Is lymphadenectomy indicated in patients with T1 moderately differentiated penile cancer?

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MALHOTRA SM, ROUSE RV, AZZI R, REESE J. Is lymphadenectomy indicated in patients with T1 moderately differentiated penile cancer? The Canadian Journal of Urology. 2009;16(6):4895-4900.

Objective: *In patients with penile squamous cell carcinomas (SCCs), lymphadenectomy can be curative and should be considered in cases deemed high risk for metastatic spread to regional lymph nodes. Management of patients without palpable lymphadenopathy remains controversial. Current guidelines for T1 penile SCCs based on previous studies have suggested that moderately differentiated tumors are at low risk for metastatic disease; however given our experience with such patients we sought to examine whether such tumors were truly observable or should be treated more aggressively.*

Materials and methods: *A retrospective chart review of penile cancer cases at three institutions was performed. All slides of patients diagnosed with T1 lesions were rereviewed by our reference pathologists to confirm the original diagnosis and stage. These patients were also reviewed regarding lymphadenectomy results and clinical outcomes.*

Results: *Between 1988 and 2004, a total of 34 cases of SCC of the penis were identified, of which 10 were stage T1. Of these 10 cases, seven had moderately differentiated carcinoma without vascular invasion on pathological evaluation. Metastatic disease was present in one patient at the time of diagnosis and subsequently developed in three of the remaining six patients during follow up. Thus a total of 4 (57%) of the patients developed metastatic disease.*

Conclusions: *Current management protocols place moderately differentiated T1 penile squamous carcinoma without vascular invasion in a low risk category for metastatic disease. As such, expectant management is currently offered as a primary option for these patients. Our experience suggests that patients in this category are in fact at higher risk for metastatic disease, and may be offered early groin dissection in place of expectant management.*

Key Words: penile cancer, moderately differentiated, lymphadenectomy

Introduction

In patients with penile SCC, the presence and extent of metastatic disease involving the inguinal lymph nodes are the most important factors in determining patient survival. Lymphadenectomy can lead to cure in select cases and is thus a clearly important consideration in the treatment of appropriately selected patients. Lymphadenectomy is indicated in any patient with T2-T4 disease (invasive into the corpus spongiosum/cavernosum, urethra, prostate or adjacent structures). Additionally, lymphadenectomy is advised in stage T1 patients presenting with lymphadenopathy that does not resolve after a 4-6 week course of antibiotics, in T1 patients with poorly differentiated disease or vascular invasion and in T1 patients with initially clinically negative nodes who develop palpable nodes.[1,2] Patients who initially present as stage T1 with palpable adenopathy that resolves on antibiotics are candidates for node sampling. However, in patients with clinically negative groin exams at the time of presentation, the role of groin dissection is controversial.

Five year survival rates with inguinal lymphadenectomy when nodes are positive for malignancy may approach 80% in some series,[1,2] but enthusiasm for dissection in all patients is tempered by the substantial morbidity the procedure can produce. Complications such as severe lymphedema of the lower extremities and scrotum, pulmonary embolism, wound infection, skin flap necrosis or phlebitis can

Accepted for publication July 2009

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all occur.[1] Furthermore, if routine lymphadenectomy were performed in all patients with clinically negative nodes, 70% of them would be subject to the morbidity of the operation with no benefit (no metastasis present).[2] The alternative therefore is to watch such patients and reserve node dissection for patients that develop palpable nodes. The development of asynchronous nodal disease, however, decreases survival by up to 60%.[2]

Current North American guidelines[1,2] recommend observation for patients with pT1 lesions that are well or moderately differentiated with no evidence of vascular invasion, as these individuals are thought to be at low risk for metastatic spread. The European guidelines on penile cancer place T1 moderately differentiated cancer in an intermediate risk category but do not recommend a specific treatment.[3] Our own clinical experience would suggest that such patients are at higher risk for metastatic spread than believed and may not be good candidates for observation.

Materials and methods

A retrospective chart review of patients with penile SCC was performed, revealing 34 patients treated at Stanford University Medical Center, Santa Clara Valley Medical Center and the Palo Alto Veterans Hospital. Patients with T1 disease had their histopathology slides rereviewed by two reference pathologists to confirm the original diagnosis and grade and stage of the lesion. A modified Broder's system of grading (well, moderate, poor) was used to classify the tumors.[4] Figure 1.

Patients were staged according to the AJCC TNM staging system. These T1 patients were then reviewed regarding clinical outcomes and lymphadenectomy results where appropriate.

Results

Between 1988 and 2004, 34 cases of SCC were identified and treated at the three institutions. Of these 34, 10 (29%) were classified as T1 lesions. All patients underwent partial or total penectomy with local control of disease and no evidence of local recurrence. Of these 10 cases, three cases were initially interpreted as well differentiated carcinoma, but on pathological rereview one was noted to be poorly differentiated with vascular invasion. Seven cases were initially classified as having moderately differentiated carcinoma without evidence of vascular invasion on pathological evaluation. On reexamination by our reference pathologists, one was found to have a small focus (< 5%) of poorly differentiated disease, otherwise reexamination confirmed moderately differentiated SCC without vascular invasion in all seven cases. Either at presentation (1) or during subsequent follow up (3), metastatic disease developed in four of these patients (57%), with inguinal lymph node dissections revealing carcinoma, Table 1. Of the four patients that presented with metastatic disease one had inguinal metastases at the time of presentation, the others presented at 4 months, 5 months and 9 months after the initial penectomy.

TABLE 1. **Clinical and pathologic features of T1 moderately differentiated penile squamous carcinomas**

Patient	Nodal status on presentation	Initial pathology	Pathology on review	Clinical outcome minimum 48 mths follow up
1	Initially (-); developed (+) nodes	Moderately differentiated	Moderately differentiated	NED
2	Negative nodes	Moderately differentiated	Moderately differentiated	NED
3	Initially (-); developed (+) nodes	Moderately differentiated	Moderately differentiated with poorly differentiated focus	Deceased of disease
4	Initially (-); developed (+) nodes	Moderately differentiated	Moderately differentiated	Deceased of disease
5	Positive nodes on presentation	Moderately differentiated	Moderately differentiated	NED
6	Negative nodes	Moderately differentiated	Moderately differentiated	NED
7	Negative nodes	Moderately differentiated	Moderately differentiated	Deceased by other cause

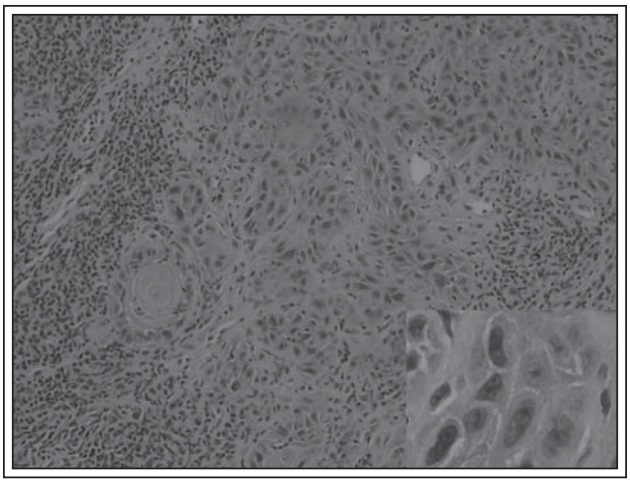

Figure 1. Infiltrating moderately differentiated squamous carcinoma showing keratin pearl formation and intercellular bridging (inset). Magnification x 100 (inset x 400).

Discussion

Previous data gathered from analyzing histopathological variables within primary penile lesions have led to classification of patients into various risk groups for lymph node metastases.[5-8] Patients with carcinoma in situ or verrucous carcinoma have been classified as having minimal or no risk for metastasis. Patients with T2 disease involving the corporal bodies or T3 disease involving the urethra or prostate are at high risk for spread of disease whether or not palpable adenopathy is present.

The data concerning T1 moderately differentiated tumors is less clear. Attempts to examine stage, grade, vascular invasion and other factors have been made in an effort to decide which penile cancer patients should undergo inguinal node dissection and which should not. Patients with stage T1 disease, involving the subepithelial connective tissue only, have previously been associated with 4%-14% incidence of nodal metastasis.[8-10] One exception to this was a study by Theodorescu et al,[6] who noted 58% (14/24) of patients with T1 disease and initially clinically negative nodes who developed subsequent inguinal nodal metastases. However, stratification for stage did not reach statistical significance and only tumor grade was statistically significant in predicting nodal recurrence. There was no evaluation of vascular invasion included in this study. Patients with well differentiated tumors were at decreased risk for metastasis versus those with moderately or poorly differentiated disease. Their data suggested that all patients with non well differentiated tumors harbored micrometastases from the time of treatment of the primary lesion, and the authors concluded that all patients with non well differentiated disease should undergo prophylactic lymphadenectomy.[6]

Tumor grade has also been examined as a predictor of the likelihood of nodal metastasis. In a study by Fraley et al, 1 of 19 patients with well differentiated tumors, 5 of 19 with moderately differentiated tumors and all 16 of 16 patients with poorly differentiated tumors developed nodal metastases. All T1 patients had well differentiated carcinoma. Vascular invasion was also studied in this paper. Eleven patients with moderately or poorly differentiated disease were noted to have vascular invasion, of which only one was reportedly cured. The authors concluded that moderately and poorly differentiated tumors were at high risk for inguinal node metastasis. In such patients they recommended immediate lymphadenectomy regardless of stage. [11]

Horenblas et al[12] showed that 17 of 59 patients (29%) with grade 1 lesions, 13 of 28 patients (46%) with grade 2 lesions, and 9 of 11 (82%) of grade 3 lesion patients had nodal involvement or developed it within 2.5 years. However, data is not provided as to the individual stages of each differentiation category; whether any patients with T1 moderately differentiated (grade 2) lesions developed metastasis is uncertain. The authors only state that while their experience with poorly differentiated T1 tumors is limited, that the probability of regional recurrence did not differ between well or moderately differentiated stage T1 tumors, implying that the risk for metastasis in any T1 lesion is low. They recommended surveillance of patients who present with unsuspected (clinically negative) nodes and stage 1 tumors, regardless of tumor grade.

Ornellas et al[13] reported on 414 patients seen between 1960 and 1987, and noted that patients with well and moderately differentiated disease had a higher survival rate at 5 years than did those with poorly differentiated carcinoma. There was no significant difference noted between well and moderately differentiated disease. Of their 56 patients with T1 disease, 10 had nodal metastases, but information regarding the differentiation of those particular tumors was not given.

A study combining the analysis of grade and stage was published by McDougal[5] in 1995. He reported on 24 patients with well or moderately differentiated noninvasive tumors, of which only one developed regional metastasis. Patients who presented with such disease and negative nodes were observed and none developed recurrence with an average follow up of 8

years. Of the eight patients who presented with such tumors and persistently palpable lymph nodes after a course of antibiotics 1 (12%) had regional spread, although four did not undergo node dissection and were instead followed for an average of 7 years. The author concluded that the risk of developing regional spread in lesions that were well or moderately differentiated and noninvasive was low (4% in his series) and did not warrant lymphadenectomy.

Another retrospective review of 48 patients by Slaton et al[14] examined both stage and grade in evaluation of the risk of developing inguinal lymph node metastases. Median follow up for the patients was 59 months. The authors found that pathological stage of the tumor (T2 or greater), the presence of vascular invasion, and having greater than 50% poorly differentiated cancer on resection of the primary lesion were independent prognostic factors for metastases. None of their 15 patients with T1 lesions exhibited metastases, regardless of histological grade, including two patients with more than 50% poorly differentiated disease. None of these patients demonstrated vascular invasion, either. They concluded that patients with T1 lesions without palpable adenopathy or vascular invasion and less than 50% poorly differentiated disease were "optimal candidates" for watchful waiting.

The importance of vascular invasion was demonstrated in a publication by Lopes et al[7] in which 145 patients were followed for a median of 33 months. Venous and lymphatic invasion were the only prognostic factors statistically significant in the incidence of lymph node metastasis. In this study, stage and grade were not correlated with lymph node metastasis on univariate or multivariate analysis.

Finally a recent study by Ficarra et al[115] evaluated 175 patients from 11 centers in Northern Italy and developed a nomogram to predict the risk of nodal metastasis in patients with penile carcinoma. Although they did not specifically look at T1 grade 2 tumors, such a tumor without vascular invasion would carry a risk of nodal disease in 5% to as high as 20% depending on the thickness of the tumor and pattern of spread.

Careful review of the literature provides conflicting opinions as to the risk of nodal metastasis in T1 lesions. Current consensus appears to have led to the conclusion that among patients with T1 grade 1-2 (well to moderately differentiated) carcinoma, the risk of metastasis is low in the absence of vascular invasion. Such candidates, if reliable and compliant, are considered optimal candidates for watchful waiting.[1,2] However, our experience in patients with T1 moderately differentiated carcinoma has revealed a disturbingly high (57%) rate of metastatic spread either at presentation or during follow up, matching the findings of Theodorescu.[6] Our review of the literature suggests that considerable biologic variability exists among moderately differentiated tumors. This could be due to true molecular differences among this category of tumors or to differences in histologic grading by the pathologist. In our own series we found one of our patients with metastases had a tiny focus of high grade tumor that had been missed during the original pathologic review. While the morbidity of groin dissection is well documented, complication rates in the hands of an experienced surgeon using modified inguinal lymphadenectomy should be acceptably low and offer a chance to properly stage and potentially cure patients. As evident in the review of the literature above, there appear to be two camps regarding patients with moderately differentiated T1 penile cancer without vascular invasion: those who believe such patients are at high risk for metastasis and those who feel such patients are at low risk for spread. Our clinical experience and data leads us to cast our vote with the former. The risk of missing occult disease outweighs the possible complications of surgery if T1 moderately differentiated disease is more likely to metastasize then historically thought. It is possible in the future that tests such as dynamic sentinel node biopsy may better distinguish those at highest risk in this select group of patients. Until that time we would advocate groin dissection in T1 moderately differentiated tumors.

Additionally, it is possible that histopathological specimens may be misinterpreted or that small foci of higher grade disease or vascular invasion may be missed. This was noted during the reexamination and restaging in our series in two of the 10 T1 cases. Such findings are potentially important and could identify a greater risk of metastasis. Our study highlights the necessity of having the slides examined meticulously by an experienced pathologist, and reviewed and confirmed to properly grade and stage disease. Even in the setting of mostly well or moderately differentiated disease, areas of poorly differentiated disease or evidence of vascular invasion should bias the surgeon towards groin dissection. Limitations of our study include the size of the cohort. It should be noted however that most of the studies referenced do not have significantly higher numbers of patients in the T1 grade 2 subgroup than in our study.[2]

Conclusions

Patients with moderately differentiated T1 penile SCC without vascular invasion may not be at low risk for metastatic spread as previously believed. Our data,

supports the findings of previously published series that suggest T1 moderately differentiated patients are at high risk for developing nodal metastasis. Instead of expectant management, we believe such patients may be offered early groin dissection. □

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EDITORIAL COMMENT

The management debate continues!

In order to decrease the morbidity of inguinal lymph node staging among patients with invasive penile cancer (and negative inguinal examinations) risk adapted strategies are now commonly used to select candidates who are at low risk for inguinal microscopic dissemination based upon primary tumor histology and anatomic structure invaded. There appears to be consensus that factors associated with a "high risk of metastasis" (i.e. ≥ 50% or more) include stage ≥T2, poorly differentiated tumors and those exhibiting vascular invasion. Alternatively it is also agreed that stage Tis, Ta, and T1 well differentiated tumors (aka grade 1) tumors are candidate for observation due to the low risk of metastatic disease (i.e., 0%-10%). Where the stage T1 grade 2 tumors should reside has been controversial to say the least[1] (references 2, 3, 5-6,14 in manuscript) related to the management implications of observation (i.e., no initial morbidity) versus prophylactic inguinal staging procedures (i.e., some potential morbidity) as management strategies.

The authors describe a small retrospective series of seven patients with stage T1 moderately differentiated penile cancer in who either had (n = 1) or developed (n = 3) metastatic penile cancer during follow up. Thus among the initially node negative group 3 of six (50%) developed metastatic disease within 9 months of follow up. Thus from the authors perspective these patients should be offered prophylactic inguinal staging. However to put this small series into perspective a recent study that specifically evaluated the risk of metastasis among T1 grade 2 tumors was published.[2] The value of this study is that it includes 117 tumors from two institutions that are very experienced in the evaluation and management of penile carcinoma. Overall the incidence of lymph node metastasis in this cohort was 13% and importantly among those that were lymph node negative the subsequent risk of metastasis with a median follow up of 44 months was only 9%. Thus based upon pathologists' interpretations at these institutions the biology of T1 grade 2 tumors was largely favorable and one could easily make an argument for careful observation of such patients to avoid dissection in 90% of patients that exhibited no palpable adenopathy.

The authors make the important observation that the controversy regarding the risk of metastasis in T1 grade 2 tumors could be either related to pathologic discrepancies related to grading or to molecular differences/tumor heterogeneity in what the pathologists recognize as a grade 2 tumor.

In order for us to improve the management of this specific subset of patients and all patients with invasive penile cancer and negative inguinal examinations two actions are required: 1) An expert panel of pathologists should re-examine the utility of the Broder's grading system[3] and other pathologic features to determine the optimal histological features associated with the risk of metastasis[4] and 2) Future definition of the molecular signature of metastasis at the mRNA or protein levels to further assist in stratifying tumors that appear histologically similar but that have different biologic potential. For the present however, it is incumbent for surgeons making management decisions regarding the inguinal lymph nodes to discuss the pathologic findings in the primary tumor with their pathologists to insure that adverse features that would favor an elective staging procedure are absent and importantly to offer surveillance strategies only to those compliant patients who will perform self examination and follow prescribed follow up visits. When a prophylactic staging procedure is performed it should be the one that the surgeon performs with expertise, accurately stages the patient, and minimizes morbidity. In this subset of patients we continue to balance maximizing cure with "doing no harm".

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REPLY BY AUTHORS

We agree with Dr. Pettaway's comments. However, as compelling as the recently published series may be (reference 2) the overall literature remains conflicted for those patients with T1 moderately differentiated tumors. Furthermore, even in that series metastatic disease was present in a significant (13%) number of patients. In a disease that remains only curable by surgery, and where delaying the surgery until metastases develop has been shown to significantly decrease survival, groin dissection must remain an important option for such patients.

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