Patient Reported Outcomes in Penile Cancer

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Research Article

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Abstract

Objective: Patient reports of their symptom burden (i.e., patient-reported outcomes or PROs) have been shown to direct clinicians’ ability to personalize care and improve outcomes. A disciplined assessment of PRO in the population of patients with penile cancer (PeCa) has not previously been undertaken. Our center has both a significant cadre of patients with PeCa and a significant experience with a well-established PRO: the Edmonton Symptom Assessment Scale (ESAS).

Methods: After IRB approval, we screened ESAS surveys of 14,781 patients completed between 2/2017 and 2/2021. Of these, those with PeCa were divided into three cohorts: (A) Those after any partial penectomy procedure without lymph node dissection (LND); (B) Those after partial penectomy procedure with LND; and (C) Those after total penectomy and LND. Patients with recurrent disease were analyzed separately. ESAS scores were collated and compared both by individual symptom and cumulatively.

Results: 22 PeCa patients completed 122 ESAS surveys in this time and are included in this analysis: a median of 4 ESAS surveys (mean=5, range=1-19) were completed by each patient. The symptom with the highest median ESAS score was Tiredness (3.00). Patients with recurrent disease had the highest cumulative symptom score (median score = 30). Patients after total penectomy with LND had a higher cumulative symptom score (14.4) than those with partial penectomy and LND (7.9).

Conclusions: PROs provide an insight into the morbidity of therapies for PeCa, and the most symptoms are reported by patients with recurrent disease.

Introduction

Patient-centered care mandates the knowledge of patient perspectives and concerns and their subsequent inclusion in any multidisciplinary therapeutic regimen. Modern patient-reported outcomes (PROs) serve a critical role informing the patient perspective as we assess objective clinical data; they correlate with diagnosis [1, 2], treatment response [3], and disease recurrence [4]. Assessment of PROs has become an important component of comprehensive oncological care since data reported by Basch and colleagues revealed improved survival and quality of life and fewer emergency room visits [5].

Our center has used PRO data specifically in the form of the Edmonton Symptom Assessment Scale (ESAS). Patients in our Radiation Oncology, Supportive Care and Head & Neck clinics fill these surveys out at each visit and results are transferred to the electronic medical record. Prior publications have analyzed ESAS data in patients with esophageal cancer [6], retroperitoneal sarcoma [7] and multiple myeloma [8], and in ruling out anemia [9].

Squamous cell carcinoma of the penis (PeCa) is a rare but highly aggressive tumor with the potential for early locoregional recurrence and distant metastasis even after multidisciplinary therapy [10]. There are no randomized data supporting post-operative radiotherapy routinely in PeCa [11, 12], although some recent data support its use in pathological N3 disease [13, 14]. Neoadjuvant chemotherapy is
recommended for patients with multiple, fixed, or bulky inguinal lymph nodes [11, 15]. Most of these patients with bulky or advanced disease will have disease recurrence. Unfortunately, patients with disease recurrence after cisplatin-based chemotherapy and surgical consolidation, have few treatment options with limited survival [16].

This manuscript attempts to define the role of PRO, specifically ESAS, in PeCa. The subject has not previously been investigated. Our clinical perspective is that penile sparing procedures will be better tolerated by patients, and that lymph node dissection, while crucially necessary, may be quite morbid.

**Patients And Methods**

**Survey**

This study was approved by the appropriate Scientific and Institutional Review Boards (Study MCC20731). The scale used for symptom burden assessment was a modified Edmonton Symptom Assessment Scale (ESAS-r-CSS) [16]. The ESAS-r-CSS surveys 12 symptoms (i.e., anxiety, constipation, depression, difficulty sleeping, drowsiness, lack of appetite, nausea, overall well-being, pain, shortness of breath, spiritual well-being, tiredness). An 11-point Likert-type scale from 0 (none) to 10 (worst possible) was used and symptom burden was collated in two ways: The sum of all scores (range 0-120) reflect total symptom burden, and values were also considered individually (range 0-10). All patients attending the Radiation Oncology and Supportive Care Clinics complete this survey at every visit except daily radiation treatments.

Because of the potential bias inherent in patients filling out multiple forms, results were grouped by patient (Table 2). This means we averaged survey scores of each patient and used the mean as that patient's value, rather than counting all the individual surveys by each patient as different surveys. Mean values between each cohort for each ESAS category were compared. Scores for each category were also compared between patients who were previously or never on radiation or chemotherapy and those currently on radiation (Table 3) or chemotherapy (Table 4).

**Population:**

At our center, PRO data are integrated with other patient and clinical data within the enterprise data warehouse: Health and Research Informatics (HRI). After Institutional Review Board approval, we queried HRI for all patients who completed an ESAS survey between February, 2017 and February 2021; 61,189 surveys from 14,781 patients were collected. Table 1 collates data for the 22 PeCa patients who completed surveys during this period. A total of 122 surveys were collected for a median of 4 completed surveys per patient (mean=5, range=1-19).

Patients were then divided into four cohorts: (A) Those after any partial penectomy procedure without lymph node dissection (LND); (B) Those after any partial penectomy procedure with LND; and (C) Those
after total penectomy and LND. Cohort D included patients with recurrent disease. Complications were quantified using the Clavien–Dindo (CD) classification system for surgical complications [17].

Results

Table 2-4 and Figures 1 and 2 summarize the ESAS survey data by patient cohort. Three patients were represented in two cohorts. Patient 3 was in cohort B until recurrence, subsequently his survey values were included in cohort D, as patient 20 was included in cohort C until recurrence, when his surveys were moved to cohort D. Similarly, Patient 9 was first evaluated in cohort A, then C, based on surgical history at the time of visit. In cohort A, of 4 patients, half were currently on chemotherapy, and three were on RT. In cohort B, of 6 patients, four were currently on chemotherapy, and two were on RT. In cohort C, half were receiving both chemotherapy and radiation currently. In cohort D, half were currently on chemotherapy, and one was receiving palliative RT.

In the entire patient cohort, the most common individual symptom was Tiredness, mirroring other work [18]. Cohort D had the highest cumulative symptom score (median 30; Figure 2), which is consistent with expectations for a cadre of patients with recurrent disease. Similarly, patients after total penectomy with LND had a higher median score (21) than those with partial penectomy and LND (5), in keeping with our theory that extent of surgery was a consideration in cumulative symptoms score. In Table 2, significant differences were noted across cohorts in mean scores for pain, tiredness, and overall wellness, with patients in cohort D having the highest scores.

When analyzed across all surveys without grouping by patients who took multiple surveys, results revealed a statistically significant difference across all cohorts for each category except nausea, and appetite. Notably, patients in cohort C and D had the first and second highest depression scores, respectively, compared to cohort A and B (mean scores 3.3 and 2.3 compared to 0.91 and 0.3, p<.0005). As noted above, this interpretation is subject to confounding by some patients contributing multiple scores.

Table 3 reveals that mean scores statistically differed between patients who had never received radiation compared to patients who previously or were currently receiving radiation for anxiety, depression, sleep, overall wellness and spirituality.

In Table 4, mean scores were statistically significantly higher for anxiety, nausea, depression and spirituality in those who had previously received chemotherapy. Patients currently receiving chemotherapy had the highest mean score for nausea.

Discussion

Patients with penile cancer are a challenging group to treat, both oncologically and psychologically. This malignancy can be highly aggressive, with high mortality rates once advanced, and local treatment is unfortunately mutilating and devastating [11]. Due to the rarity of this cancer, there is scarce level one
data on organ preservation, so men requiring penectomies are ultimately impacted both functionally and psychologically.

The high median symptom score for cohort A patients may be explained by the fact that 3 of the 4 were treated pre-operatively on the International Penile Advanced Cancer Trial (InPACT) trial [19], with known inguinal disease in these cases. InPACT is co-sponsored by the US National Cancer Institute and the UK Institute of Cancer Research. InPACT has a two-part construct: the first deals with the role of therapy prior to ILND and the second with management of the pelvis. The trial is well designed and to date has accrued over a quarter of the patient goal.

In our study, men who had undergone total penectomy (Cohort C) had the highest scores for anxiety and depression. While treatment varies significantly by stage at presentation, PeCa therapy has been shown to cause psychiatric symptoms in 50% of patients [20]. Ficarra and associates demonstrated that patients having more significant treatments were more likely to have impaired well-being [21], with rates of anxiety and depression as high as 58% and 39% respectively [22, 23]. Often men are confronted with the psychologic impact of a penectomy only after the intervention, which can lead to body image disorders, and negative changes in male identity, sexuality and partnerships [24].

The high risk of psychological trauma stemming from genital surgery leads to a need for more organ-preserving treatment when appropriate. Men who have undergone partial penectomy have reported normal to slightly reduced sexual satisfaction, and no significant levels of anxiety or depression [25]. Our patients who had undergone partial penectomy (Cohorts A and B) had lower rates of anxiety and depression combined, and better overall wellness scores. However, penile cancer of any extent is not without its own risk. One SEER analysis of 6155 patients with penile cancer found a suicide risk of 0.2%, all in men who had undergone a surgical intervention [26]. Early referral to a Supportive Care service is crucial for this patient population. Several studies show that early supportive/palliative care improves both quality and quantity of life in advanced cancer patients [27, 28] particularly in men [28].

**Conclusion**

Penile cancer is a disease with great psychologic implications. Management of this malignancy can be highly disfiguring, causing psychological trauma. Patients undergoing partial penectomy with LND have the fewest overall symptoms, and those with recurrent disease report the highest symptoms. Comprehensive care and support groups are critical in these patients.

**Declarations**

**Conflict of interest:**

There are no conflicts of interest to disclose.

**Funding:**
No funding was received for conducting this study.

**Ethics approval:**

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Moffitt Cancer Center.

**Consent:**

Informed consent was obtained from all individual participants included in the study.

**Authors contribution statement:**

Irini Youssef, MD: Writing, Methodology, Formal Analysis,
Aasha I. Hoogland, Ph.D.: Resources, Data Curation,
Jad Chahoud, MD, MPH: Writing
Philippe E. Spiess, MD: Writing, Supervision
Heather Jim, Ph.D.: Investigation, Validation, Writing, Supervision
Peter A. S. Johnstone, MD: Conceptualization, Investigation, Validation, Writing, Supervision

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**Tables**

**Table 1**: Demographics
| Pt # | Cohort | Age | Surveys completed | Complications? (C-D grade) |
|------|--------|-----|-------------------|---------------------------|
| 1    | A      | 46.2| 3                 | Y (I)                     |
| 2    | C      | 74  | 1                 | N                         |
| 3    | B -> D | 69.6| 10                | Y (IIIA)                  |
| 4    | D      | 68.7| 1                 | N                         |
| 5    | D      | 71.7| 6                 | N                         |
| 6    | C      | 43.5| 19                | N                         |
| 7    | D      | 88  | 3                 | N                         |
| 8    | A      | 62.9| 1                 | N                         |
| 9    | A -> C | 78  | 4                 | Y (IIIB)                  |
| 10   | B      | 73.1| 4                 | N                         |
| 11   | D      | 61.6| 4                 | Y (I)                     |
| 12   | B      | 51.7| 5                 | Y (I)                     |
| 13   | D      | 34.1| 11                | N                         |
| 14   | B      | 79.8| 1                 | N                         |
| 15   | B      | 47.5| 8                 | Y (I)                     |
| 16   | D      | 73.3| 1                 | N                         |
| 17   | C      | 59.1| 1                 | N                         |
| 18   | D      | 67.8| 11                | N                         |
| 19   | D      | 74.7| 1                 | N                         |
| 20   | C -> D | 75.8| 6                 | N                         |
| 21   | A      | 46.9| 4                 | N                         |
| 22   | B      | 49.2| 7                 | N                         |

Pt = patient; C-D= Clavien-Dindo

**Table 2:** Comparing grouped means between cohorts. In this analysis, surveys of each patient were averaged, and the mean value was used, rather than counting each individual survey by each patient as unique data. Significant values are **bolded**.
|                     | Cohort A | Cohort B | Cohort C | Cohort D | P-value |
|---------------------|----------|----------|----------|----------|---------|
| Breath              | 0.90     | 0.21     | 0.86     | 1.28     | 0.63    |
| Pain                | 0.94     | 1.32     | 1.97     | 4.82     | **0.00**|
| Tired               | 3.58     | 0.86     | 1.20     | 4.35     | **0.01**|
| Anxiety             | 1.27     | 0.68     | 1.14     | 1.57     | 0.75    |
| Nausea              | 2.17     | 0.47     | 0.25     | 1.94     | 0.46    |
| Depression          | 0.73     | 0.18     | 2.22     | 1.35     | 0.20    |
| Sleep               | 4.06     | 1.22     | 1.97     | 3.09     | 0.31    |
| Drowsy              | 3.40     | 0.54     | 1.84     | 1.93     | 0.28    |
| Appetite            | 1.85     | 1.29     | 0.36     | 3.62     | 0.12    |
| Constipation        | 1.67     | 0.07     | 1.15     | 1.05     | 0.52    |
| Overall Wellness    | 1.29     | 0.90     | 0.65     | 4.00     | **0.05**|
| Spirituality        | 0.06     | 0.13     | 0.75     | 0.68     | 0.50    |
| Sum                 | 21.85    | 7.86     | 14.35    | 29.68    | **0.02**|

**Table 3:** Mean symptom score by timing of radiotherapy. Significant values are **bolded.**
|                  | N  | C  | P  | P-value |
|------------------|----|----|----|---------|
| Breath           | 1.2| 0.8| 1.1| .716    |
| Pain             | 3.1| 1.6| 2.6| .065    |
| Tired            | 2.9| 2.9| 3.5| .638    |
| Anxiety          | 1.4| 1.6| 4.7| .000    |
| Nausea           | 1.1| 1.3| 0.7| .647    |
| Depression       | 1.5| 1.2| 4.4| .000    |
| Sleep            | 2.4| 2.3| 4.6| .015    |
| Drowsy           | 1.7| 1.8| 3.3| .065    |
| Appetite         | 1.6| 2.8| 1.6| .094    |
| Constipation     | 1.2| 1.5| 0.5| .307    |
| Overall Wellness | 2.0| 1.5| 3.5| .031    |
| Spiritual Score  | 0.8| 0.7| 3.7| .000    |
| Sum              | 20.8| 20.0| 34.3| .016    |

**Table 4:** Mean symptom score by timing of chemotherapy. Significant values are **bolded.**
|                  | N  | C  | P  | P-value |
|------------------|----|----|----|---------|
| Breath           | 1.48| 0.43| 0.94| .100    |
| Pain             | 2.40| 2.10| 2.86| .58     |
| Tired            | 2.81| 3.62| 2.86| .498    |
| Anxiety          | 1.52| 1.10| 2.86| .019    |
| Nausea           | 1.38| 2.14| 0.45| .019    |
| Depression       | 1.36| 0.95| 2.80| .006    |
| Sleep            | 2.14| 2.90| 3.24| .218    |
| Drowsy           | 1.90| 2.00| 2.06| .961    |
| Appetite         | 1.64| 2.33| 2.12| .586    |
| Constipation     | 1.24| 2.00| 0.71| .073    |
| Overall Wellness | 1.79| 1.67| 2.55| .280    |
| Spiritual Score  | 0.71| 0.52| 2.00| .006    |
| Sum              | 20.4| 21.76| 25.45| .437    |

Figures
Figure 1

Average ESAS Scores by Cohort and Category

Figure 2

Sum Score by Cohort
Sum Score by Cohort