two: *Management of bulky/unresectable inguinal nodes and management of enlarged nodes,* page PN-5
A) "Management of bulky/unresectable inguinal nodes"
- Multiple or bilateral inguinal LN mobile or fixed
- Needle biopsy positive
- Neoadjuvant chemotherapy

B) "Management of enlarged potentially resectable pelvic nodes"
- Pelvic nodes enlarged
- Potentially resectable
- Needle biopsy positive
- Neoadjuvant chemotherapy with paclitaxel, ifosfamide and cisplatin (TIP)

Recommendation: Add neoadjuvant chemoradiation.

Rationale: Presumably there is concern over the risk of morbidity should the nodes become resectable. This is very reasonable. Similar to women with locally advanced vulvar cancer, men with advanced penile cancer tend to be older and can have significant comorbidities. Men with a smoking history, diabetes or vascular disease may be at greater risk of morbidity. However, on the basis of the Gynecologic Oncology Group (GOG) guidelines and many Phase II studies in vulvar cancer, chemoradiation *has become integral* to the management of locally advanced vulvar cancer.

Q: Is chemoradiation safe when given before surgery/inguinal lymph node dissection (ILND)?
Again, we will use examples from the gynecologic oncology literature to address this point. A very early GOG trial looked at preoperative chemoradiation in 46 women with unresectable N2/N3 vulvar cancer. In that study, only 20 patients had a GOG performance status of 0. All patients were treated with simple two-field beam arrangements. Thirty-seven of the initial 46 patients underwent lymph node dissections. Two patients died in the postoperative period. Seven who developed wound breakdown following surgery all healed with conservative management. These patients were enrolled between 1989 and 1994. Since the time of that study (1989-1994), radiation techniques have evolved significantly. With the advent of intensity-modulated radiation therapy (IMRT), dosimetric modeling studies performed on vulvar cancer patients reveal a dramatic advantage over the older 2-field approaches used before IMRT.

In GOG 101, 12 women with unresectable inguinal nodes received chemoradiation to modest doses. Although their toxicity is not reported separately from that of the other 46 women in the study, overall there were only 2 patients who reported 'lymphatic' toxicity (both grade 1) and 12 who reported 'other' skin toxicity (not defined); of these, 10 were grade 1 or 2. These patients did not receive IMRT.

In a study from Pittsburgh reported on 18 patients treated with preoperative chemotherapy combined with IMRT followed by surgery. Seven patients had an ILND. All had minor lymphedema following treatment. One patient required a surgical drain for three months. There were no other complications.

The small numbers of treated patients are frustrating and explained best by the fact that like penile cancer, vulvar cancer is rare. Unlike the situation with penile cancer, within the gynecologic oncology community there is great enthusiasm for the use of chemoradiation. High complete response rates, which range from 60-70% even in advanced disease, have lead the gynecologic oncology community to move away from the morbid radical vulvectomy and ILND to organ preservation with surgery reserved for those who don't respond to their initial therapy provided they don't develop early metastatic disease, as so often occurs in non-responders. It is for this reason that we propose considering this approach in penile-cancer patients but agree it should be labeled 'level 3.'

References:
Montana GS et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2000;48: 1007-1013

Beriwal S et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. Int J Radiat Oncol Biol Phys 2006;64: 1395-1400

More DH et al. 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. Gyne Oncol 2012;124: 529-533

Beriwal S et al. Preoperative intensity-modulated radiation therapy and chemotherapy for locally advanced vulvar cancer. Gyne Oncol 2008;109: 291-295

Finding Three: *Management of Recurrent Disease*, on page PN-7
"Local recurrence in inguinal region"

- Consider systemic chemotherapy and/or
- Consider radiation therapy and/or
- Consider surgical resection

Recommendation: We wouldn't recommend radiation therapy alone, except in patients too ill to receive chemotherapy. Could an asterisk be added with a comment such as *Chemoradiation recommended in all patients except those who cannot receive chemotherapy?

Finding Four: *Primary Margin Site Positive*, page PN-B
Brachytherapy in select cases

Recommendation: We would only recommend brachytherapy following wide excision of a small primary tumor with positive margins or after an excisional biopsy, and only in a brachytherapy center of excellence. We do not know if the latter concept can be added to the NCCN guidelines but do view it as very important. Could an asterisk be added with a comment such as "*Brachytherapy is not recommended following penectomy or partial penectomy but could be performed in experienced hands following wide local excision or excisional biopsy of small lesions, see Crook J et al. World J Urol 2009;27: 189-196 for details."?

Finding Five: *Chemotherapy*, page MS-8
"A patient who presents with resectable bulky disease will rarely be cured with a single treatment modality."

Recommendation: Please consider adding chemoradiation.

Rationale: Much of the basis for recommendations for neoadjuvant chemotherapy appear to be the MDAnderson Cancer Center experience with cisplatin-based chemotherapy for advanced penile cancer as reported in the Journal of Clinical Oncology in 2010 by Lance Pagliaro. The median age of the 30 subjects in this study was 57 years with a range of 24-78. This implies a degree of patient selection, which was necessary as cisplatin was used along with ifosfamide and paclitaxel. The complete response rate was 10% and the partial response rate was 40%. The median time to progression considering all patients was 8 months and 60% of the patients died, but the median follow-up for all patients was not given. True, responders did better than non-responders but this fact is not unique to this study or this patient population. It may be reasonable to compare this data to complete and partial response rates seen in one or two other squamous cell carcinomas treated with chemoradiation.

Briefly, shown below are the data from two prospective randomized trial in other squamous cell malignancies looking at responses to chemoradiation. In the GOG 205 trial, the complete pathological response rate at the vulvar primary site among all evaluable patients, and among patients experiencing a complete clinical response, was 50% (29/58) and 78% (29/37), respectively, allowing these patients to avoid radical vulvectomy and in many cases colostomy and cystectomy with ileal loop formation. The trial presented by the European Organization for the Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups was one of three early prospective randomized trials in anal cancer

demonstrating that chemoradiation was associated with high rates of pathologic complete response and allowed avoidance of colostomy for either tumor persistence, progression or side effects in the majority of patients. Like the early GOG trials, the early anal cancer trials changed the management of anal cancer completely. We selected a few trials for presentation for the sake of brevity but there are many others that could have been included.

Author	Tumor	No Pts	CR Rate	Median Age and Range	Median Time - Progression
Moore GOG 205	Vulvar preop chemorads with surgical salvage	58	Primary: 37 evaluable cCR* 64% 34 biopsied 78% pCR**	4<40 yo 14 > 70 Median NS***	NS Median FUp[#] 24.8 mo 35 alive 25 DCD[##]
Bartelink 1987-1992	Anal chemorads vs. radiation with surgical salvage	103	cCR 96% chemorads vs. 80% rads	56 pts < 60 47 pts ≥ 60	Median Fup 48 mo (9-88 range) 6 colostomies[$] chemorads 15 colostomies radiation

*clinical complete response
** pathologic complete response
*** not stated
[#]follow-up
[##]dead with disease
[$]Early in study, 15 off-protocol colostomies performed, all patients had pCRs

References:

1. LC Pagliaro et al. Neoadjuvant Paclitaxel, Ifosfamide, and Cisplatin Chemotherapy for Metastatic Penile Cancer: A Phase II Study. J Clin Oncol 2010;28: 3851–3857.
2. More DH et al. 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. Gyne Oncol 2012;124: 529-533

3. Bartelink H et al. Concomitant chemotherapy and radiotherapy is superior to radiation therapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for the Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997;15: 2040-2049