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Impact of sexual function on prostate cancer treatment

■■■ 가톨릭의대 / 김 세 응

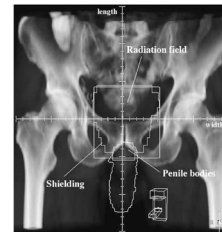
Radiation Therapy & ED

Etiology of post-radiation erectile dysfunction

- 주요 가설 - Due to vascular damage
Goldstaine et al, JAMA 1984
 - Zelefsky et al. Int J Radiat Oncol Biol Phys 1998
- Among 98 EBRT patients
 32% cavernosal dysfunction
 63% arteriogenic dysfunction
 Only 3% neurogenic dysfunction
- Hormonal manipulation, smoking, age
 → Did not influence the type of dysfunction.

Dose relationship with potency

- Fisch et al. Urology 2001;57:955-9
70 Gray 이상의 dose 를 받은 환자에게서 radiation induced-ED 가 나타남.
- Selek et al. Int J Radiat Oncol Biol Phys 2004;59:1039-46
Dose 와 ED는 직접적인 연관이 없었음.
IMRT (intensity-modulated radiation Tx)
- penile bulb 의 radiation 을 제한하는 것이 중요함.
(corpora cavernosa at the crurae of the penis)
- Buyyounouski et al. Int J Radiat Oncol Biol Phys 2004;59:1383-91
penile bulb에 radiation을 제한했을 때 cancer control에 미치는 영향에 대해서는 현재 data 없음.



- Example of an ant.-post. conformal radiation field for prostate cancer.
- Relation of the penile bodies and radiation field.

Incidence of ED after EBRT

Table 3
Erectile dysfunction after external-beam radiotherapy (EBRT) for prostate cancer: prospective studies from the 1990s

Authors	Patients, n	Mean age ^a years (range)	Patients potent prior to EBRT ^a (%)	Mean follow-up months (range)	ED, n (%)
Zinreich et al. [17]	27	68 (52-80)	10 (37)	n.a.	20 (74) at 12 months
Pfilsch et al. [33]	230	71 ^b (60-84)	102 (44)	54 ^c (n.a.)	21 (9.1) at 102
Beckendorf et al. [37]	67	68 (54-84)	40 (60)	n.a. (8-12)	33 (49)
Beard et al. [8]	121	n.a.	69 (57)	n.a.	57 (47) at 3 months 54 (44) at 12 months
Bergheide and Hoedlin [9]	184	67 (66-85)	134 (73)	46 (24-96)	7 (3.8) at 34
Treum et al. [46]	200	69 (44-82)	182 (91)	23 ^d (n.a.)	18 (9.0) at 12 months 39 (19.5) at 36 months

n.a., data not available.
^a Mean age for entire group.
^b Median.

- In general, Incidence of ED after EBRT reaches about 60–70% in prospective studies.

- 1990년대에 들어서야 post-radiation ED 에 초점을 맞춘 체계적인 발표가 이루어짐
- Time elapsed since RT 중요함
RT 후 1,2년 까지는 ED 증가하다가 3년부터는 stable
∴ 적어도 18–24개월 후 평가

Ejaculatory and other sexual dysfunctions

- Sexual activity의 deterioration은 ejaculatory dysfunction과 연관이 깊다. (esp. in volume or an absence of semen)

Arai et al. J Urol 2000;164:1206–11

Ejaculatory and other sexual dysfunctions

- EBRT 후의 변화

A lack of ejaculation	2–56%
Dissatisfaction with sex life	25–60%
Decreased libido	8–53%
Decreased sexual desire	12–58%

<기타>

decreased intensity of orgasm
Decreased frequency and rigidity of erections
Decreased importance of sex

Therapy of Post-radiation ED

- Intracavernosal injection (ICI)
- Vacuum devices
- Penile implants
- Sildenafil
 - Sildenafil 이후 위의 세가지 치료법은 잘 쓰이지 않음

Sildenafil citrate

- Efficacy of Sildenafil after EBRT
- open-label study 에서 70~90% 까지 보고됨

Zelevsky et al. Urology 1999;53:775–8
Kedia et al. Urology 1999;54:308–12
Weber et al. J Clin Oncol 1999;17:3444–9
Valicenti et al. Urology 2001;57:769–73

RAPID COMMUNICATION

SILDENAFIL CITRATE (VIAGRA) AND ERECTILE DYSFUNCTION FOLLOWING EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY

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Incrocci et al. Int. J Radiat Oncol Biol Phys 2001;51:1190-5

- double blind study 결과 55% 효과

Table 2. Mean score (SD) of the IIEF questionnaire before and after 6 weeks of treatment with sildenafil (open) or placebo.

Questions	Baseline score	Score after sildenafil	Score after placebo
1. Erection frequency	1.7 (1.6)	2.9 (1.6)	1.8 (1.3)
2. Erection firmness	1.9 (1.9)	2.8 (1.9)	1.9 (1.3)
3. Penetration ability	1.9 (1.6)	2.8 (1.7)	1.6 (1.3)
4. Maintenance frequency	1.9 (1.6)	2.6 (1.7)	1.5 (1.0)
5. Maintenance ability	1.9 (1.7)	2.8 (1.7)	1.8 (1.4)
6. Intercourse frequency	1.2 (1.1)	2.8 (1.1)	2.1 (0.9)
7. Intercourse satisfaction	1.9 (1.9)	2.7 (1.6)	1.9 (1.3)
8. Intercourse enjoyment	1.9 (1.9)	2.8 (1.6)	1.9 (1.3)
9. Ejaculation frequency	2.4 (1.9)	3.0 (1.6)	2.1 (1.6)
10. Ejaculation satisfaction	2.4 (1.9)	3.0 (1.7)	2.1 (1.6)
11. Overall frequency	2.4 (1.2)	3.0 (1.1)	2.1 (1.2)
12. Overall level	2.7 (1.9)	3.0 (1.6)	2.4 (1.6)
13. Overall satisfaction	2.4 (1.9)	3.0 (1.4)	2.1 (1.2)
14. Relationship satisfaction	2.7 (1.9)	3.2 (1.1)	2.4 (1.4)
15. Erectile confidence	2.1 (1.1)	3.0 (1.1)	2.4 (1.3)

¹ Between baseline and sildenafil treatment $p < 0.001$, except for #1 ($p = 0.04$) and #12 ($p = 0.06$).
² Between sildenafil treatment and placebo $p < 0.01$, except for #9 ($p = 0.04$) and #14 ($p = 0.05$).
³ Significant difference between baseline score and placebo ($p < 0.04$).

Sildenafil citrate

- F/U 결과 only 24%만이 2년 이상 사용 중

<사용 중단 이유>
 lack of efficacy 60%
 costs 24%
 side effects 16%

Incrocci et al. Urology 2003;62:116-20

Prevention of Post RT – ED

- Prevention is a difficulty matter !
- Radiation 이 vascular damage를 일으킨다는 가설
 → pelvic vascular structure로의 dose를 줄이는 것이 ED 예방
 Nguyen et al. Urology 1998;51:991-7
- Radiation field size 와 ED 의 연관 가설
 → smaller the field size, the better sexual functioning
 Beard et al. J Clin Oncol 1997;15:223-9

Prevention of Post RT – ED

- 현재까지는 ED와 EBRT 간의 관계를 밝히는 유의한 데이터가 없음.
 Incrocci et al. Int J Radiat Oncol Biol Phys 2002;52:681-93
 Incrocci et al. Urology 2002;60:1-7
- 1996년 이후 Prostate cancer 치료에 IMRT가 도입되면서 선택적인 radiation 가능
- Fisch 등의 주장처럼 penile bulb의 radiation 을 줄이는 것이 권고될 수 있음.

Brachytherapy, Cryotherapy & ED

Brachytherapy & ED

- The studies investigating ED following brachytherapy are few.
- Data suggest that Brachytherapy also is associated with delayed-onset ED
 - 171 men undergoing Brachytherapy for organ-confined P ca. mean age – 69 years followed for 25 months
 2년 후 51% 에서 complete or partial ED
 Sanchez-Ortiz et al. Int J Impot Res 2000, 12:S18-S24

Cryotherapy & ED

- Only a small number of patients have been followed for evaluation of erectile function
 - *Chaikin et al. Urology 1996;48:100-104*
36 men – followed 12 months
using Global Assessment Question (GAQ)
90% reported severe or complete ED
 - *Robinson et al. Int J Radiat Oncol Biol Phys 2002;54:1063-1068*
38 patients – followed for 36 months
13% – potency
34% – sildenafil, injection 등의 방법으로 유지
53% – ED

Cryotherapy & ED

- *Long et al. Urology 2001;57:518-523*
975 patients
January 1993 to January 1998
median follow-up 24 months

이들 중 84%에서 ED 를 호소함

Hormonal Therapy & ED

Androgen Deprivation Tx

- ADT
Until recently, reserved for Pt with metastatic P ca
Now, asymptomatic Pts are candidates,
without evidence of metastatic disease
but with biochemical recurrence
or increase PSA
- Early initiation of ADT
→ affect his quality of life
→ increase detrimental effects on health

Androgen Deprivation Tx

- Orchiectomy
- Luteinizing hormone-releasing hormone (LHRH) analogs

- Most frequently recognized side effect
 - loss of libido
 - erectile dysfunction
 - hot flashes, etc.

Incidence

- > 80% associated with a loss of libido and erectile capability

Kirby et al. Prost Cancer Prost Dis 1998;1:179-84
Rousseau et al. Arch Sex Behav 1998;17:87-98
Fossa et al. Eur Urol 1997;3(suppl 3):3-8

Libido vs ED

- Sexual life 에는 개인차가 있다.
 - Age
 - Physical well-being
 - Pretreatment testosterone levels
 - Probably many others
- Libido는 testosterone level 만으로 결정되는 것이 아님.
Potosky et al. J Clin Oncol 2001;19:3750-3757
- Loss of libido → ED 의 원인 중 하나일 뿐

Libido vs ED

- Libido 가 유지되는 환자
 - ED 치료의 많은 option 가능
- Libido 가 유지되지 않은 환자
 - little benefit
- The most familiar medical Tx
 - sildenafil

기타 intracavernosal injection, vacuum, penile prosthesis

Erection의 유지 - 장점

- ADT 기간 중에 sexual desire가 감소될지라도 erection 을 유지하는 것은 penile tissue 의 oxygenation을 좋게 하여 fibrosis를 방지하는 효과가 있다.
Zippe et al. Curr Urol Rep 2001;2:495-503

Intermittent ADT

- Alternative investigational approach
 - 1) prevent progression of prostate cancer
 - 2) delay development of the androgen-independent state.

Bruchovsky et al. Mol Urol 2000;4:191-9
Goldenberg et al. Urology 1995;45:839-44

Intermittent ADT

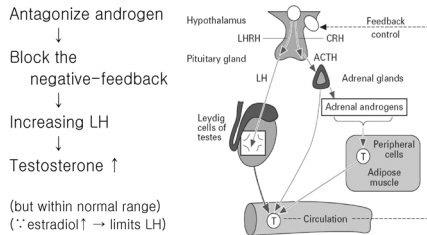
- Intermittent regimen 중 LHRH agonist나 기타 약제의 용량이 줄어들면 libido 가 향상되는 것이 관찰됨
- Quality of life를 고려한다면 erection 유지가 용이한 intermittent ADT에 대한 연구가 더욱 진행될 필요가 있음.
- Southwest Oncology Group
■ The National Cancer Institute } randomized studies
- 기타 restore anemia // maintain bone density 에 장점

Antiandrogen Monotherapy

- Monotherapy with a nonsteroidal antiandrogen is a treatment option.
 - less impact on sexual interest & function
- Bicalutamide
- Flutamide
- Nilutamide

Boccon-Gibod L. Eur Urol 1998;33:159-64

Theoretical Basis – 1



Theoretical Basis – 2

- Animal experiments suggest that Metabolites of testosterone (e.g. estrone after the peripheral conversion of testosterone by aromatase) → sexual drive
Wood et al. *Physiol Behav* 1996;59:833-41
Rasia-Filho et al. *Braz J med Biol Res* 1991;24:1041-9
- These pathways would be unaffected by the nonsteroidal antiandrogens

Effect of nonsteroidal antiandrogens

- Nilutamide 100 mg 3 times daily
7/15 maintained libido and potency (10 months)
Decensi et al. *J Urol* 1991;146:377-81
- Flutamide monotherapy vs castration
median time to progression and overall survival – similar for the two treatments
Boccon-Gibod et al. *Eur Urol* 1997;32:391-6
- About 2/3 retained potency during Tx with flutamide
Brunfsky et al. *Urology* 1997;49:913-20

Bicalutamide 150mg/day

- Bicalutamide 150mg/day vs castration
→ No overall difference in survival or time to progression
Iversen et al. *J Urol* 2000;164:1579-82
- Castration is no more effective than bicalutamide 150mg/day monotherapy
Boccardo et al. *J Clin Oncol* 1999;17:2027-38
Chatelain et al. *Br J Urol* 1997;80(Suppl 2):263(A1111)

Bicalutamide 150mg/day

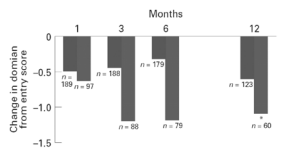


Fig. 2. The changes in sexual interest with time in patients with locally advanced prostate cancer. * $P=0.029$. Red columns represent bicalutamide and green represent castration.

- significant advantage for sexual interest compared with castration ($P=0.029$)

Tyrrell et al. *Eur Urol* 1998;33:447-56
Iversen et al. *Urology* 1998;51:389-96

Notification to the Patients

- 환자들이 느끼는 심각성
Loss of penile length or volume
Loss of testicular mass
Penile fibrosis can also be a long-term consequence
→ 치료시작시에 대부분의 환자들은 이러한 가능성을 주지받지 못함
- It is important to note that ED is also a frequent, and usually irreversible, consequence of prostatectomy or radiotherapy.
- In severe case of loss of penile length
→ surgical options may be indicated.

Conclusion

- In the middle and older age group
Risk factors for ED are significant
- All prostate cancer treatment
→ increase the risk of ED
- Organic ED 외에 psychogenic ED 및 partner 와의 sexual dysfunction 도 고려대상
- Effect of the currently available treatment on sexual interest & function varies and may be an important consideration when selecting therapy
- Penile rehabilitation program
 - preserve smooth muscle and endothelial function
 - tissue anoxia와 corporal fibrosis를 예방하여 irreversible ED 를 방지