Sexual Function in Cancer Survivors: Updates to the NCCN Guidelines® for Survivorship

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Cancer Treatments Impact Sexuality in Multiple Ways

- Surgery, radiation, chemotherapy, and endocrine therapies all impact sexual function.
- Rates of sexual dysfunction vary based on cancer type and treatments.
- Appropriate interventions to treat sexual dysfunction also vary based on cancer type.
  - Hormone replacement/supplementation is not an option for hormone sensitive cancers.

Impact of Surgery

- Oophorectomy results in acute estrogen and testosterone deprivation.
- Hysterectomy may result in changes in vaginal length/size.
- Prostate surgery may lead to erectile dysfunction and impotence.
- Breast and colorectal surgery impacts body image and self esteem.

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Impact of Chemotherapy

- Chemotherapy may cause nausea, vomiting, diarrhea, weakness and fatigue, all which may curb sexual desire.

- Supportive care medications (anti-emetics, pain meds, antidepressants) may also contribute to fatigue and decreased libido.

- Agents causing alopecia can impact body image detrimentally.

Impact of Endocrine Therapy

- Estrogen deprivation often results in:
  - Vasomotor symptoms
  - Sleep disturbance
  - Urogenital atrophy
    - Vaginal dryness/friability
    - Urinary frequency/incontinence/UTI

- Estrogen deprivation also associated with:
  - Mood changes
  - Hair and skin changes
  - Weight gain/redistribution
  - Decreased libido, inability to achieve orgasm
What is the evidence?

What are the issues?

**Early-stage cervical carcinoma, radical hysterectomy, and sexual function**

- 173 patients with LN-neg cervical carcinoma treated with radical hysterectomy (RH) and pelvic LND compared with an age-matched control group
- Self-assessment questionnaire from 5 weeks to 24 months after RH
- Patients experienced:
  - Severe orgasmic problems and uncomfortable sexual intercourse during the first 6 months after RH
  - Severe dyspareunia during the first 3 months
  - Sexual dissatisfaction during the 5 weeks after RH
  - Persistent lack of sexual interest and lubrication throughout the first 2 years after RH

Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer

- 81 women and 99 men who underwent curative rectal cancer surgery from 1980-2003 were administered either the Female Sexual Function Index (FSFI) or International Index of Erectile Function (IIEF), and the EORTC QLQ-C30/CR-38
- Fewer patients were sexually active after surgery
  - 32% of women and 50% of men were sexually active, compared with 61% and 91% preoperatively (P < 0.04)
- Both genders reported a negative body image
- Specific sexual problems in women were libido 41%, arousal 29%, lubrication 56%, orgasm 35%, and dyspareunia 46%
- In men, libido 47%, impotence 32%, partial impotence 52%, orgasm 41%, and ejaculation 43%
- Patients seldom were treated for dysfunction


Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study

- Study compared quality of life (QOL) changes over time in 763 disease-free breast cancer survivors (average 6.3 years from diagnosis)
- Hot flashes, night sweats, vaginal discharge, and breast sensitivity were less frequent than baseline survey
- Symptoms of vaginal dryness and urinary incontinence were increased
- Sexual activity with a partner declined statistically significantly between the two assessments (from 65% to 55%, P = .001)

Prevalence and correlates of sexual morbidity in long-term breast cancer survivors

- 83 breast cancer survivors median of 7 years post diagnosis
- Demographics, treatment information, sexual activity, sexual function (Female Sexual Function Index [FSFI]), body image, and distress (Female Sexual Distress Scale-revised; FSDS-R) were collected
- 77% of all and 60% of sexually active participants qualified for sexual dysfunction based on the FSFI
- Body satisfaction worse than normative values
- Sexual morbidity predictors included mastectomy (associated with worse sexual/body change distress)
- Post-treatment weight gain predicted greater body dissatisfaction and body change stress

Raggio GA et al. Psychol Health 2014;29:632-50

Acute effects of tamoxifen and aromatase inhibitors (AIs) on menopausal symptoms in breast cancer patients

- Prospective study of 181 consecutive postmenopausal women starting hormonal therapy
- Both first-line tamoxifen and AIs increased occurrence and severity of hot flashes
- Musculoskeletal pain and dyspareunia significantly increased with AIs
- Sexual interest decreased significantly with tamoxifen
- Younger age was associated with more hot flashes and vaginal dryness

Morales et al. Anti-Cancer Drugs 2004
### Changes in menopausal symptoms with AI vs. Tamoxifen

<table>
<thead>
<tr>
<th>Symptom</th>
<th>AI (Baseline)</th>
<th>AI (3 mo)</th>
<th>TAM (Baseline)</th>
<th>TAM (3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>54/46/0</td>
<td>23/69/8</td>
<td>52/44/4</td>
<td>13/64/23</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>36/57/7</td>
<td>18/46/36</td>
<td>56/40/4</td>
<td>40/53/6</td>
</tr>
<tr>
<td>Vaginal Dryness</td>
<td>67/32/0</td>
<td>50/46/4</td>
<td>65/27/8</td>
<td>53/32/15</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>68/21/11</td>
<td>37/37/25</td>
<td>74/18/8</td>
<td>50/38/12</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>63/21/16</td>
<td>31/37/31</td>
<td>53/37/10</td>
<td>21/32/47</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>45/50/5</td>
<td>53/47/0</td>
<td>35/56/8</td>
<td>27/64/9</td>
</tr>
</tbody>
</table>

(% with no or mild symptoms / moderate-severe symptoms / intolerable symptoms)

Morales et al. Anti-Cancer Drugs 2004

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**Sexual function is a major area of concern among cancer survivors**

- Is it safe to get pregnant after breast cancer?
- What can help my libido?
- Will periods come back after chemotherapy?
- Is vaginal estrogen safe?
- When should ovaries be removed?
- What are safe contraceptive options?
- Should ultrasound surveillance be done if I'm taking tamoxifen?
- When should endometrial biopsies be performed?
**The first step is to ask**

- Ask about sexual function at regular intervals (See screening questions on SURV-A)
- Discuss treatment-associated infertility if indicated, with appropriate referrals

**Screening questions do not indicate an issue**

- Re-evaluate and discuss potential impact of treatment on sexual function at future visits

**Screening questions indicate an issue, but survivor does not want to discuss further**

- Refer to sexual health specialist, if survivor is interested

**Screening questions indicate an issue and survivor wants to discuss further**

**H&P**
- Review oncologic history (diagnosis/stage, surgeries, systemic treatment, local RT, endocrine therapy)
- Consider use of a screening tool
- Explore treatment related impact on sexual function
- Assess for signs or symptoms of estrogen or androgen deprivation or refer to appropriate specialist
- Review medical history for conditions associated with sexual dysfunction (e.g., depression [See SANXDE-1 and NCCN Guidelines for Distress Management], diabetes, hypertension)
- Assess total morning testosterone in males as indicated
- Review medication list for drugs that impact sexual function (e.g., SSRIs, beta blockers)

**See Treatment for Females (SSF-2) or for Males (SSF-3)**
- Appropriate referrals for:
  - Psychotherapy
  - Sexual/couples counseling
  - Gynecologic care
  - Urology
  - Sexual health specialist, if available
Case Presentation

- 40 yo G2P2 female with a grade 3 3.8 IDC, ER+/PR+ Her2 neu negative; 4/7 LN involved
  - Treated with lumpectomy, adjuvant chemotherapy, (AC-paclitaxel), and radiation
  - Placed on an ovarian suppression and aromatase inhibitor
  - After 3 months, she has severe joint pain, hot flashes that disrupt sleep, and decreased libido
  - Intercourse is painful due to vaginal dryness
  - She is also upset about weight gain during and after chemotherapy
  - She would like treatment options for her many symptoms

G2P2: 2 pregnancies, 2 live births; IDC: invasive ductal carcinoma
Questions

1. What treatments should be suggested for hot flashes?

2. What can be offered for vaginal dryness and dyspareunia?

3. Is there ANY hope for her decreased libido?

4. At what point would you recommend oophorectomy in lieu of ovarian suppression shots?

Aromatase Inhibitors in Breast Cancer

- Trials in postmenopausal women have shown Al's to reduce risk of breast cancer recurrence compared with tamoxifen

- SOFT trial in premenopausal women showed superiority of OS+AI compared to tamoxifen or OS + tamoxifen (improved DFS)\(^1\)

- Optimal length of treatment is unknown - 5, 10, 15 years?

More younger women are being treated with longer courses of AI so we will be seeing more vaginal dryness and sexual complaints.

**Menopause-associated vaginal atrophy**

- Characterized by decreased vaginal secretions, thinned vaginal tissue, and elevated vaginal pH

- Estrogen influences glycogen content in vaginal epithelium

- Glycogen maintains lactobacilli in the vagina

- Lactobacillus-dominant flora helps maintain vaginal pH in the range of 3.6 – 4.5.

- Elevated vaginal pH (>4.5) is associated with vaginitis
Management of Vaginal Atrophy and Menopausal Symptoms in Patients with Non-Hormonally Sensitive Cancer

- Systemic and topical estrogens are known to be effective in managing vasomotor symptoms and urogenital atrophy
- Menopausal hormone replacement therapy (MRT) has not been recommended since findings of the Women’s Health Initiative (WHI)\(^1\)
  - Women with a uterus randomized to conjugated equine estrogen (CEE) 0.625 plus 2.5 medroxyprogesterone acetate vs. placebo
  - Women with hysterectomy randomized to CEE 0.625 vs. placebo
  - Average age 63 (range 50-79 years); 49% were current or prior smokers!
  - Combination MRT study terminated early in May 2002 because of increased risk of breast cancer, heart attacks, stroke and DVT


More on WHI and MRT safety

- Study of estrogen only did not find an increased risk of breast cancer but terminated 1 year early (increased risk of cerebrovascular accident [CVA] and no protection for heart disease)
- Analysis of WHI showed excess risk of heart disease seen primarily in older women with combination MRT
- No increased risks of heart disease with ERT and some suggestion of benefit in younger women, < 10 yrs from menopause

When WHI reanalyzed by age, a significant 30% mortality reduction was seen in women < 60 using MHT

MHT may be appropriate to manage sexual and menopausal symptoms in some patients
Management of Vaginal Dryness
Limited Evidence in Breast Cancer Patients

- Recent review found lack of data from RCTs evaluating safety of drugs for treating atrophy in breast patients

- Treatment nodes are sized to reflect numbers of patients randomized to each of the interventions in relation to the total number of patients studied across studies.


Vaginal Moisturizers/Gels

- Topical emollients
  - Typically use is 2-3 x per week, but can be daily
  - Some claim to restore “healthy” vaginal pH

- Replens vs placebo showed improvement in vaginal itching, irritation and dyspareunia in breast cancer pts, but was no better than placebo (Loprinzi et al. JCO 1997)
Vaginal pH-Balanced Gel for the Control of Atrophic Vaginitis Among Breast Cancer Survivors

- Breast cancer pts who experienced menopause after chemo or endocrine therapy were randomized to a vaginal topical pH-balanced gel or placebo gel 3x/week for 12 wks
- Vaginal dryness and dyspareunia were measured by visual analog scale, vaginal health index, and vaginal pH
- pH-balanced gel caused more irritation upon application

Lee et al. Obstet Gynecol 2011

Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief?

- 144 postmenopausal women (<70 yo) randomized to receive hyaluronic acid vaginal gel (5 g per application) OR estriol vaginal cream (0.5 mg estriol per application) every 3 days x 10 applications
- After 3 applications, improvement in vaginal dryness was reported by 49% with hyaluronic acid gel vs. 53% using estriol vaginal cream (p = 0.31)
  - After final administration, final improvement rates were 84 and 89 % (p = 0.13)
- Vaginal itching, burning, and dyspareunia were improved by about 86, 85, and 57 % for hyaluronic acid gel, and 82, 87, and 62 % for estriol cream
- After treatment, vaginal pH was significantly lower in estriol-treated women compared to those having received hyaluronic acid

Authors report study had multiple shortcomings so non-inferiority of hyaluronic acid was not proven

Stute P. Arch Gynecol Obstet. Dec 2013
Other non-hormonal options

• Oils: Coconut, olive, mineral

• Topical Vitamins: D and E
  – Trial of 44 women showed topical D reduced pain and decreased vaginal pH vs. placebo at 8 weeks (Rad P, Iran J Nurs Midwifery Res. 2015)

• Vaginal lubricants for sexual activity

• Ospemifene
  – Not appropriate for patients with a history of estrogen-dependent cancer but useful for some other cancer survivors

Ospemifene, a non-estrogen SERM for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy

• 314 women randomized to ospemifene 60 mg qd (n=160) or placebo (n=154).

• Significant improvements in the percentages of parabasal and superficial cells and vaginal pH observed with ospemifene vs. placebo (p<0.001)

Mean change from baseline in severity score of vaginal dryness reported by women receiving ospemifene compared placebo approached statistical significance (p=0.080).

Do Vaginal Estrogens (Rings or Tablets) Increase Serum Estradiol in Breast Cancer Patients on AIs?

- Initial study with estradiol vaginal tablet 25 mcg dose suggested yes\(^1\)
- Wills 2012 (10 estradiol vaginal tablet 25 mcg and 6 estradiol vaginal ring pts on AI)\(^2\)
  - Prior exposure to vaginal estrogen preparation for >3 months
  - Post-insertion E2 were significantly higher in the estradiol vaginal tablet group than controls (45 vs 3.72 pmol/L, \(p < .001\))
  - No change in mean E2 at 60 days for pts using estradiol vaginal ring (15 pmol/L)
- Goldfarb 2012 (26 pts estradiol vaginal tablet 10 mcg)\(^3\)
  - E2 measured by radioimmunoassay, high values were repeated
  - Median change in E2 from BL to wk 12 was 0.2 (range - 3 to 14.6; \(p=.29\))
  - 5/26 (19%) had a sporadic one time modest E2 outside of the post-menopausal range


Does testosterone improve sexual functioning in breast cancer patients?

- 21 pts given 300 mcg testosterone vaginal cream daily for 28 days showed benefit in improving sexual functioning without rises in estradiol or testosterone levels (Witherby et al. Oncologist 2011;16:424–431)
- 13 pts on AIs given 300 μg testosterone vaginal cream daily for 4 weeks showed improvements in FSFI scores (Dahir M et al, Sex Med.2014 Apr;2(1):8-15)
- 72 breast cancer pts received testosterone (T) combined with anastrozole (A) in subcutaneous implants (Glaser et al. ASCO 2014)
  - Therapeutic T levels were achieved without elevating E2
  - Significant improvement in menopausal symptoms, vaginal dryness, sexual functioning and desire
  - Over 950 T/T+A pellet insertions have been performed in breast cancer survivors since 2006
Is vaginal testosterone safer than vaginal estrogen?

- 75 pts on AI randomized to 12 weeks of treatment with estradiol vaginal ring or vaginal testosterone cream (5000 mcg 3x/wk)
  - Serum estradiol and testosterone measured at baseline, week 4 and 12
  - Sexual QOL surveys at baseline, week 4 and 12
  - Gynecologic exams performed at baseline and week 12

- Sexual interest and sexual dysfunction improved in both arms
- Objective improvement in vaginal atrophy in both arms
- 12% of patients in testosterone arm but none in estradiol vaginal ring arm had sustained elevations in estradiol outside of postmenopausal range

Melisko et al. Presented in part at SABCS 2009
Full data submitted for publication

A Practical Solution for Dyspareunia in Breast Cancer Survivors: A Randomized Controlled Trial.

- 46 breast cancer pts with severe dyspareunia were randomized to either saline or 4% aqueous lidocaine to vulva for 3 minutes before vaginal penetration
- All pts received open label lidocaine for 2 mos after 1 mo of blinded study
- Lidocaine users reported less pain during intercourse in the blinded phase (1.0 vs. 5.3; P = .007)
- After open-label lidocaine use, 37/41 (90%) reported comfortable penetration
- 17/20 (85%) pts who had abstained from intercourse who completed the study resumed comfortable penetration
- Sexual distress decreased and sexual function improved
- No penile numbness was reported

Goetsch et al, JCO 2015 Oct 20
Novel Approaches for Vaginal Dryness

- OVERcome trial: Acceptability, feasibility, and efficacy of a novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR) found significant improvements in dyspareunia, sexual function, and quality of life at 12 and 26 weeks in 25 breast cancer patients (Juraskova, J Sex Med 2013;10:2549–2558)

- Micro ablative CO2 laser - 12 week prospective trial in 77 postmenopausal women, found significant improvement in the total score and scores in each specific domain of the FSFI at 12-week follow-up compared to baseline
  - FDA approved in 2014
  - No Data in Breast Cancer Patients
Medical Treatments for Sexual Desire

- **Bupropion**
  - Non-randomized trials of bupropion 150 mg qd in 20 breast cancer patients who had received chemo and were on hormonal therapy showed improvement in sexual functioning at 4 and 8 weeks (Mathias et al. Annals of Oncol 2006)

- **Sildenafil Citrate**
  - No data in cancer patients
  - Minimal positive data for women in general

- **Flibanserin**
  - Acts to ↑ dopamine and norepinephrine (responsible for sexual excitement) and ↓ serotonin (responsible for sexual satiety/inhibition)
  - Now FDA approved for premenopausal women
  - Not contraindicated in breast cancer but no data


- In August 2015, FDA approved flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women
- Medical databases and trial registries were searched through 6/17/2015
- Randomized clinical trials assessing flibanserin in premenopausal and postmenopausal women were eligible
- Five published and 3 unpublished studies including 5914 women included
- Risk ratio for study discontinuation due to adverse events (AEs) was 2.19 (95% CI, 1.50-3.20)
- Risk ratios for:
  - Dizziness was 4.00 (95% CI, 2.56-6.27) in flibanserin vs placebo,
  - Somnolence was 3.97 (95% CI, 3.01-5.24)
  - Nausea was 2.35 (95% CI, 1.85-2.98)
  - Fatigue was 1.64 (95% CI, 1.27-2.13) for fatigue.

Meta Analysis Pooled Results

Pooled mean differences for SSE (satisfying sexual events) change from baseline were **0.49 (95% CI, 0.32-0.67)** between flibanserin and placebo, **1.63 (95% CI, 0.45-2.82)** for eDiary desire, and **0.27 (95% CI, 0.17-0.38)** for FSFI desire.

Other Interventions for Sexual Dysfunction

- Set goals, team approach, education
- Open communication important for both partners
- Alter sexual behavior as needed to accommodate for physical, emotional and social changes
- Lifestyle changes – regular exercise, decrease stress, pelvic muscle strengthening, improve relationship/emotional intimacy
- Therapists that specialize in sex therapy

Should the Ovaries Come Out?

- If recurrent disease after tamoxifen and planned AI therapy: **YES**: Because need for permanent ovarian suppression
- If high-risk disease or long-term AI therapy planned with minimal likelihood of remaining ovarian function: **YES**
- If low-risk disease and likelihood of ovarian function when treatment complete: **NO** because there may be other health benefits of keeping the ovaries
- Need to counterbalance risks of subsequent heart disease and osteoporosis
Treatment of Hot Flashes

- **Low dose antidepressants** – venlafaxine, paroxetine, fluoxetine, citalopram, escitalopram, desvenlafaxine
  - Side effects: dry mouth, appetite changes, fatigue, nausea, constipation and **sexual disturbances**
- Clonidine
- Gabapentin and pregabalin
- Vitamin E
- Soy supplements
- **Herbal Products:** black cohosh (best studied), Chinese herbs
- Tibolone (in Europe)
- **Alternative Therapies** - CBT, exercise, mindfulness, acupuncture, relaxation techniques

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Venlafaxine for Hot Flashes

![Graph showing the effectiveness of Venlafaxine for hot flashes over 6 weeks. The graph shows a decrease in hot flash score as weeks progress, with the highest reduction seen at 75 mg/d. Loprinzi et al, Lancet 2000]
Conclusions and Key Take Home Points

- Sexual Function is an important survivorship issue
- Sexual dysfunction is likely to become more prevalent in young breast cancer survivors with increasing use of ovarian suppression
- There is increasing understanding of the safety/risks associated with hormonal interventions
- Further research and data is required for evidence based interventions for decreased libido in postmenopausal woman

Pandya KJ et al. Lancet 2005
Sexual Function in Cancer Survivors: Addressing Sexual Health Issues in Men after Cancer Treatment

Joseph B. Narus, DNP, GNP-BC, ANP
Male Sexual and Reproductive Medicine Program
March 31, 2016

Outline

- Describe the risk factors that impact male sexual health in men treated for cancer


- Explain treatment options to improve male sexual function after cancer treatment
Case 1

- A 57 yr-old married man with a history of prostate cancer (Gleason 3+4, surgical margins -, extracapsular extension=focal, seminal vesicle +, lymph node invasion Neg) five months post robotic assisted laparoscopic prostatectomy (RALP) presents with his spouse complaining of erectile dysfunction (ED).
- Denies a history of ED prior to RALP. Reports sexual intercourse with spouse two times a week prior to prostatectomy.
- History of elevated cholesterol, hypertension (HTN). Denies tobacco or recreational drug use.
- Current medications include sildenafil 25mg QHS, HCTZ 25mg daily, simvastatin 10mg daily. Has attempted sexual intercourse using sildenafil 100mg achieving a 40% rigid erection.

Audience Polling Results

You are going to educate him about second-line therapy for ED. Second-line therapies include:
1. Intracavernosal injection therapy
2. Implantable penile prosthesis
3. Intraurethral suppository of alprostadil
4. Option 3 only
5. Options 1 & 3
6. All of the above

Audience responses:
- Option 1: 4%
- Option 2: 2%
- Option 3: 3%
- Option 4: 3%
- Option 5: 26%
- Option 6: 60%
Historical Background

- American Cancer Society’s 2015 estimates of leading four cancer sites among men:
  1. **Prostate**
  2. Lung and Bronchus
  3. **Colon/Rectum**
  4. **Urinary Bladder**

- Treatments: surgery, radiotherapy and/or systemic therapy

- Important to address and assess potential sexual function issues/quality of life post-cancer treatment before, during and after completion of treatment
### Barriers for Discussing Sexual Health

<table>
<thead>
<tr>
<th>Clinician Barriers:</th>
<th>Patient Barriers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Embarrassment to raise subject</td>
<td>- Emotional factors (anxiety, embarrassment)</td>
</tr>
<tr>
<td>- Focused on other health issues</td>
<td>- Age/Cultural</td>
</tr>
<tr>
<td>- Lack of training on sexual medicine issues</td>
<td>- Perception not a medical problem</td>
</tr>
<tr>
<td>- Discomfort using psychosocial counseling interventions</td>
<td>- Lack of knowledge of treatment options</td>
</tr>
<tr>
<td>- Lacks awareness of association with other conditions</td>
<td>- Insurance coverage/Cost</td>
</tr>
</tbody>
</table>

Mulhall, et al., *Cancer and Sexual Health*. 2011

### Risk Factors Impacting Sexual Health

- **Cancer diagnosis**
- **Also:**
  - Cardiac (coronary artery disease, dyslipidemia, hypertension)
  - Diabetes
  - Endocrine (hypogonadism, thyroid)
  - Depression/Anxiety
  - Life style (smoking/alcohol/recreational drugs)
  - Psychological (partner, sexual orientation)
Survivorship: Sexual Function (Female and Male)

DIAGNOSTIC EVALUATION

- Ask about sexual function at regular intervals (See screening questions on SURV-A)
- Discuss treatment-associated infertility if indicated, with appropriate referrals

Screening questions do not indicate an issue → Re-evaluate and discuss potential impact of treatment on sexual function at future visits

Screening questions indicate an issue, but survivor does not want to discuss further → Refer to sexual health specialist, if survivor is interested

Screening questions indicate an issue and survivor wants to discuss further

Survivorship: Sexual Function (Female and Male)

- H&P
  - Review oncologic history (diagnosis/stage, surgeries, systemic treatment, local RT, endocrine therapy)
  - Consider use of a screening tool
  - Explore treatment related impact on sexual function
  - Assess for signs or symptoms of estrogen or androgen deprivation or refer to appropriate specialist
  - Review medical history for conditions associated with sexual dysfunction (eg, depression [See SANXDE-1 and NCCN Guidelines for Distress Management]), diabetes, hypertension
  - Assess total morning testosterone in males as indicated
  - Review medication list for drugs that impact sexual function (eg, SSRIs, beta blockers)

See Treatment for Females (SSF-2) or for Males (SSF-3)
Appropriate referrals for
- Psychotherapy
- Sexual/couples counseling
- Gynecologic care
- Urology
- Sexual health specialist, if available

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### Assessment of Sexual Dysfunction

- **Medical History**
  - Include oncologic history
    - Diagnosis/Stage, Surgery, Systemic Treatment, Local RT, endocrine therapy
- **Surgical History**
- **Validated Sexual Function Screening Tool**
- **Social History**
  - Relationship status
  - Use of prescription/otc medications (hormone therapy, opioids, SSRIs)
  - Alcohol, tobacco, recreational drugs
- **Physical Examination**
  - Vital Signs, waist circumference, gynecomastia, hair distribution
  - Genital exam (suprapubic fat, penis & scrotum)
  - Prostate
- **Tests**
  - Laboratory (testosterone deficiency)
  - Biothesiometry
  - Duplex doppler ultrasound
  - Penile nocturnal tumescence test


### Sexual History

- **Sexual Response**
  - “How is your sexual function?” (Reality vs. Internet......appearance & endurance)
  - “Are you satisfied with your relationship and sexual function?”
  - “Have you maintained interest in sex?”
  - “Are you able to achieve and maintain an erection?”
    - Partner vs. Masturbation
Instruments to Evaluate Erectile Dysfunction

- **Sexual Health Inventory for Men (SHIM)**
  - Questionnaire based, reliable self-administered symptom scales
  - Abridged version of IIEF
  - 2 domains: (5 questions, rating 1 – 5)
    - Erectile function (4 questions)
    - Satisfaction (1 question)
  - Results:
    - 1-7 = severe
    - 8-11 = moderate
    - 12-16 = mild-to-moderate
    - 17-21 = mild
    - 22-25 = normal

Instruments to Evaluate Erectile Dysfunction

- **International Index of Erectile Function (IIEF)**
  - 5 domains: (15 questions, rating 0 or 1 – 5)
    - Erectile function (6 questions)
    - Orgasmic function (2 questions)
    - Sexual desire (2 questions)
    - Intercourse satisfaction (3 questions)
    - Overall satisfaction (2 questions)
  - Results:
    - $\leq 10 =$ severe
    - $11 – 17 =$ moderate
    - $18 – 25 =$ mild
    - $\geq 26 =$ normal

\[^{1}\text{Rosen et al. (1997) Urology, 49, 822-830.}\]

Male Sexual Dysfunction

- **Erectile Dysfunction**
  - Organic
  - Psychogenic
  - Mixed

- **Ejaculation/Orgasm disorders**
  - Anejaculation/Retrograde
  - Dysorgasmia (painful orgasm)
  - Anorgasmia/Retarded orgasm
  - Premature

- **Sexual Incontinence**
  - Arousal Incontinence
  - Climacturia

- **Penile Changes**
  - Curvature (Peyronie’s Disease)

- **Hypogonadism**


**Erectile Dysfunction**

- is the consistent inability to achieve or maintain a penile erection sufficient for “adequate” sexual relations

- The effects of ED interfere with:
  - Self-esteem
  - Interpersonal relationships
  - Sense of well-being

- Post-prostatectomy erectile dysfunction rates range from 12-96% with a meta-analysis reporting an overall erectile function recovery rate of 58%.


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**Flaccid**

- $P_0 = 35-40 \text{ mmHg}$
  - Increased TGF-β, Secretion
  - Collagen Production
  - Fibrosis and venous leak

**Erect**

- $P_0 = 70-100 \text{ mmHg}$
  - Increased PGE Secretion
  - Decreased Collagen Production
  - Preserved erectile tissue integrity

Venous Leak

- Tunica albuginea
- Subtunical venule
- Smooth muscle

JP Mulhall, MS Damaser, JUIR 13:236-239, 2001

Management of Sexual Issues

- Treatment options should be motivated by patient and spouse/partner after all interventions including risks, benefits and costs reviewed

- Partner/Spouse support/buy-in crucial
Evolution Of ED Therapy

- 1960's: Sex therapy
- 1970's: Penile Prosthetics
- 1980's: Penile injection therapy
- 1997: Intraurethral prostaglandin suppository
- 1998: Introduction of Sildenafil citrate

Management of Erectile Dysfunction

- **First-line therapy**
  - Lifestyle modification
    - Modify reversible causes
  - Oral agents
- **Second-line therapy**
  - Vacuum erection device
  - Intracavernosal Injection
  - Intraurethral suppository
- **Third-line therapy**
  - Implantable penile prosthesis
Ejaculation/Orgasm Disorders

- **Anejaculation/Retrograde Ejaculation**
- **Dysorgasmia** (painful orgasm)
  - Tamsulosin HCl 0.4mg or alfuzosin 10mg
  - Side effects: dizziness and low blood pressure & use with PDE5Is
  - Pelvic physical therapy
- **Premature ejaculation**
  - SSRIs & Sprays
- **Anorgasmia** (no orgasm)/**Retarded orgasm** (delayed)
  - Penile vibratory therapy
  - Testosterone replacement therapy if indicated.

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**NCCN Guidelines Version 1.2016**

**Survivorship: Sexual Function (Male)**

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>TREATMENT OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>• Oral phosphodiesterase type 5 (PDE5) inhibitors as needed, if not contraindicated</td>
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<tr>
<td></td>
<td>• If total morning testosterone &lt;300 ng/dL, then testosterone therapy may be indicated</td>
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<tr>
<td></td>
<td>• Daily low-dose oral phosphodiesterase type 5 (PDE5) inhibitors, if not contraindicated</td>
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<tr>
<td></td>
<td>• Lifestyle modification (HL-1) (eg, increased physical activity, smoking cessation, reduction of alcohol consumption)</td>
</tr>
<tr>
<td></td>
<td>• Pelvic physical therapy</td>
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<tr>
<td>Global symptoms of distress, anxiety, depression or other psychological concerns</td>
<td>• Anxiolytics</td>
</tr>
<tr>
<td>Problems with ejaculation (dry, retrograde, delayed or climacturia)</td>
<td>• Antidepressants</td>
</tr>
<tr>
<td></td>
<td>• Integrative therapies (eg, yoga, meditation)</td>
</tr>
<tr>
<td>Problems with orgasm (eg, less intensity, difficulty achieving)</td>
<td>• If total morning testosterone &lt;300 ng/dL, then testosterone therapy may be indicated</td>
</tr>
<tr>
<td></td>
<td>• Psychological evaluation</td>
</tr>
<tr>
<td></td>
<td>• SSRIs (paroxetine, sertraline, citalopram, fluoxetine)</td>
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<tr>
<td></td>
<td>• Clozapine dosed daily</td>
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<tr>
<td>Low or lack of desire, libido, or intimacy</td>
<td>• If total morning testosterone &lt;300 ng/dL, then testosterone therapy may be indicated</td>
</tr>
<tr>
<td></td>
<td>• Psychological evaluation</td>
</tr>
<tr>
<td></td>
<td>• Pelvic physical therapy</td>
</tr>
</tbody>
</table>

See Follow-Up

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Sexual Incontinence

- Common after radical pelvic cancer surgeries
- Two types:
  - Arousal
  - Climacturia (orgasm leakage)
- Patient and partner distress
- Interventions:
  - Kegel exercise
  - Condom
  - Clomipramine (on-demand)
  - Penile constriction loop
  - Artificial urinary sphincter
Penile Changes

- **Curvature (Peyronie’s Disease)**
  - Fibrous scar tissue replaces normal elastic fibers in tunica around corporum tissue
  - Presents as:
    - curvature
    - indentation
    - shortening
    - hourglass deformity
  - Reason why plaque forms is unclear, but may be related to post-operative changes, secondary to nerve damage or lack of blood flow
  - Early assessment and intervention recommended to stabilize and prevent worsening

- **Assessment:**
  - Duplex Doppler ultrasound

- **Treatment:**
  - Intralesional verapamil
  - Intralesional collagenase clostridium histolyticum
  - Penile traction device

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Hypogonadism

- **Testosterone**
  - Major sex hormone in men
  - Normal total level = 300 ng/dl – 1000 ng/dl
  - < 300 ng/dl may warrant therapy

- **Causes of low testosterone:**
  - Disruption in hypothalamic-pituitary-testicular axis
    - Surgery
    - Chemotherapy/hormonal therapy
    - Radiation
    - Prescription/OTC medications

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\(^{1}\)Tal & Mulhall, *Sexual Function in the Prostate Cancer Patient*, 2009

Mulhall, et al., *Fertility Preservation in Male Cancer Patients*. 2013
Types of Hypogonadism

Primary:
- Abnormality at birth
- Trauma
- Inflammatory/Infectious Diseases
- Medications (glucocorticoids, ketoconazole)
- Chemotherapy
- Radiation (total body, pelvic)
- Tumor (testicular)
- Aging

Secondary:
- Abnormality at birth
- Tumor (Pituitary adenoma, metastatic lesions, glioma)
- Inflammatory/Infectious Diseases
- Hemorrhage/ischemia
- Medications (LHRH–agonists, opioids)
- Surgery
- Radiation therapy (brain)
- Aging

Mulhall, et al., *Fertility Preservation in Male Cancer Patients*. 2013

Side Effect of Low Testosterone

- Reduction in general well-being
- Low sex drive/desire (libido)
- Increased fatigue/loss of energy
- Inability to concentrate
- Depression
- Erectile problems (erectile tissue/orgasm)
- Osteopenia/osteoporosis (bone loss)
Testosterone Replacement Therapy

- Controversial
  - 2014 FDA issued statement on use for low testosterone due to aging
  - Possible increased risk of heart attack and stroke
  - Products approved only for men with underlying causes of low testosterone due to disorders of testicles, pituitary gland or brain
  - NCCN: Contraindicated in men with prostate cancer on active surveillance and prostate cancer under therapy with androgen deprivation

- Sexual Medicine Society of North America (SMSNA) Position Statement
  - Studies cited are not planned experimental study with controlled groups and defined goals; retrospective analyses of data collected for other reasons

Summary

- Important to understand the effects of cancer treatment on sexual health
- Refer to NCCN Guidelines for Survivorship
- Early evaluation and treatment for sexual health issues can improve outcomes in the long-term
- Treatment interventions motivated by patients after discussion of risk/benefits/cost
- Not all treatments work for all men
- Ask for a referral to a sexual and reproductive clinician when needed