Metastatik Prostat Kanseri Tedavisinde Tartışmalı konular (Erken ve geç tedaviler, kombinasyon tedavileri ve optimal ne olmalı?)

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Tıbbi Onkoloji

Sunum Planı

- **Prostat Kanseri İnsidans ve Mortalite**
- **Hormon Duyarlı Metastatik Prostat Kanseri**

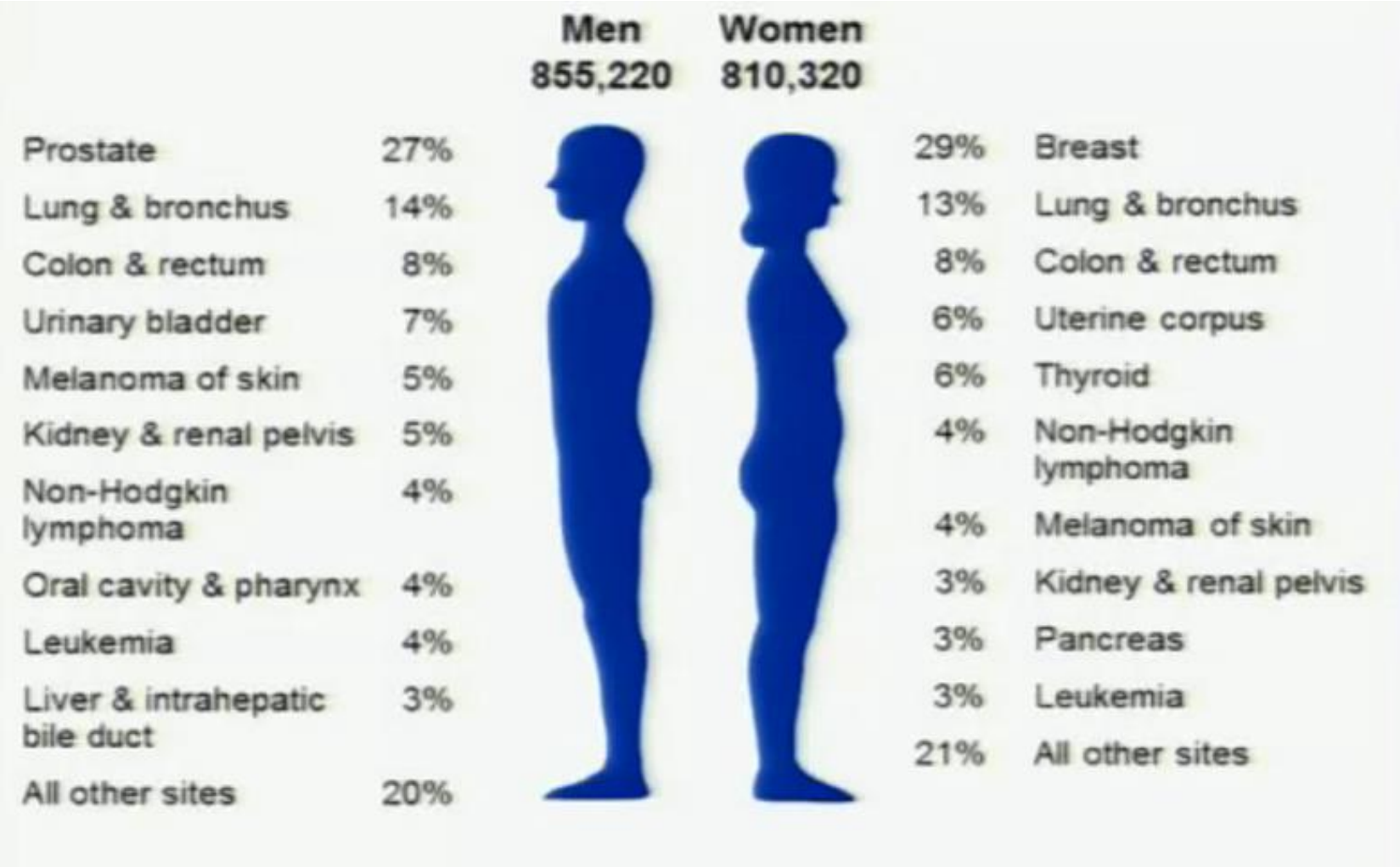
  Androjen Baskılama Tedavisi(ADT)

  Cerrahi Kastrasyon vs. Medikal Kastrasyon

  Kombine Androjen Blokajı vs. Monoterapi

  İntermittant vs. Continue
- **Hormon Duyarlı Metastatik Prostat Kanseri kemoterapinin yeri**
- **Sonuç**

Prostat Kanseri İnsidans ve Mortalite



SEER 2016 verileri; 180.890 yeni tanı ve 26.120 kişi prostat kanseri nedeniyle ölmektedir.

Prostat Kanseri İnsidans ve Mortalite

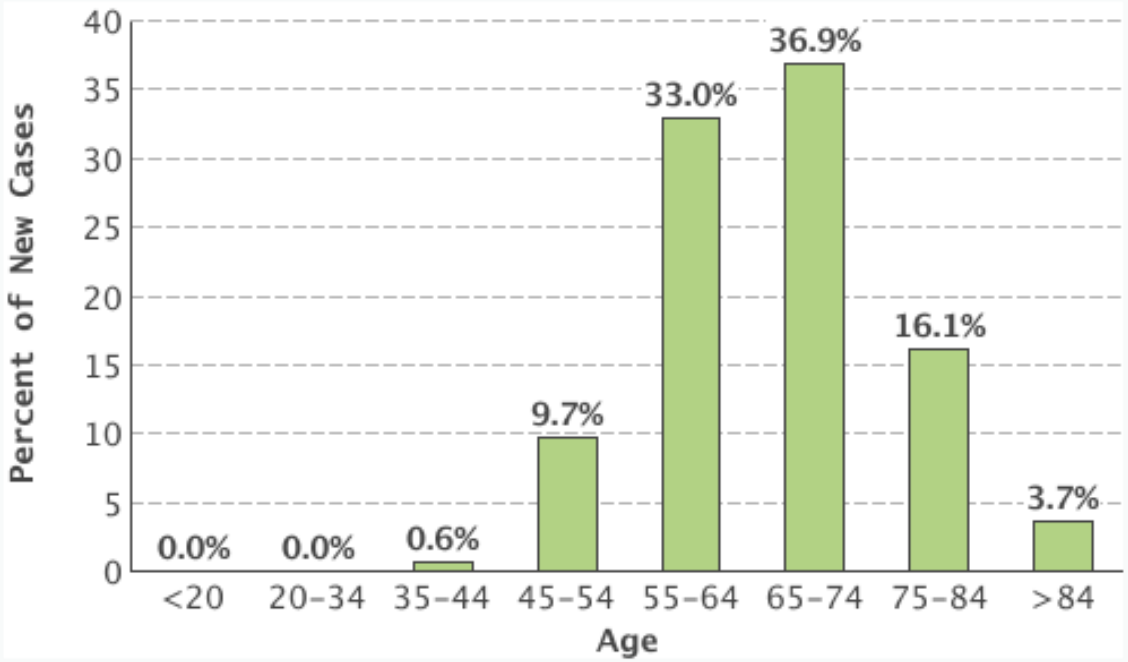
	Common Types of Cancer	Estimated New Cases 2015	Estimated Deaths 2015
1.	Breast Cancer (Female)	231,840	40,290
2.	Lung and Bronchus Cancer	221,200	158,040
3.	**Prostate Cancer**	**220,800**	**27,540**
4.	Colon and Rectum Cancer	132,700	49,700
5.	Bladder Cancer	74,000	16,000
6.	Melanoma of the Skin	73,870	9,940
7.	Non-Hodgkin Lymphoma	71,850	19,790
8.	Thyroid Cancer	62,450	1,950
9.	Kidney and Renal Pelvis Cancer	61,560	14,080
10.	Endometrial Cancer	54,870	10,170

Prostate cancer represents 13.3% of all new cancer cases in the U.S.

In 2015, it is estimated that there will be 220,800 new cases of prostate cancer and an estimated 27,540 people will die of this disease.

Prostat Kanseri İnsidans ve Mortalite

Percent of New Cases by Age Group: Prostate Cancer

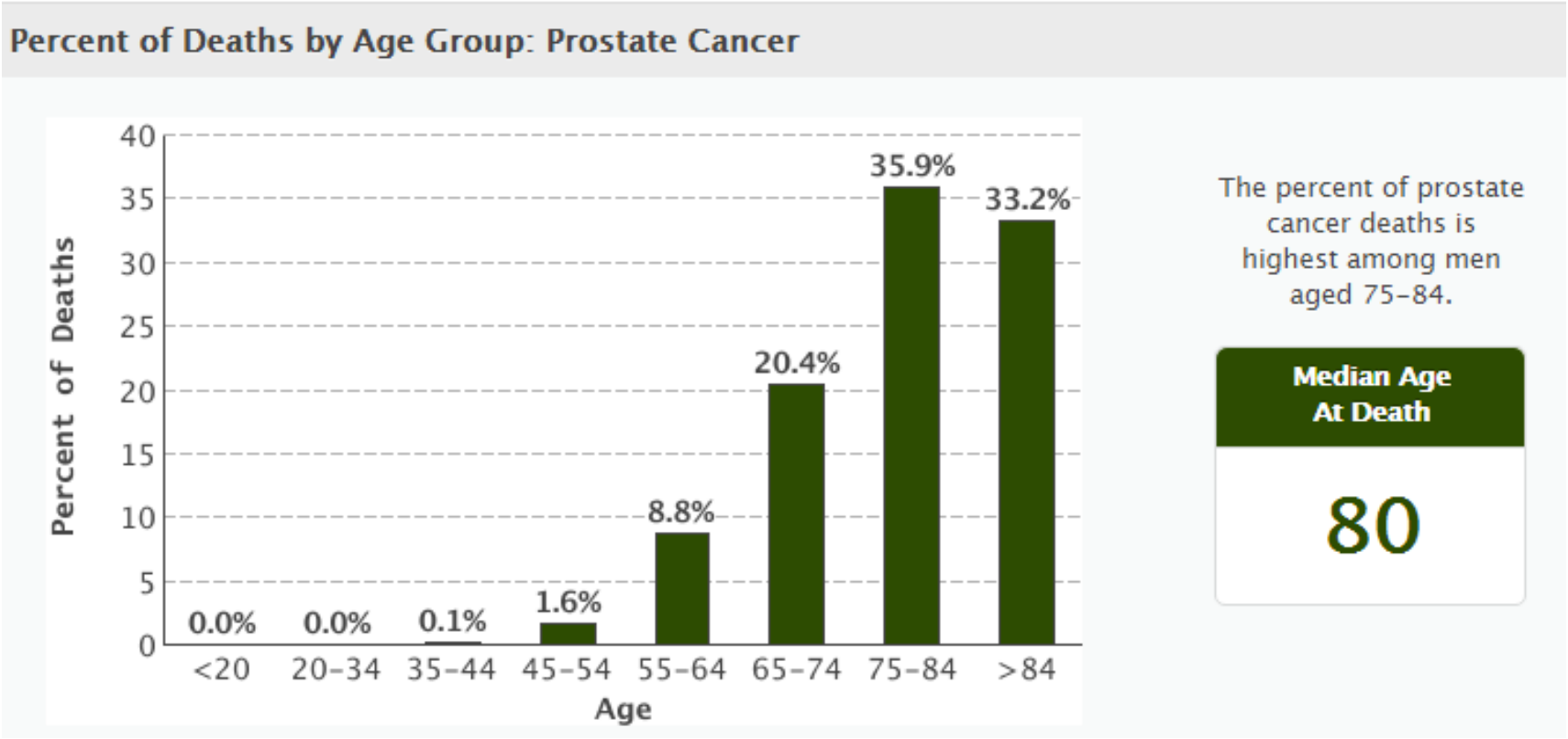


Prostate cancer is most frequently diagnosed among men aged 65–74.

Median Age At Diagnosis

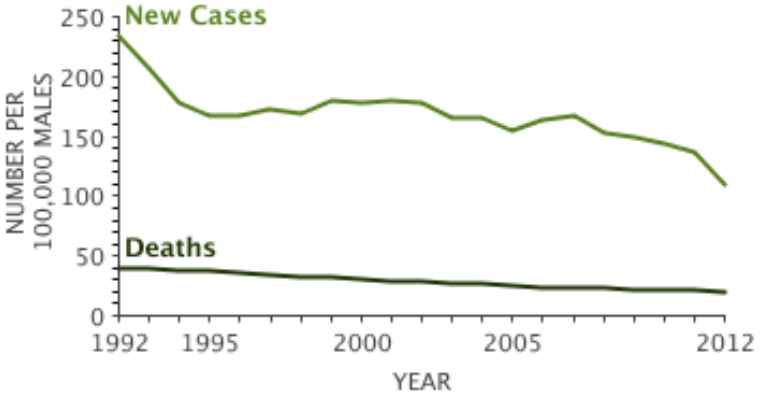
66

Prostat Kanseri İnsidans ve Mortalite



Prostat Kanseri İnsidans ve Mortalite

Estimated New Cases in 2015	220,800
% of All New Cancer Cases	13.3%
Estimated Deaths in 2015	27,540
% of All Cancer Deaths	4.7%



Percent Surviving 5 Years

98.9%

2005–2011

Number of New Cases and Deaths per 100,000: The number of new cases of prostate cancer was 137.9 per 100,000 men per year. The number of deaths was 21.4 per 100,000 men per year. These rates are age-adjusted and based on 2008–2012 cases and deaths.

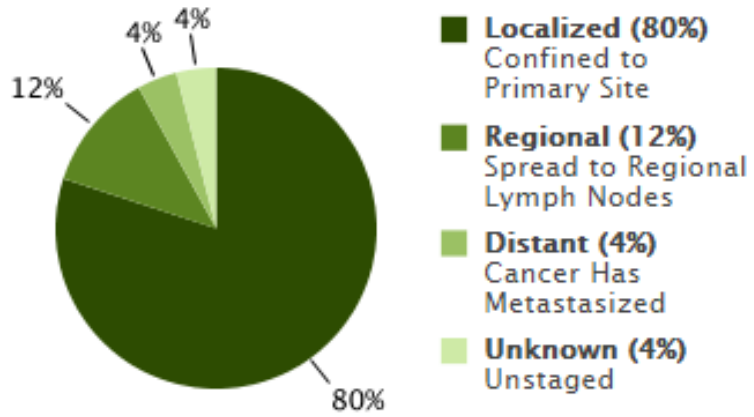
Lifetime Risk of Developing Cancer: Approximately 14.0 percent of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2010–2012 data.

Prevalence of This Cancer: In 2012, there were an estimated 2,795,592 men living with prostate cancer in the United States.

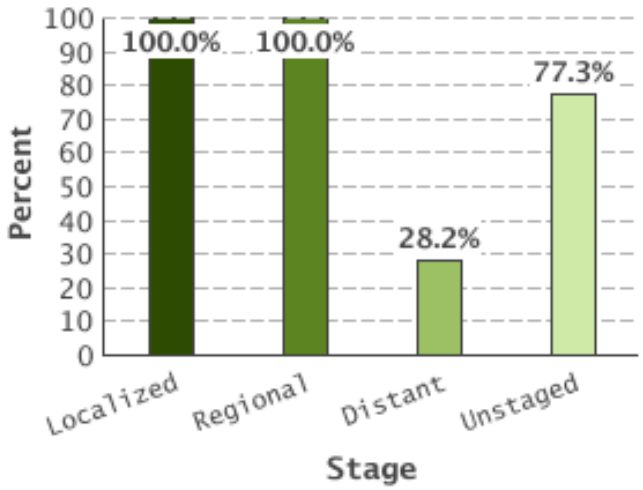
Prostat Kanseri İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Prostate Cancer

Percent of Cases by Stage

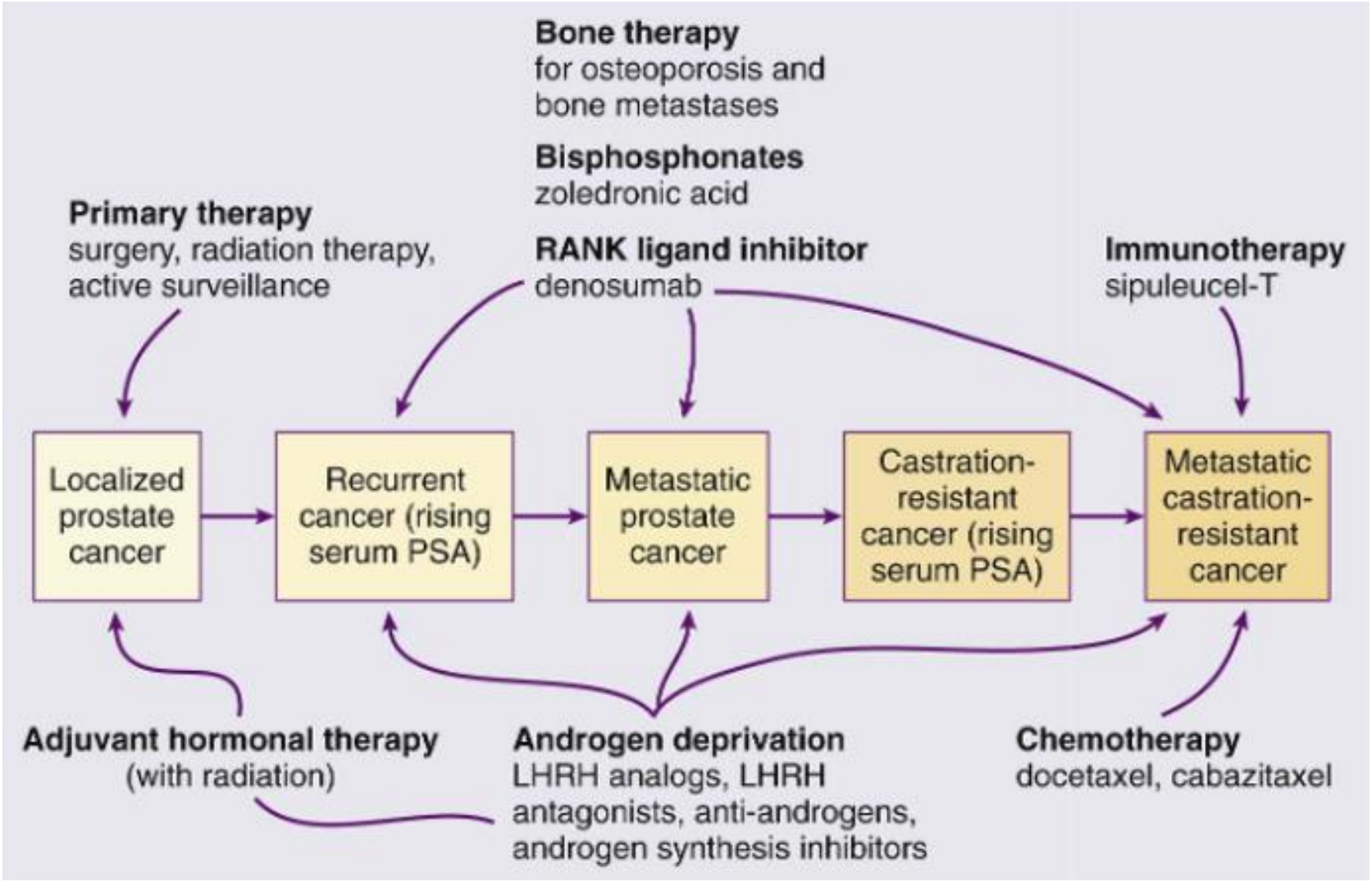


5-Year Relative Survival



SEER 18 2005-2011, All Races, Males by SEER Summary Stage 2000

Prostat Kanseri Tedavi Yakalaşımları



Şekil; Abeloff's Clinical Oncology, 10th edition

Hormon Duyarlı Metastatik Prostat Kanseri

Androjen Baskılama Tedavisi(ADT)

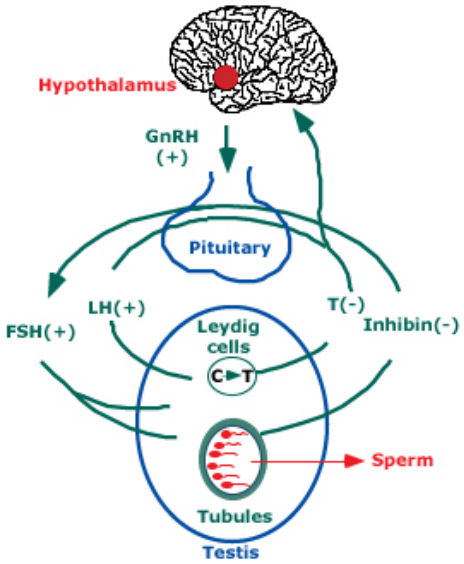
- ❑ Cerrahi Kastrasyon(Bilateral orişektomi)

- ❑ Medikal Kastrasyon
  - ✓ LHRH analogları, LHRH antagonistler
  - ✓ Total androjen blokajı(Antiandrojenlerin eklenmesi)

- ❑ Uygulama seçenekleri
  - ✓ Continue androjen baskılanması
  - ✓ İntermittan androjen baskılanması

Hormon Duyarlı metastatik Prostat Kanseri

Hypothalamic-pituitary-testicular axis



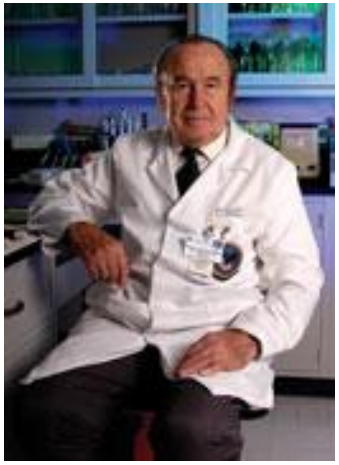
Schematic representation of the hypothalamic-pituitary-testicular axis shows the site of action of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the testes. Testosterone (T) and inhibin are produced by the testes. Testosterone has a negative feedback on the hypothalamus and LH production, while inhibin has a negative feedback on FSH production.

C: cholesterol; GnRH: gonadotropin releasing hormone.

Adapted from Griffin JE, Wilson JD. In: Metabolic Control and Disease, 8th ed, Bondy PK, Rosenberg LE (Eds), Saunders, Philadelphia 1980. p. 1535.

Graphic 50484 Version 2.0

Hormon Duyarlı metastatik Prostat Kanseri



- Charles Brenton Huggins(1901-1997)
- 1927'de Chicago Üniversitesinde Üroloji kliniğinde akademik kadro aldı
- Köpeklerde yaptığı deneylerle, prostat hücrelerinin büyümesinde testosteron hormonuna bağımlı olduğunu tespit etti
- Prostat kanseri olanlarda orişektomi ile tümörün küçüldüğünü belirledi.
- Bu çalışmalarıyla 1966 Nobel ödülü aldı
- Dr. Andrew V. Schally LHRH analoğu keşfi ile 1977 Nobel ödülü alıyor

Hormon Duyarlı Metastatik Prostat Kanseri

Cerrahi Kastrasyon vs. Medikal Kastrasyon

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Ann Intern Med. 2000 Apr 4;132(7):566-77.

Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis.

Seidenfeld J[1], Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, Wilt TJ.

Author information

Erratum in
Ann Intern Med. 2005 Nov 15;143(10):764-5.

Abstract

PURPOSE: To compare luteinizing hormone-releasing hormone (LHRH) agonists with orchiectomy or diethylstilbestrol, and to compare antiandrogens with any of these three alternatives.

DATA SOURCES: A search of the MEDLINE, Cancerlit, EMBASE, and Cochrane Library databases from 1966 to March 1998 and Current Contents to 24 August 1998 for articles comparing the outcomes of the specified treatments. The search was limited to studies on prostatic neoplasms in humans. Total yield was 1477 studies.

STUDY SELECTION: Reports of efficacy outcomes were limited to randomized, controlled trials. Twenty-four trials involving more than 6600 patients, phase II studies that reported on withdrawals from therapy (the most reliable indicator of adverse effects), and all studies reporting on quality of life were abstracted.

DATA EXTRACTION: Two independent reviewers abstracted each article by following a prospectively designed protocol. The meta-analysis combined data on 2-year overall survival by using a random-effects model and; reported results as a hazard ratio relative to orchiectomy.

DATA SYNTHESIS: Ten trials of LHRH agonists involving 1908 patients reported no significant difference in overall survival. The hazard ratio showed LHRH agonists to be essentially equivalent to orchiectomy (hazard ratio, 1.1262 [corrected] [95% CI, 0.915 to 1.386]). There was no evidence of difference in overall survival among the LHRH agonists, although CIs were wider for leuprolide (hazard ratio, 1.0994 [CI, 0.207 to 5.835]) and buserelin (hazard ratio, 1.1315 [CI, 0.533 to 2.404]) than for goserelin (hazard ratio, 1.1172 [CI, 0.898 to 1.390]). Evidence from 8 trials involving 2717 patients suggests that nonsteroidal antiandrogens were associated with lower overall survival. The CI for the hazard ratio approached statistical significance (hazard ratio, 1.2158 [CI, 0.988 to 1.496]). Treatment withdrawals were less frequent with LHRH agonists (0% to 4%) than with nonsteroidal antiandrogens (4% to 10%).

CONCLUSIONS: Survival after therapy with an LHRH agonist was equivalent to that after orchiectomy. No evidence shows a difference in effectiveness among the LHRH agonists. Survival rates may be somewhat lower if a nonsteroidal antiandrogen is used as monotherapy.

Comment in
Hormonal therapy for advanced prostate cancer. [Ann Intern Med. 2000]

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Cost-effectiveness of androgen suppression therapies in advanced p [J Natl Cancer Inst. 2000]
Maximum androgen blockade in advanced prostate cancer: a meta-analysis ([Urology. 1997]
Review Non-steroidal antiandrogen monotherap [Cochrane Database Syst Rev. 2014]
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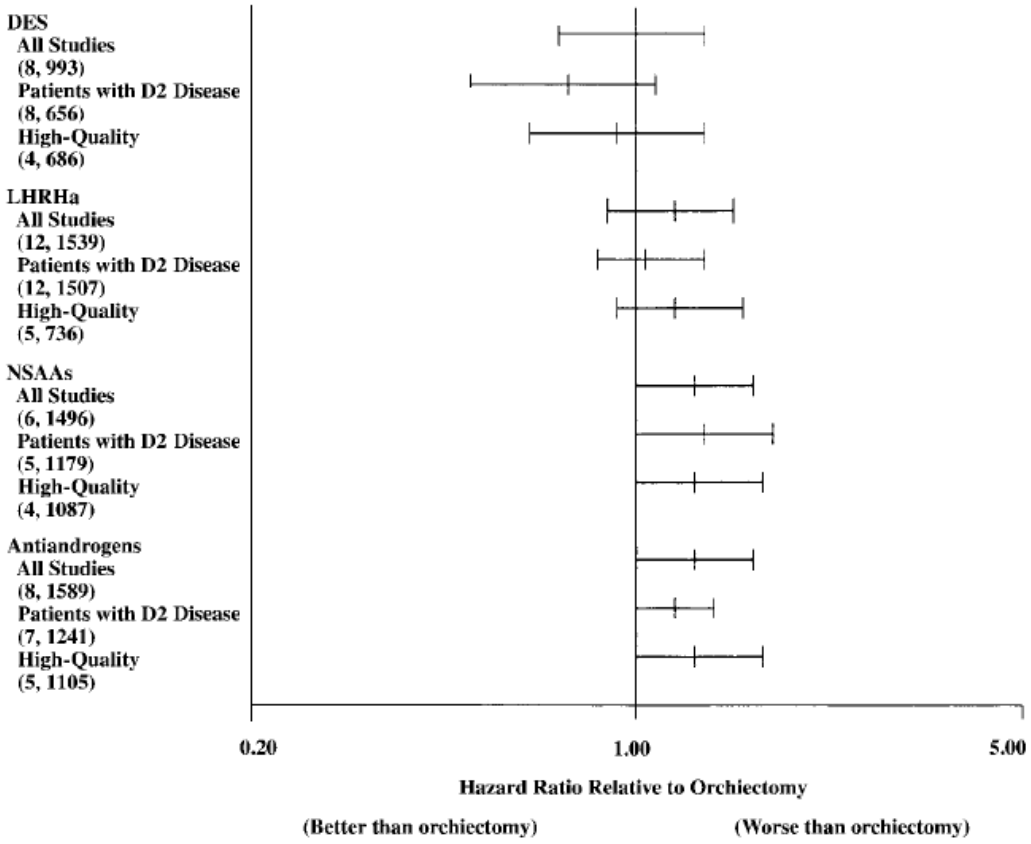
Cited by 41 PubMed Central articles
Review Therapeutic Rationales, Progresses, Failures, and Future Direction [Int J Biol Sci. 2016]
Review Surgery and hormonal treatment for prostate cancer and se: [Transl Androl Urol. 2015]
Review Cardiovascular effects of hormone therapy for prost [Drug Healthc Patient Saf. 2015]
See all...

Hormon Duyarlı Metastatik Prostat Kanseri

Cerrahi Kastrasyon vs. Medikal Kastrasyon



Bilateral Orişektomi, LHRH analoglarıyla benzer 2 yıllık sağkalıma sahip .
Antiandrojenler bu iki guruba göre daha kötü bir sağkalım gösterir

Hormon Duyarlı Metastatik Prostat Kanseri

Kombine Androjen Blokajı vs. Monoterapi

		PFS	OS
Intergroup trial INT[1] 0036	Leuprolide+Flutamide Leoprolide	16.5 ay vs. 13.9 ay *P*= 0.039	35.6 ay VS. 28.3 *P=0.035*
Intergroup trial INT[2] 0105	Orşiektomi+Flutamide Orşiektomi	20 ay vs. 19 ay *P*=0.21	34 ay vs. 30 ay *P*=0.14
Metaanaliz[3]	Medikal/Cerrahi kastrasyon+/-Antiandrojenler(Flutamide,Nilutamide)		5 yılık sağkalım %27.6 vs %24.7 P=0.005

ASCO 2016, NCCN 2016

CAB tedavi maliyeti ve toksik yan etki yüksek, sağ kalım yararı minimal (%2-3) olduğu için, hormon duyarlı Metastatik prostat kanseri başlangıç tedavisi olarak önerilmez.

(Semptomatik hastalarda Flare sendromunu engellemek için LHRH anologlarından en az 7 gün, LHRH anologları öncesi veya eş zamanlı)

1-Crawford ED , et al. N Engl J Med. 1989, 2- Eisenberger MA, et al. N Engl J Med. 1998, 3-Prostate Cancer Trialists' Collaborative Group. Lancet. 2000

Hormon Duyarlı Metastatik Prostat Kanseri

İntermittant vs. Continue

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Abstract

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N Engl J Med. 2013 Apr 4;368(14):1314-25. doi: 10.1056/NEJMoa1212299.

Intermittent versus continuous androgen deprivation in prostate cancer.

Hussain M[1], Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Kanaga Sundaram S, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, Thompson IM Jr.

Author information

Abstract

BACKGROUND: Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

METHODS: Men with newly diagnosed, metastatic, hormone-sensitive prostate cancer, a performance status of 0 to 2, and a prostate-specific antigen (PSA) level of 5 ng per milliliter or higher received a luteinizing hormone-releasing hormone analogue and an antiandrogen agent for 7 months. We then randomly assigned patients in whom the PSA level fell to 4 ng per milliliter or lower to continuous or intermittent androgen deprivation, with patients stratified according to prior or no prior hormonal therapy, performance status, and extent of disease (minimal or extensive). The coprimary objectives were to assess whether intermittent therapy was noninferior to continuous therapy with respect to survival, with a one-sided test with an upper boundary of the hazard ratio of 1.20, and whether quality of life differed between the groups 3 months after randomization.

RESULTS: A total of 3040 patients were enrolled, of whom 1535 were included in the analysis: 765 randomly assigned to continuous androgen deprivation and 770 assigned to intermittent androgen deprivation. The median follow-up period was 9.8 years. Median survival was 5.8 years in the continuous-therapy group and 5.1 years in the intermittent-therapy group (hazard ratio for death with intermittent therapy, 1.10; 90% confidence interval, 0.99 to 1.23). Intermittent therapy was associated with better erectile function and mental health (P<0.001 and P=0.003, respectively) at month 3 but not thereafter. There were no significant differences between the groups in the number of treatment-related high-grade adverse events.

CONCLUSIONS: Our findings were statistically inconclusive. In patients with metastatic hormone-sensitive prostate cancer, the confidence interval for survival exceeded the upper boundary for noninferiority, suggesting that we cannot rule out a 20% greater risk of death with intermittent therapy than with continuous therapy, but too few events occurred to rule out significant inferiority of intermittent therapy. Intermittent therapy resulted in small improvements in quality of life. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00002651.).

Hormon Duyarlı Metastatik Prostat kanseri

SWOG 9346 Çalışma Protokolü

Hormon Duyarlı Metastatik Prostat kanseri hastalarda iki kol arasında sağ kalım ve yaşam kalitesinin karşılaştırılması

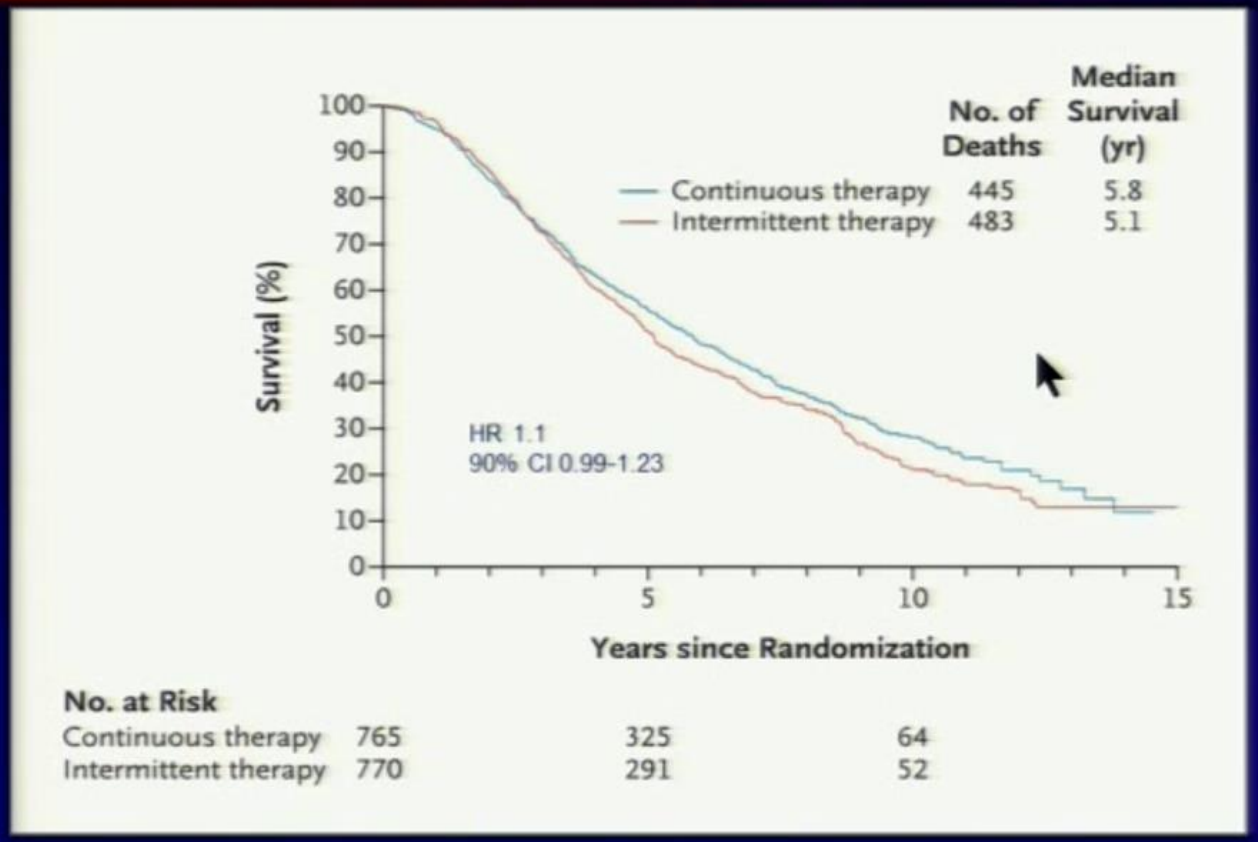
7 ay indüksiyon ADT sonra PSA< 4 ng/dl olan hastalar çalışmaya dahil edilmiş

I. Kol(Continue) ; progresyona kadar ADT devam eden kol

II. Kol(İntermittan kol); PSA düzeyi 20 ng/dl olan yada semptomatik PSA 10 ng/dl olanlara ADT tekrar başlanmış

Hormon Duyarlı Metastatik Prostat kanseri

Hormone sensitive metastatic, Overall survival SWOG 9346



Hussain et al NEJM 2013

Hormon Duyarlı Metastatik Prostat Kanseri

SWOG 9346 ; İntermittant vs. Continue

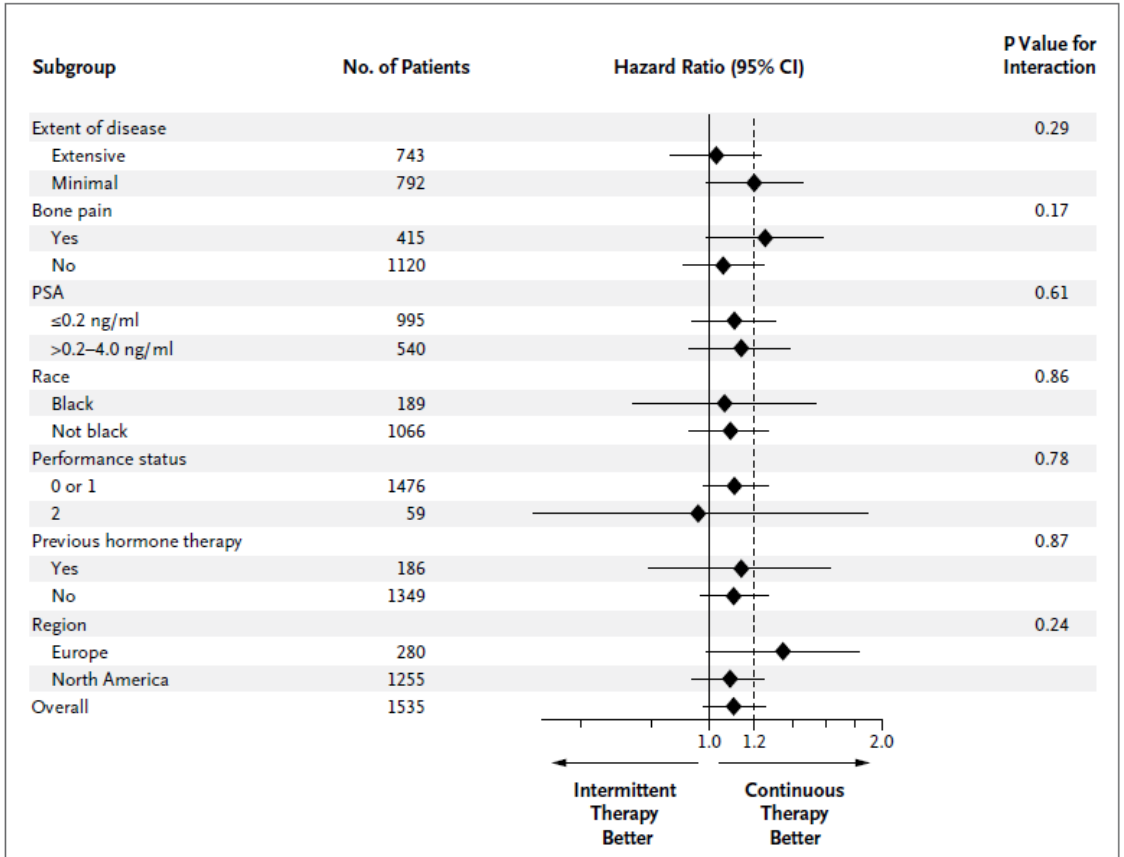


Figure 2. Survival According to Subgroups.

Minimal disease was considered to be disease confined to the spine, pelvic bones, or lymph nodes, and extensive disease as disease present in the ribs, long bones, or visceral organs (the definitions used in the trials of the Southwest Oncology Group). A performance status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction; 1, that the patient is ambulatory but restricted to light work; and 2, that the patient is ambulatory and capable of all self-care and is up and about more than 50% of waking hours but is unable to carry out any work activities. Race was self-reported. PSA denotes prostate-specific antigen.

Hormon Duyarlı Metastatik Prostat Kanseri

SWOG 9346 ; İntermittant vs. Continue

Table 2. Difference in the Mean Change from Randomization to Follow-up in Primary Quality-of-Life Outcomes, According to Treatment Group.

Outcome	Intermittent Therapy	Continuous Therapy	Difference, Intermittent–Continuous (95% CI)	P Value
Erectile dysfunction*				
Patients with erectile dysfunction at randomization (%)	82	85		
3-mo analysis				
No. of patients included	466	450		
Change from randomization	−7%	2%	−10 percentage points (−14 to −5)	<0.001
9-mo analysis				
No. of patients included	438	393		
Change from randomization	−8%	2%	−10 percentage points (−15 to −5)	<0.001
15-mo analysis				
No. of patients included	385	363		
Change from randomization	−3%	2%	−4 percentage points (−10 to 1)	0.12
High libido†				
Patients with high libido at randomization (%)	29	26		
3-mo analysis				
No. of patients included	68	45		
Change from randomization	16%	−2%	18 percentage points (1 to 36)	0.04
9-mo analysis				
No. of patients included	66	35		
Change from randomization	20%	−11%	31 percentage points (9 to 53)	0.01
15-mo analysis				
No. of patients included	46	31		
Change from randomization	13%	3%	10 percentage points (−16 to 36)	0.46
Vitality‡				
Score at randomization	59.7	59.8		
3-mo analysis				
No. of patients included	465	446		
Change from randomization	−0.11	−1.42	1.32 (−0.83 to 3.46)	0.23
9-mo analysis				
No. of patients included	439	392		
Change from randomization	−0.36	−3.07	2.71 (0.26 to 5.16)	0.03
15-mo analysis				
No. of patients included	386	372		
Change from randomization	−2.02	−3.02	1.00 (−1.59 to 3.59)	0.45

Yan etki olarak intermittan kol, continue kola göre daha iyi sonuçlara sahip

Hormon Duyarlı Metastatik Prostat Kanseri

İntermittant vs. Continue

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

Saroj Niraula, Lisa W. Le, and Ian F. Tannock

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3116w-2029w/$20.00

DOI: 10.1200/JCO.2012.46.5492

A B S T R A C T

Purpose
Uncertainty exists regarding benefits of intermittent androgen deprivation (IAD) compared with continuous androgen deprivation (CAD) for treatment of prostate cancer. On the basis of a systematic review of evidence, our aim was to formulate a recommendation for either IAD or CAD to treat relapsing, locally advanced, or metastatic prostate cancer.

Methods
We searched literature published up to September 2012 from MEDLINE, EMBASE, the Cochrane Library, and major conference proceedings. We included randomized controlled trials comparing IAD and CAD if they reported overall survival (OS) or biochemical/radiologic time to disease progression.

Results
Nine studies with 5,508 patients met our criteria. There were no significant differences in time-to-event outcomes between the groups in any studies. The pooled hazard ratio (HR) for OS was 1.02 (95% CI, 0.94 to 1.11) for IAD compared with CAD, and the HR for progression-free survival was 0.96 (95% CI, 0.76 to 1.20). More prostate cancer–related deaths with IAD tended to be balanced by more deaths not related to prostate cancer with CAD. Superiority of IAD for sexual function, physical activity, and general well-being was observed in some trials. Median cost savings with IAD was estimated to be 48%.

Conclusion
There is fair evidence to recommend use of IAD instead of CAD for the treatment of men with relapsing, locally advanced, or metastatic prostate cancer who achieve a good initial response to androgen deprivation. This recommendation is based on evidence against superiority of either strategy for time-to-event outcomes and substantial decrease with IAD in exposure to androgen deprivation, resulting in less cost, inconvenience, and potential toxicity.

J Clin Oncol 31:2029-2036. © 2013 by American Society of Clinical Oncology

Hormon Duyarlı Metastatik Prostat Kanseri

Intermittant vs. Continue

Table 1. Important Features of Included Studies

Study	Sample Size (No.)	End Points	Median Follow-Up (months)	Study Population	Drugs Used for ADT	Strategy to Stop ADT	Strategy to Start ADT	Predefined QoL Measures
de Leval et al[28] (2002)	68	Primary: TTP	31 (mean)	Locally advanced, metastatic, or relapsing PSA after radical prostatectomy for localized CaP	Goserelin + flutamide	PSA ≤ 4 ng/mL on 2 successive measurements 2-3 months apart	PSA ≥ 10 ng/mL	Not mentioned
Schasfoort et al[25] (2003)	193	Primary: TTP; secondary: OS, QoL	25	Locally advanced or metastatic CaP	Buserelin + nilutamide	PSA < 4 ng/mL	PSA ≥ 20 ng/mL (for metastatic); PSA ≥ 10 ng/mL (for locally advanced)	Not mentioned
Miller et al[26] (2007)	335	Primary: TTP; secondary: OS, QoL, tolerability	51	Locally advanced or metastatic CaP	Goserelin + bicalutamide	PSA < 4 ng/mL or < 90% of baseline	PSA ≥ 10 ng/mL	EORTC/AUO questionnaire
Calais da Silva et al[24,30] (2011)	626	Primary: TTP; secondary: OS, QoL	57	Locally advanced or metastatic CaP	GnRH agonist (not named) + cyproterone	PSA < 4 ng/mL or < 80% of baseline after 3 months of ADT	PSA ≥ 10 ng/mL or ≥ 20% above nadir	EORTC QLQ-C30 QoL questionnaire and the EORTC Prostate Cancer Module
Tunn et al[29] (2007)	167	Primary: TTP; secondary: QoL	Not given	Localized CaP with relapsing PSA after radical prostatectomy	Leuprolide + cyproterone	PSA < 0.5 ng/mL	PSA ≥ 3 ng/mL	Not mentioned
Crook et al[21] (2012)*	1,386	Primary: OS; secondary: TTP, QoL	83	Localized RT-treated CaP with relapsing PSA	Multiple combinations	PSA < 4 ng/mL and no clinical progression	PSA ≥ 10 ng/mL	EORTC QLQ-C30 QoL questionnaire and trial-specific questionnaires
Mottet et al[22] (2012)	173	Primary: OS; secondary: TTP, QoL	47	Metastatic CaP	Leuprolide + flutamide	PSA < 4 ng/mL	PSA > 10 ng/mL or symptomatic progression	EORTC QLQ-C30 QoL
Salonen et al[27,31] (2012, 2013)	554	Primary: TTP; secondary: OS, treatment failure	65	Locally advanced or metastatic CaP	Goserelin + cyproterone (first 12 days)	PSA < 10.0 ng/mL or decreased at least by 50% (baseline PSA < 20.0 ng/mL)	PSA > 20 ng/mL or > baseline	Validated 30-item questionnaire
Hussain et al[23] (2012)*	1,535	Primary: OS, QoL; secondary: TTP	100	Metastatic hormone-sensitive CaP	Goserelin + bicalutamide	PSA ≤ 4 ng/mL	PSA ≥ 20 ng/mL or > baseline if baseline PSA < 20 ng/mL	SWOG QOL questionnaire: impotence, libido, energy, physical and emotional function

NOTE. TTP and progression-free survival have been used interchangeably.

Abbreviations: ADT, androgen-deprivation therapy; AUO, Association of Urologic Oncology; CaP, prostate cancer; EORTC, European Organisation for Research and Treatment of Cancer; GnRH, gonadotropin-releasing hormone; OS, overall survival; PSA, prostate-specific antigen; QLQ-C30, Quality of Life Questionnaire C30; QoL, quality of life; RT, radiotherapy; SWOG, Southwest Oncology Group; TTP, time to progression.

*Designed to test noninferiority of intermittent androgen deprivation compared with continuous androgen deprivation.

Hormon Duyarlı Metastatik Prostat Kanseri

İntermittant vs. Continue

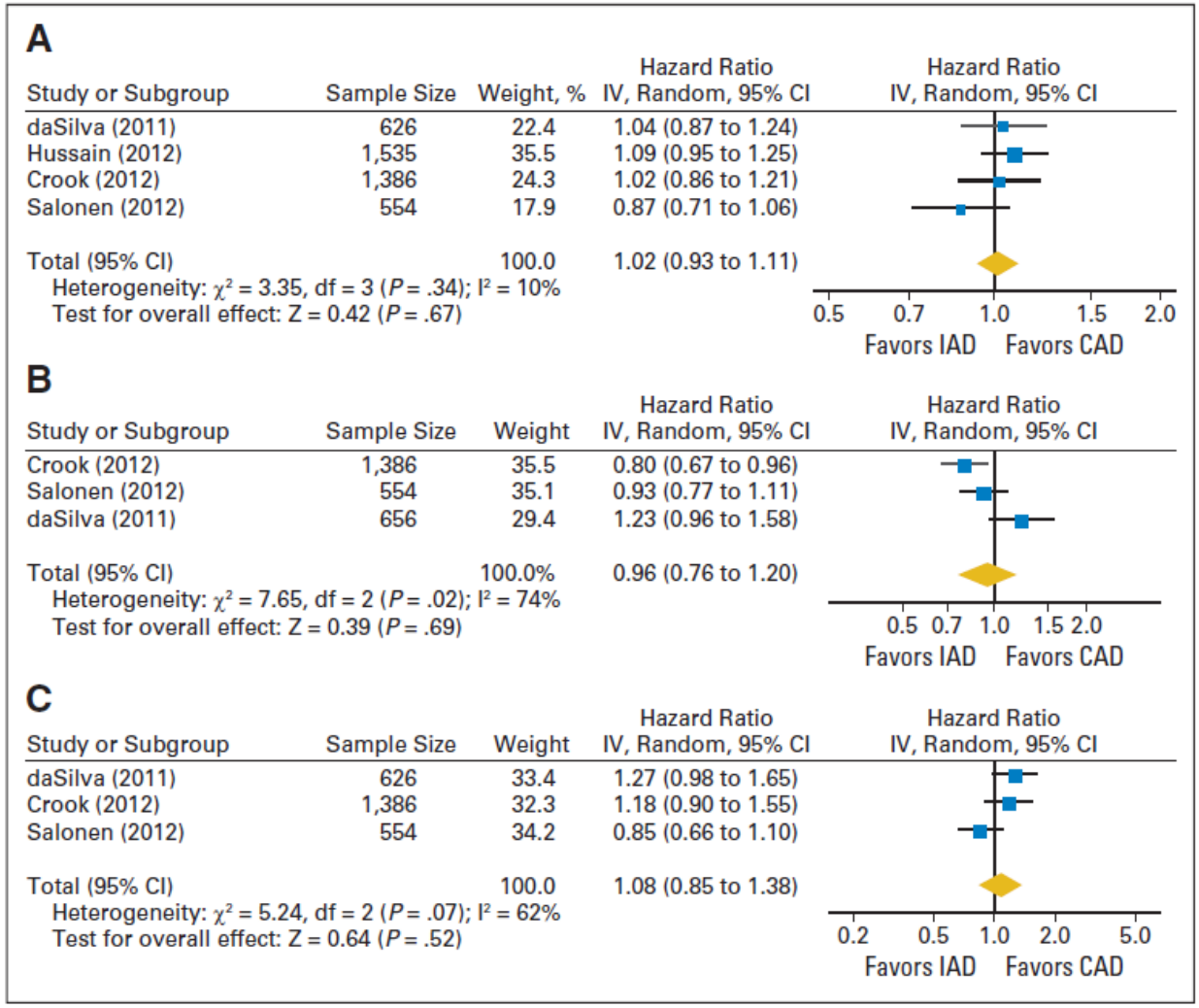

Fig 3. Pooled estimate of hazard ratios for (A) overall survival, (B) time to progression, and (C) prostate cancer–specific survival of intermittent androgen deprivation (IAD) compared with continuous androgen deprivation (CAD) in men with prostate cancer.

62 yaşında erkek hasta, semptomu yok, insidental olarak PSA 50 ng/ ml saptanıyor. Yaygın multiple kemik metastazı var. Genel durumu iyi(ECOG PS 0) bu hasta için en uygun tedavi şekli ne olmalı?

1-Androjen baskılama tedavisi(ADT)

2-ADT+ Dositaksel

3-ADT+Dositaksel+/-Deksametazon

4- Hepsi olabilir

- Pasifik Porsuk Ağacı
- Taxaceae familyasından, *Taxus* cinsinden
- Türkiyede; Kuzey Anadolu, Toroslar bölgesinde genelde yetişir
- Uzun ömürlü, 2000-3000 yılık olanlar vardır
- Yaprakları oldukça zehirlidir.
- Kızıl deriler zehirli ok uçları bu ağaçtan elde etmişler
- NCI ilk çalışmalarında; bir gram taksol elde etmek için, yüz kadar prosuk ağacı gerekmiştir.

Kastrasyona Dirençli Metastatik Prostat kanseri

J Clin Oncol. 2008 Jan 1

Docetaxel plus
the TAX 327 stu

Berthold DR[1], Pond G

⊕ **Author informa**

Abstract

PURPOSE: The TA
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METHODS: Investig

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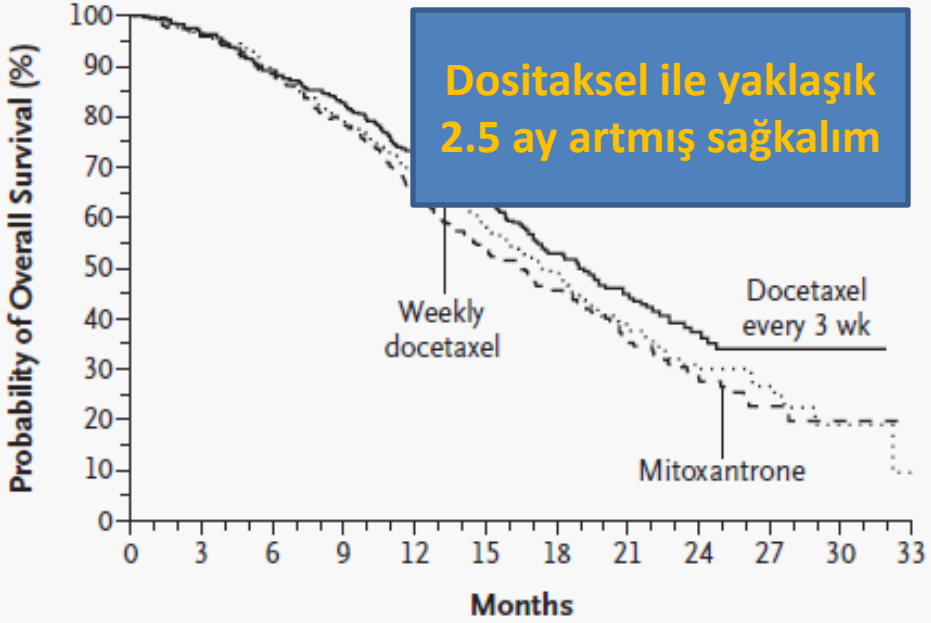

No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Lancet Oncol.

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Gravis G[1], Fi
D, Mourey L,
E, Eymard JC

⊕ **Author i**

Abstract

BACKGRO
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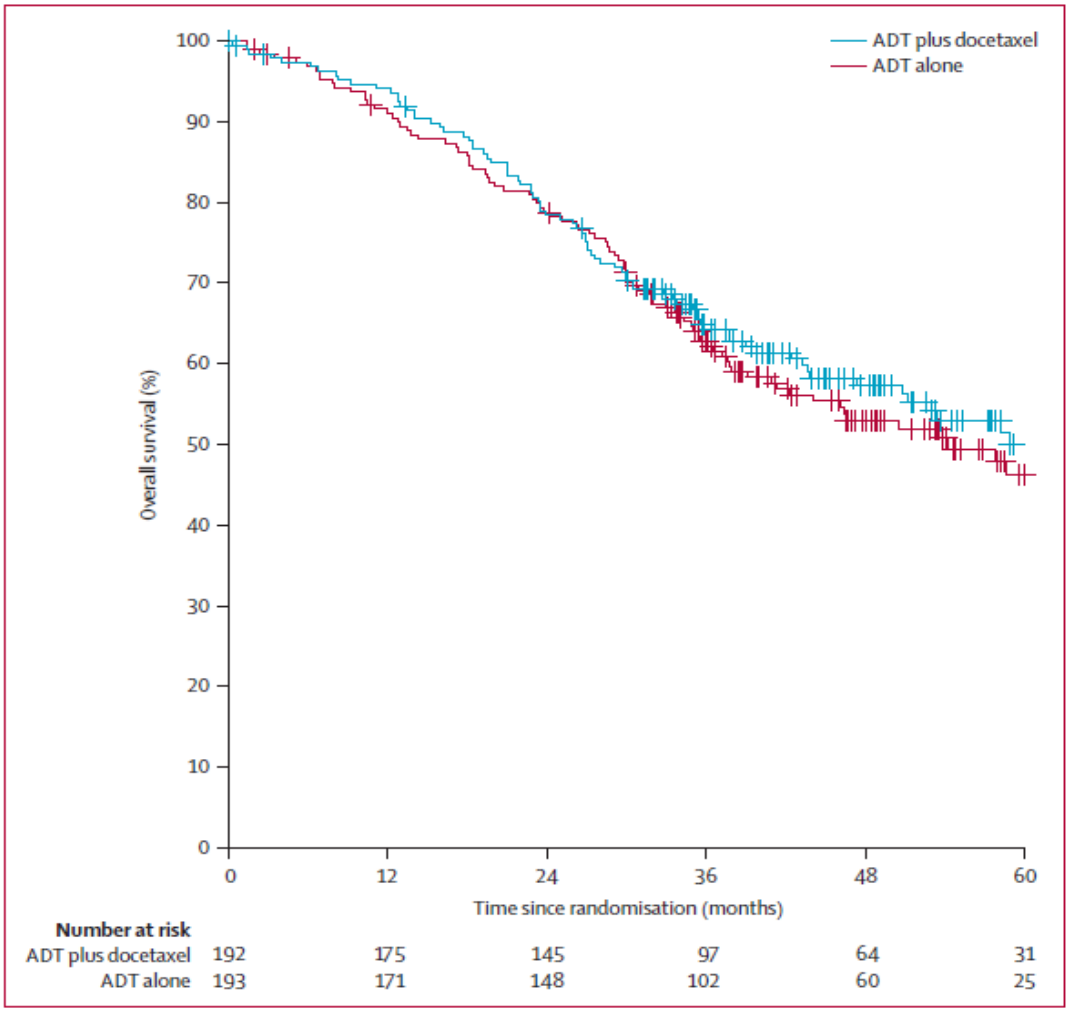

Figure 2: **Kaplan-Meier curves for overall survival by treatment group**
Crosses indicate censoring. ADT=androgen-deprivation therapy.

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JP, El Kouri C, Ravaud A, Suc

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prostate cancer.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

ABSTRACT

BACKGROUND

Androgen-deprivation therapy (ADT) has been the backbone of treatment for metastatic prostate cancer since the 1940s. We assessed whether concomitant treatment with ADT plus docetaxel would result in longer overall survival than that with ADT alone.

METHODS

We assigned men with metastatic, hormone-sensitive prostate cancer to receive either ADT plus docetaxel (at a dose of 75 mg per square meter of body-surface area every 3 weeks for six cycles) or ADT alone. The primary objective was to test the hypothesis that the median overall survival would be 33.3% longer among patients receiving docetaxel added to ADT early during therapy than among patients receiving ADT alone.

RESULTS

A total of 790 patients (median age, 63 years) underwent randomization. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT plus docetaxel (combination therapy) than with ADT alone (57.6 months vs. 44.0 months; hazard ratio for death in the combination group, 0.61; 95% confidence interval [CI], 0.47 to 0.80; P<0.001). The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group (hazard ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). The rate of a prostate-specific antigen level of less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group (P<0.001). In the combination group, the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%.

From the Department of Medicine (C.J.S.) and the Department of Biostatistics and Computational Biology (Y.-H.C.), Dana–Farber Cancer Institute, Boston; Harvard Medical School, Boston (C.J.S.); Johns Hopkins University, Baltimore (M.C., M.E.); University of Wisconsin Carbone Cancer Center (G.L., D.F.J.) and School of Medicine and Public Health (D.F.J.), Madison; Fox Chase Cancer Center, Temple University Health System, Philadelphia (Y.-N.W.); Indiana University Melvin and Bren Simon Cancer Center, Indianapolis (N.H.); Mayo Clinic, Rochester, MN (M.K.); University Hospitals Case Medical Center, Seidman Cancer Center (M.M.C.), and Cleveland Clinic Taussig Cancer Institute (J.A.G.) — both in Cleveland; University of Virginia Cancer Center, Charlottesville (R.D.); Comprehensive Cancer Centers of Nevada, Las Vegas (N.J.V.); Siteman Cancer Center, Washington University School of Medicine, St. Louis (J.P.); NorthShore University HealthSystem, Evanston, IL (D.S.); University of Michigan Comprehensive Cancer Center, Ann Arbor (M.H.); and Rutgers Cancer Institute of New Jersey, New Brunswick (R.S.D.). Address reprint requests to Dr. Sweeney at christopher_sweeney@dfci.harvard.edu.

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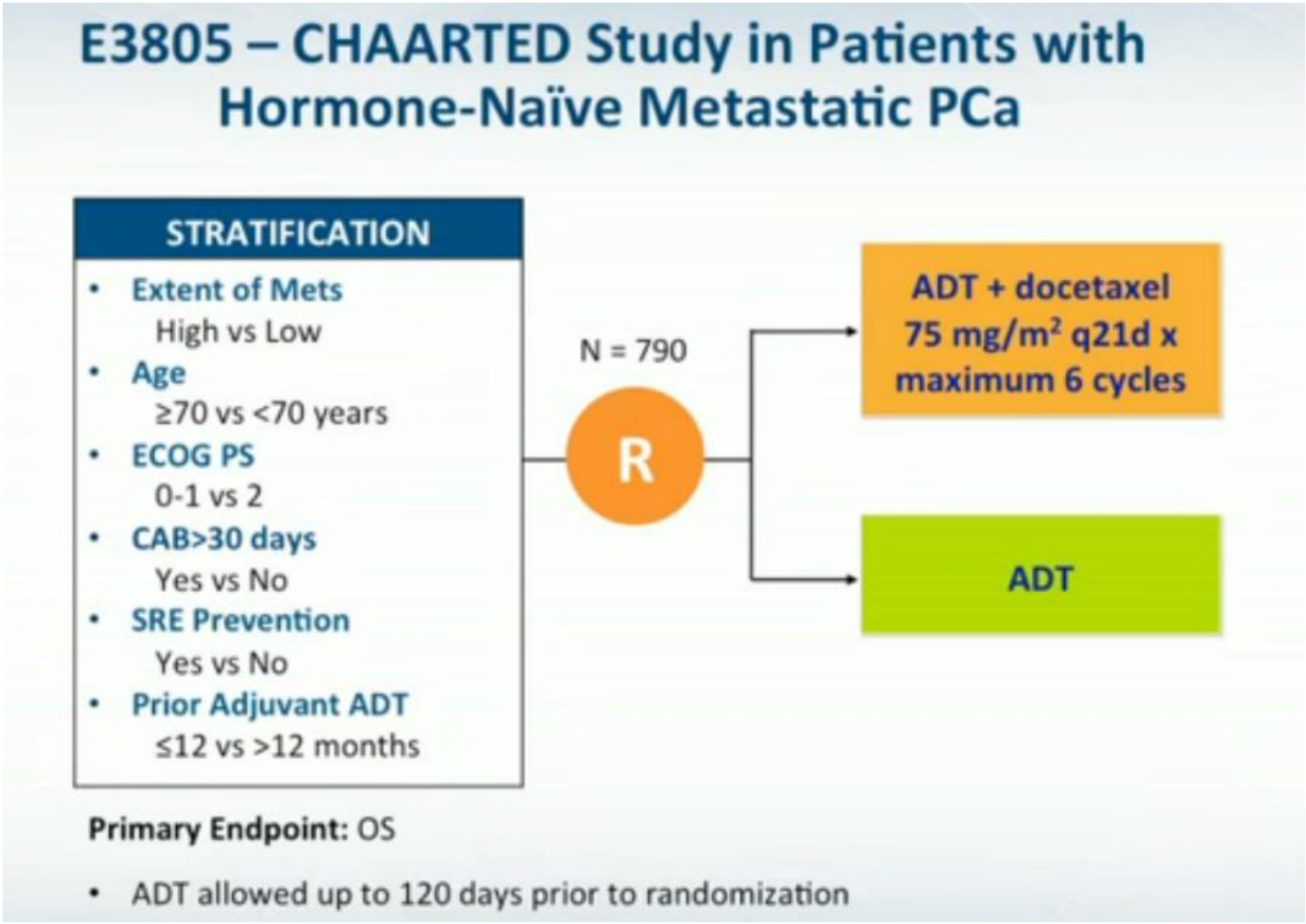
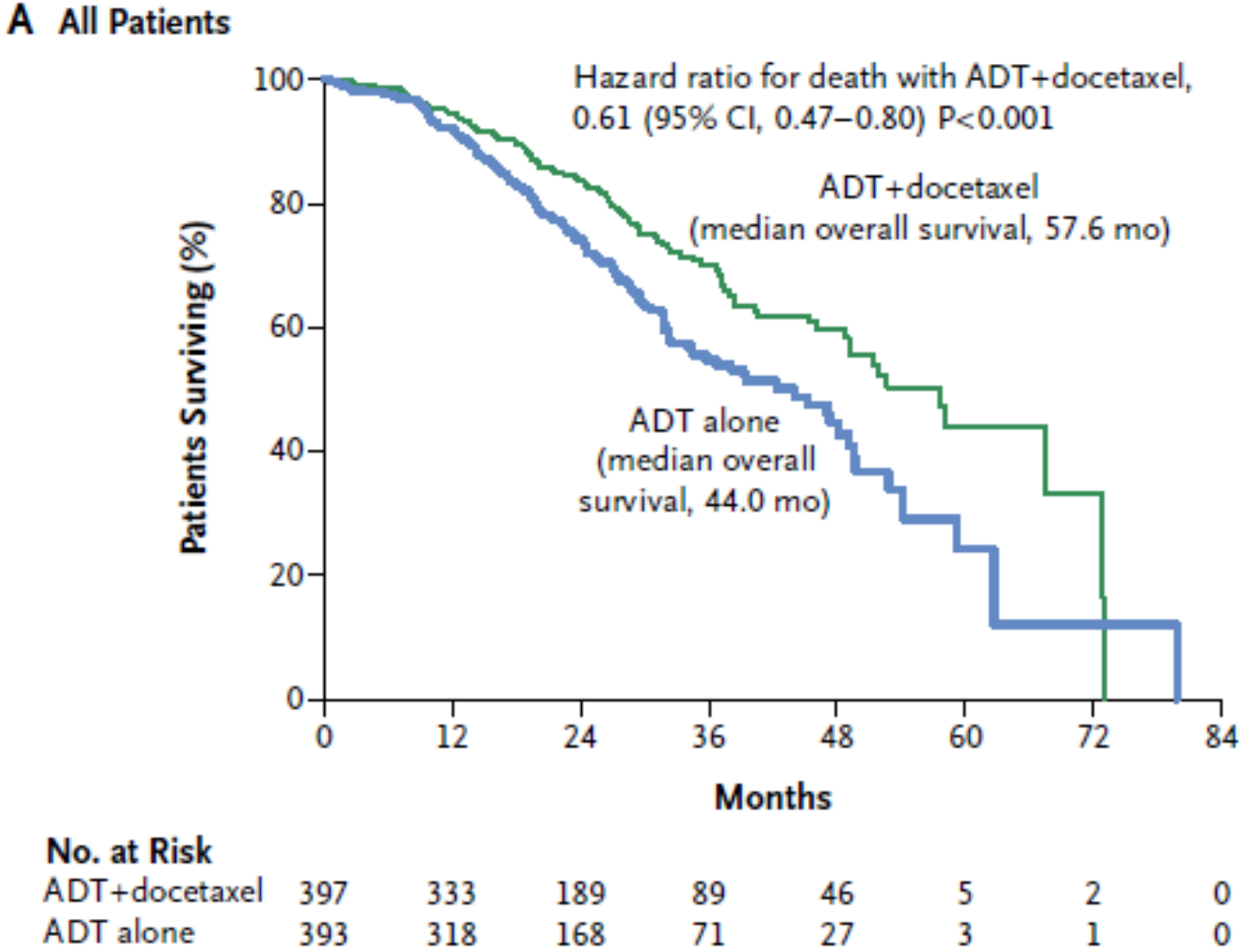
Hormon Duyarlı Metastatik Prostat Kanseri

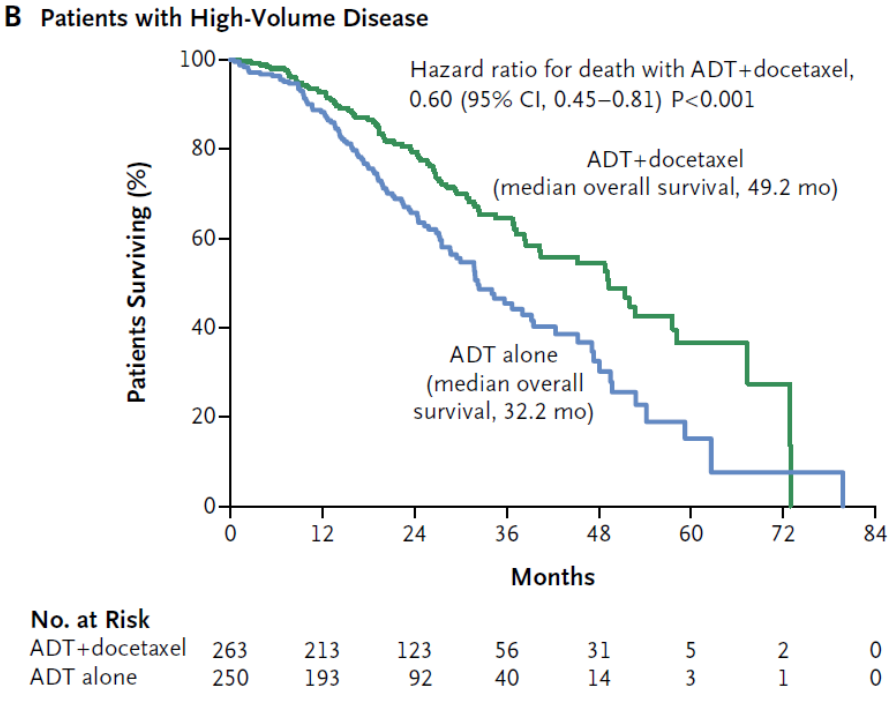
ADT + Erken Dönem Kemoterapi

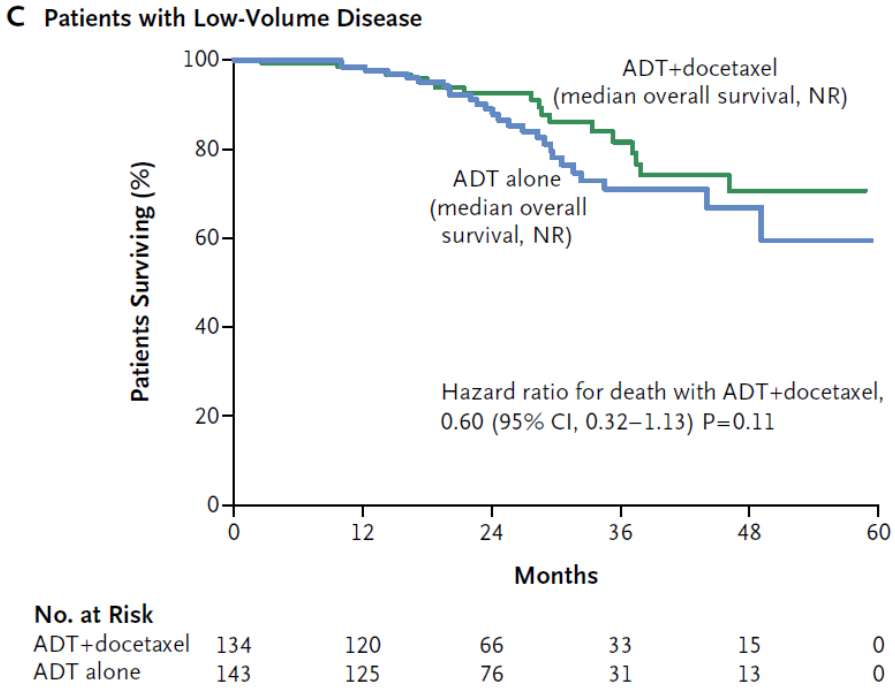


ADT + Erken Dönem Kemoterapi



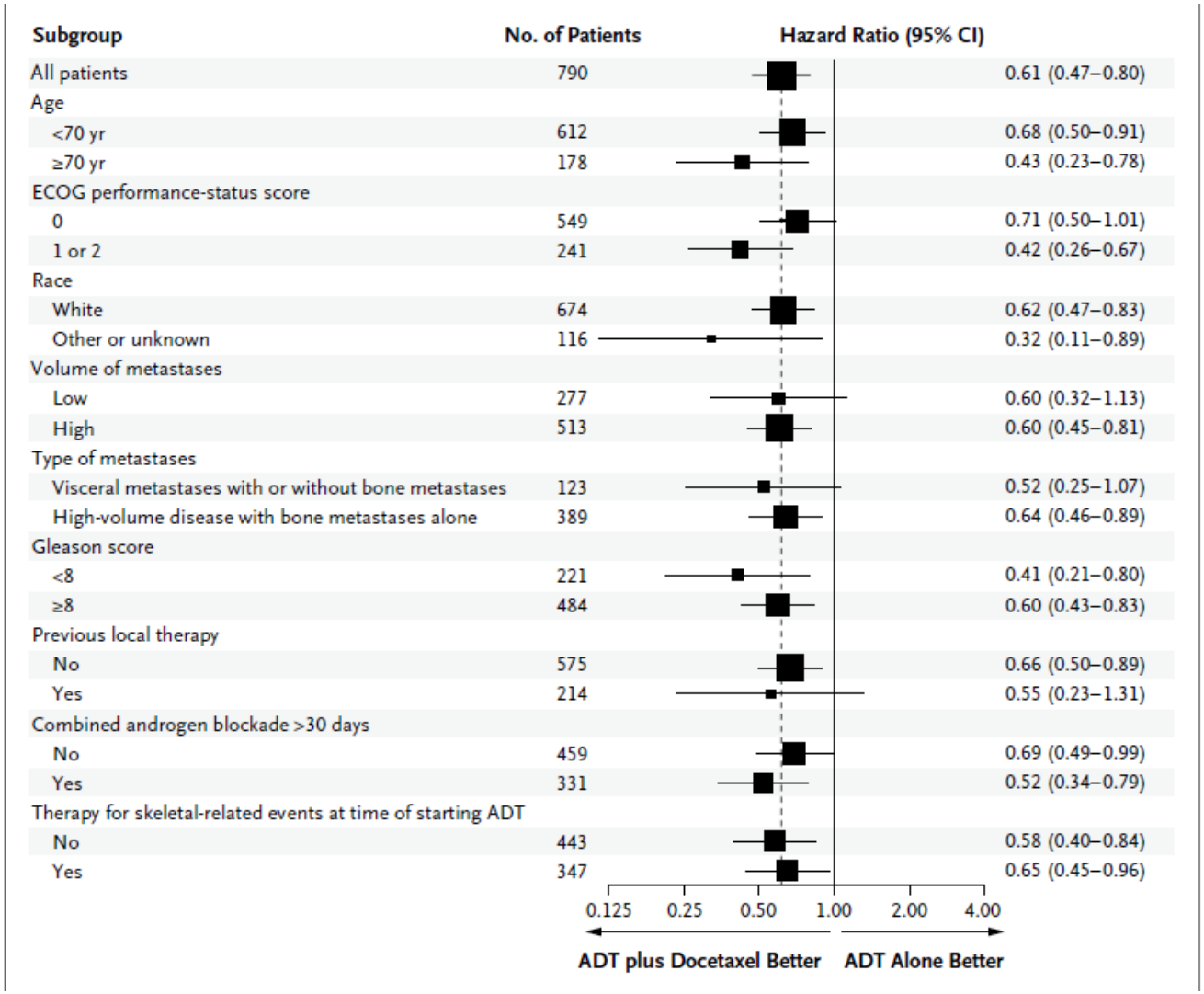
ADT + Erken Dönem Kemoterapi





Yüksek volümlü hastalığı olanlar; viseral organ metastazı olan yada ≥4 kemik lezyonu olan ve en az ≥1 vertebra, pelvis dışı kemiklerde metastaz olmalı

ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi

	ADT + doc (n = 397)	ADT alone (n = 393)	Hazard ratio	*p*-value
Primary endpoint				
Overall survival	57.6 mo	44.0 mo	0.61	0.0003
High-volume mets	**49.2 mo**	**32.2 mo**	**0.60**	**0.0006**
Low-volume mets	Not reached	Not reached	0.63	0.1398
Secondary endpoints				
Median time to CRPC (biochemical, symptoms or radiographic)	20.7 mo	14.7 mo	0.56	<0.0001
Median time to clinical progression (symptoms or radiographic)	32.7 mo	19.8 mo	0.49	<0.0001

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı
Kastrasyona dirençli metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	TAX327	CHARTED
HR	0.79	0.61
OS	2.4 ay	13.6 ay
KT sayısı	10	6
F.nötropeni	3%	6%
Prednisolon	var	yok

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı

Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	GETUG	CHARTED
HR	1.01	0.61
OS	4.7 ay	13.6 ay
KT sayısı	9	6
F.nötropeni	8 %	6%
Prednisolon	yok	yok

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı
Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri

	GETUG	CHARTED
Yüksek volüm	?	%66
Viseral metastaz	%10-15	?
Medyan PSA	27	56
Kötü risk gurubu	%22	?
Kemik metastazı	%81	?
M1 hastalık	%67	%73
Gleason Skoru 8-10	%55	%67

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Dositaksel KT metastatik prostat kanserinde erken kullanımı

Hormon duyarlı metastatik prostat kanseri vs. Hormon duyarlı metastatik prostat kanseri(GETUG Vs CHARTED)

- GETUG, 192 hasta KT almış
- %22 kötü risk gurubu, %50 iyi risk gurubunda, %81 kemik met, <%15 viseral metastaz

CHARTED ve GETUG sonuçlar neden Farklı

- Tam olarak bilinmiyor?
- Yüksek volüm hastalığı olanlar, anti mikrotubuler tedaviye daha duyarlı olabilir
- Farklı genetik karekter olabilir(RB1, AR durumu?)
- GETUG çalışmasında hasta sayısının düşüklüğü, yetersiz power?

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Methods Standard of care was hormone therapy for at least 2 years; radiotherapy was encouraged for men with N0M0 disease to November, 2011, then mandated; radiotherapy was optional for men with node-positive non-metastatic (N+M0) disease. Stratified randomisation (via minimisation) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC + ZA), standard of care plus docetaxel (SOC + Doc), or standard of care with both zoledronic acid and docetaxel (SOC + ZA + Doc). Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4-weekly until 2 years, and docetaxel (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. There was no blinding to treatment allocation. The primary outcome measure was overall survival. Pairwise comparisons of research versus control had 90% power at 2·5% one-sided α for hazard ratio (HR) 0·75, requiring roughly 400 control arm deaths. Statistical analyses were undertaken with standard log-rank-type methods for time-to-event data, with hazard ratios (HRs) and 95% CIs derived from adjusted Cox models. This trial is registered at ClinicalTrials.gov (NCT00268476) and ControlledTrials.com (ISRCTN78818544).

Lancet 2016; 387: 1163–77

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See Comment page 1135

*Members listed at end of paper

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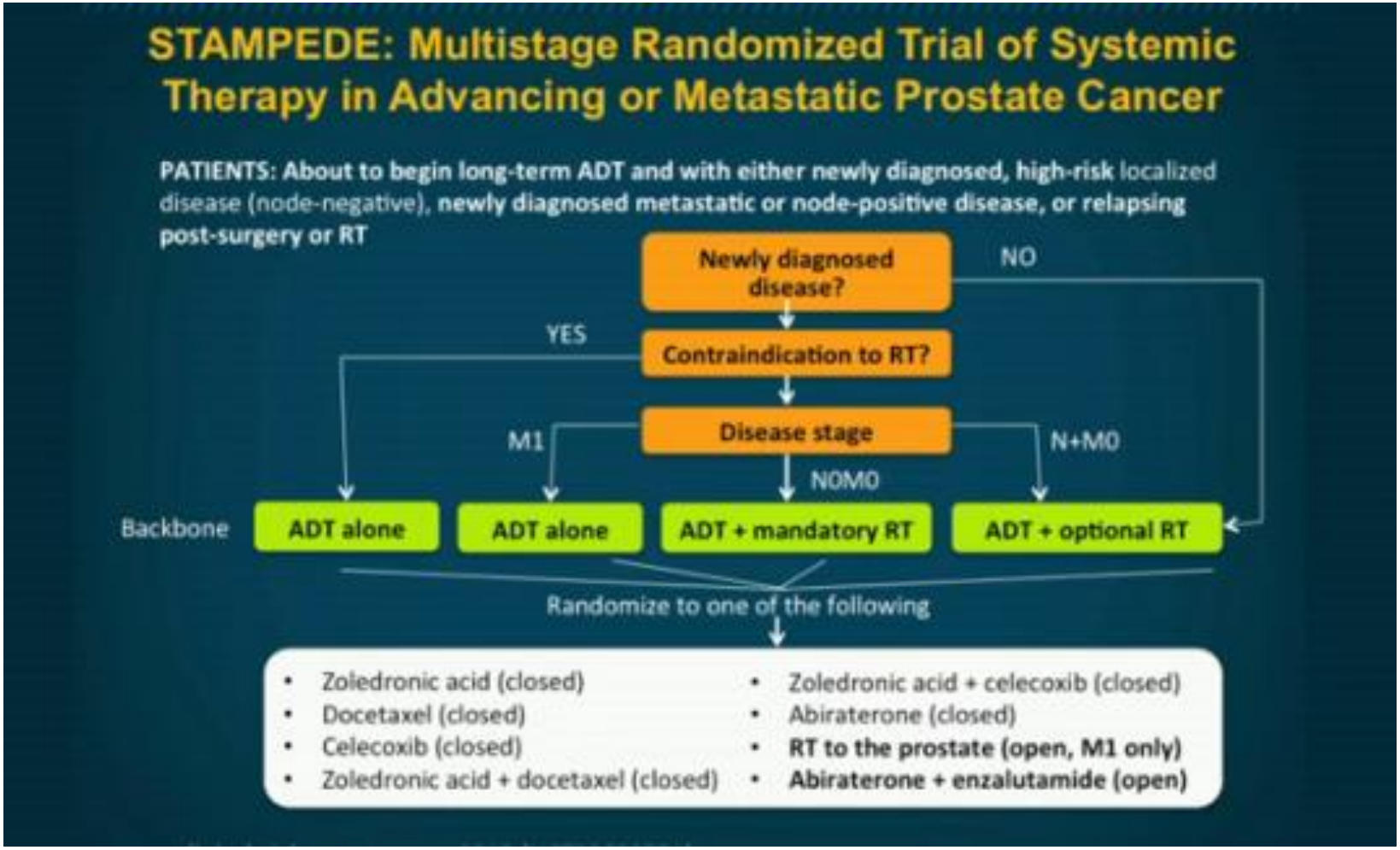
Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi



ADT + Erken Dönem Kemoterapi

STAMPEDE: Docetaxel and/or Zoledronic Acid in Hormone-Naïve Metastatic PCa

First overall survival analysis of patients enrolled in the following 4 study arms:

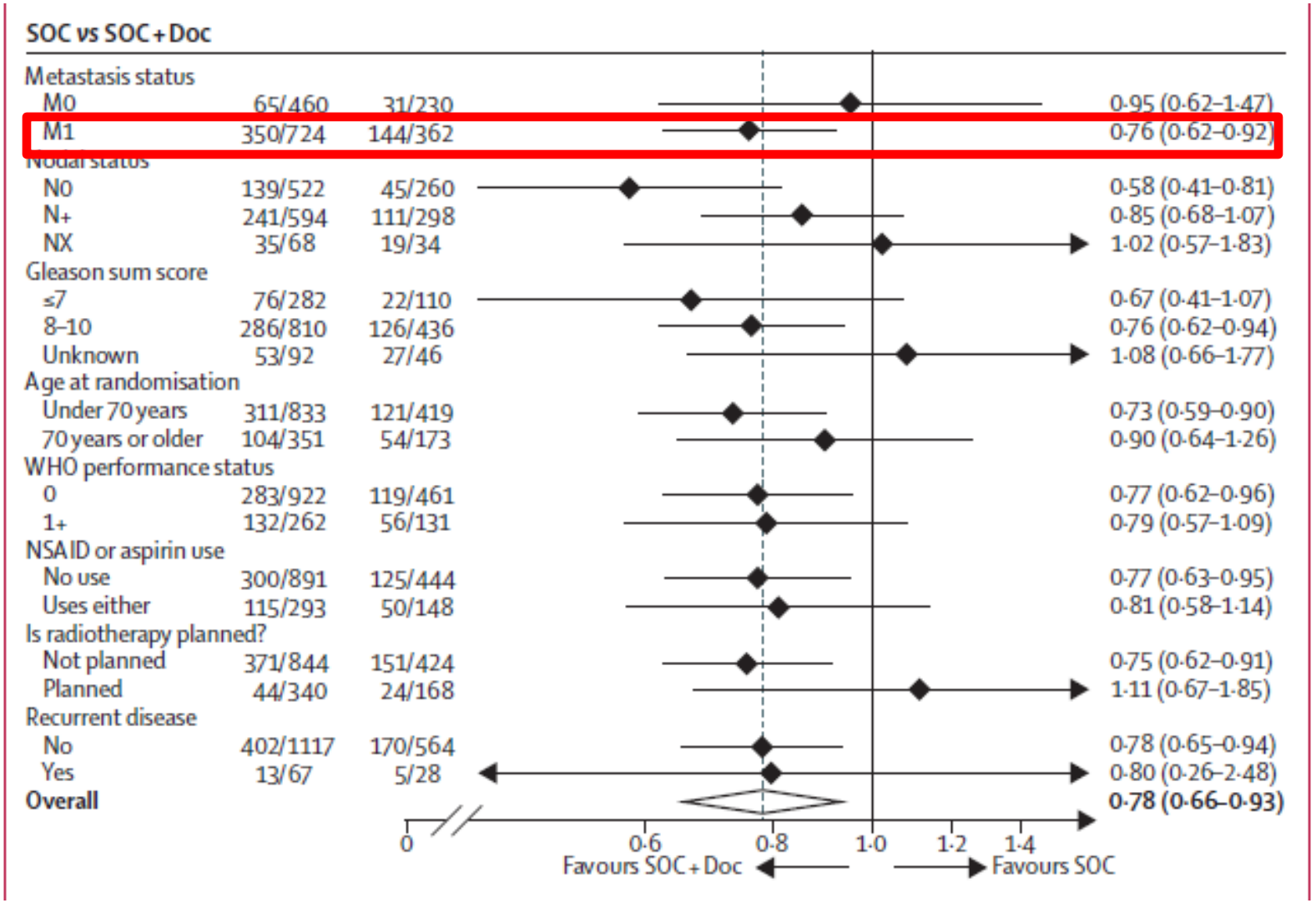
- Standard of care (SOC; n = 1,184)
- Docetaxel (Doc) + SOC (n = 592)
- Zoledronic acid (ZDA) + SOC (n = 593)
- Doc + ZDA + SOC (n = 593)

	SOC	Doc + SOC	ZDA + SOC	Doc + ZDA + SOC
Median overall survival	67 mo	77 mo	80 mo	72 mo
Hazard ratio (*p*-value)	**Ref***	**0.76 (0.003)**	**0.93 (0.44)**	**0.81 (0.02)**
Median failure-free survival	21 mo	37 mo	21 mo	37 mo
Hazard ratio (*p*-value)	**Ref***	**0.62 ($<0.1 \times 10^{-10}$)**	**0.93 (0.26)**	**0.62 ($<0.1 \times 10^{-10}$)**

* Pairwise comparisons to control SOC study arm were calculated for each research arm.

- **Docetaxel, and not ZDA, improves overall survival compared to SOC**
- **Docetaxel + ZDA improves survival but offers no obvious benefit over docetaxel alone**

ADT + Erken Dönem Kemoterapi



Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Journal of Clinical Oncology, 2015 ASCO Annual Meeting (May 29 - June 2, 2015).
Vol 33, No 18_suppl (June 20 Supplement), 2015: LBA5002

A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521).

Howard M. Sandler, Chen Hu, Seth A. Rosenthal, Oliver Sartor, Leonard G. Gomella, Mahul Amin, James Purdy, Jeff M. Michalski, Mark Garzotto, Nadeem Pervez, Alexander G. Balogh, George Rodrigues, Luis Souhami, M. Neil Reaume, Scott G. Williams, Raquibul Hannan, Eric M. Horwitz, Adam Raben, Rebecca Paulus and William U. Shipley

Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Sutter Cancer Center, Sacramento, CA; Tulane University School of Medicine, New Orleans, LA; The Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Cedars-Sinai Medical Center, Los Angeles, CA; UC Davis, Sacramento, CA; Washington University in St. Louis, St. Louis, MO; Portland VAMC, Portland, OR; Cross Cancer Institute, Edmonton, AB, Canada; Tom Baker Cancer Center, Calgary, AB, Canada; Department of Radiation Oncology, London Regional Cancer Program, London, ON, Canada; Department of Radiation Oncology, McGill University Health Centre, Montreal, QC, Canada; Ottawa Hospital Cancer Center, Ottawa, ON, Canada; Peter MacCallum Cancer Centre, East Melbourne, Australia; The University of Texas Southwestern Medical Center, Dallas, TX; Fox Chase Cancer Center, Philadelphia, PA; Helen F Graham Cancer Ctr, Newark, DE; Radiation Therapy Oncology Group, Statistical Center, Philadelphia, PA; Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract Disclosures

Abstract

LBA5002

Background: High-risk, localized prostate cancer (PCa) patients have a relatively poor prognosis. We hypothesized that the addition of adjuvant docetaxel and prednisone to long-term (24 month) AS and radiation therapy (RT) would improve overall survival (OS). **Methods:** RTOG 0521 opened December 2005 and closed August 2009 with targeted accrual of 600 cases. It was designed to detect improvement in 4-year OS from 86% to 93% with a 51% hazard reduction (HR = 0.49). Under a 0.05 1-sided type I error and 90% power, at least 78 deaths were required to analyze the OS endpoint. Patients had 1) Gleason (Gl) 7-8, any T-stage, and PSA > 20, or 2) Gl 8, ≥ T2, any PSA, or 3) Gl 9-10, any T-stage, any PSA. All had PSA ≤ 150. RT dose was 75.6 Gy. CT consisted of 6, 21-day cycles of docetaxel + prednisone starting 28 days after RT. **Results:** Of 612 enrolled, 50 were excluded for eligibility issues, leaving 562 evaluable. Median age = 66, median PSA = 15.1, 53% had Gl 9-10, 27% had cT3-4. Median follow-up = 5.5 yrs. 4-yr OS rates were 89% [95% CI: 84-92%] for the AS+RT arm and 93% [95% CI: 90-96%] for the AS+RT+CT arm (1-sided p = 0.03, HR = 0.68 [95% CI: 0.44, 1.03]). There were 52 centrally-reviewed deaths in the AS+RT arm and 36 in the AS+RT+CT arm, with fewer deaths both due to PCa/treatment (20 vs 16) and due to other causes/unknown (32 vs 20) in the AS+RT+CT arm. 5-yr disease-free survival rates were 66% for AS+RT and 73% for AS+RT+CT (2-sided p = 0.05, HR = 0.76 [95% CI: 0.57, 1.00]). There was 1, Gr 5 unlikely-related adverse event (AE) in the AS+RT arm and 2, Gr 5 possibly/probably-related AEs with AS+RT+CT. **Conclusions:** For high-risk, localized PCa, adjuvant CT improved the OS from 89% to 93% at 4 years. Toxicity was acceptable. This trial was designed with a short OS assessment period and additional follow-up is warranted to determine the long-term benefit of CT to the current standard of care of long-term AS+RT. This project was supported by grants U10CA21661, U10CA180868, U10CA180822, from the National Cancer Institute and Sanofi with additional support from AstraZeneca for Australian site participation. Clinical trial information: NCT00288080.

Hormon Duyarlı Metastatik Prostat Kanseri

ADT + Erken Dönem Kemoterapi

RTOG-0521: Androgen Suppression (AS) and Radiation Therapy (RT) with or without Docetaxel (Doc) in Localized, High-Risk PCa

	AS + RT	AS + RT + Doc	Hazard ratio	*p*-value
Primary endpoint				
4-year overall survival rate	89%	93%	0.70	0.04
Secondary endpoints				
Biochemical failure at 6 years	74%	66%	0.81	0.19
Disease-free survival at 6 years	55%	65%	0.76	0.04

"For the first time, improvement in overall survival observed with tolerable adjuvant chemotherapy for localized, high-risk hormone-sensitive prostate cancer."

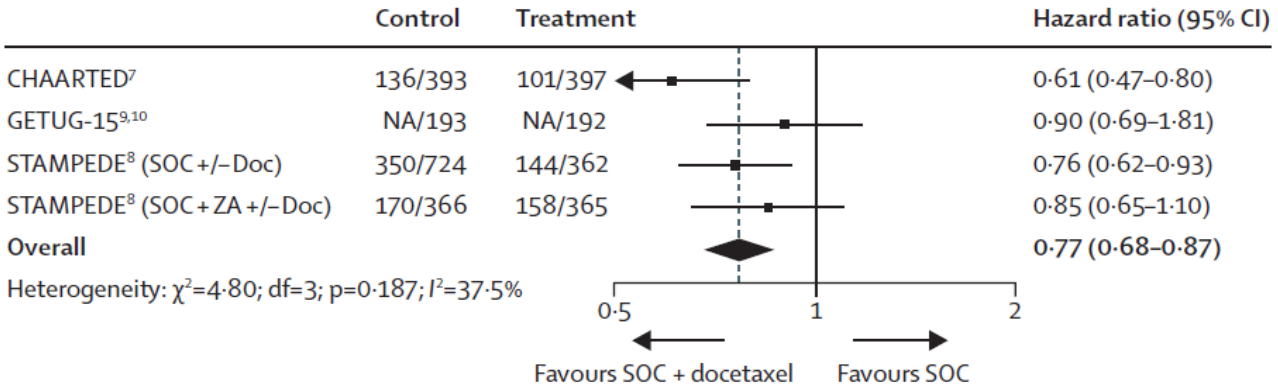
Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi

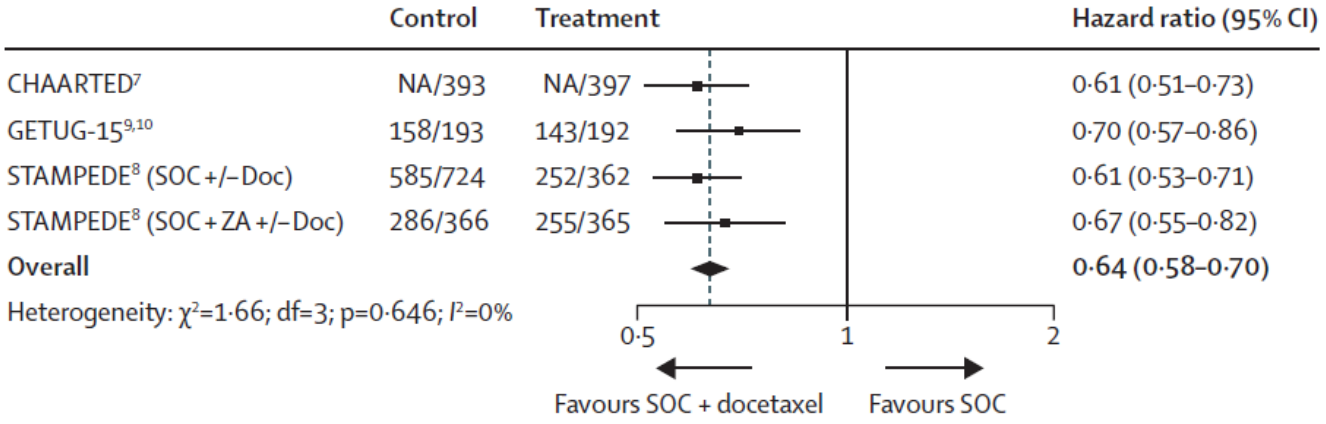
	Accrual period	Number of patients	Control	Treatment	Metastatic status	Median age (range)	Gleason score of 8–10 (%)	Performance status of 0–1 (%)	Median follow-up (survival)	Treatment on progression (control group only)
Docetaxel trials										
GETUG-12[25,26]	November, 2002–December, 2006	413	ADT (goserelin 10·8 mg every 3 months for 3 years)	ADT plus docetaxel (70 mg/m² for four cycles) plus estramustine	M0	63 (46–77)	42%	Unknown	7 years, 6 months	Not reported
TAX 3501[9]	December, 2005–September, 2007	228	ADT (leuprolide 22·5 mg every 3 months for 18 months)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0	61·9*	52%	Unknown	3 years, 3 months	Not reported
RTOG 0521[28]	December, 2005–August, 2009	612	ADT (LHRH agonist plus oral anti-androgen plus RT)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone	M0	66 (unknown)	84%	Unknown	6 years	Not reported
STAMPEDE (standard of care with or without docetaxel)[8]	September, 2005–March, 2013	1776	ADT (plus radiotherapy for M0 patients)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus predisone	M0 and M1	65 (40–82)	70%	99%	3 years, 6 months	40% received docetaxel (49% received life-extending treatments)
STAMPEDE (standard of care plus zoledronic acid with or without docetaxel)[8]	September, 2005–March, 2013	1186	ADT (plus radiotherapy for M0 patients) plus zoledronic acid (4 mg every 3–4 weeks for 2 years)	ADT (plus radiotherapy for M0 patients) + zoledronic acid (4 mg for 3–4 weeks for 2 years) plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0 and M1	66 (42–84)	71%	99%	3 years, 6 months	36% received docetaxel (45% received life-extending treatments)
GETUG-15[9,10]	October, 2004–December, 2008	385	ADT (LHRH agonist or surgical castration or combined androgen blockade)	ADT plus docetaxel (75 mg/m² every 3 weeks for up to nine cycles)	M1	63·5 (57–70)	56%	100%	6 years, 11 months	62% received docetaxel
CHAARTED[7]	July, 2006–November, 2012	790	ADT (LHRH agonist or LHRH antagonist) or surgical castration	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M1	64 (36–91)	61%	98%	2 years, 5 months	147 (51%) of 287 men received docetaxel (104 of 287 men received abiratarone or enzalutamide)

Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi



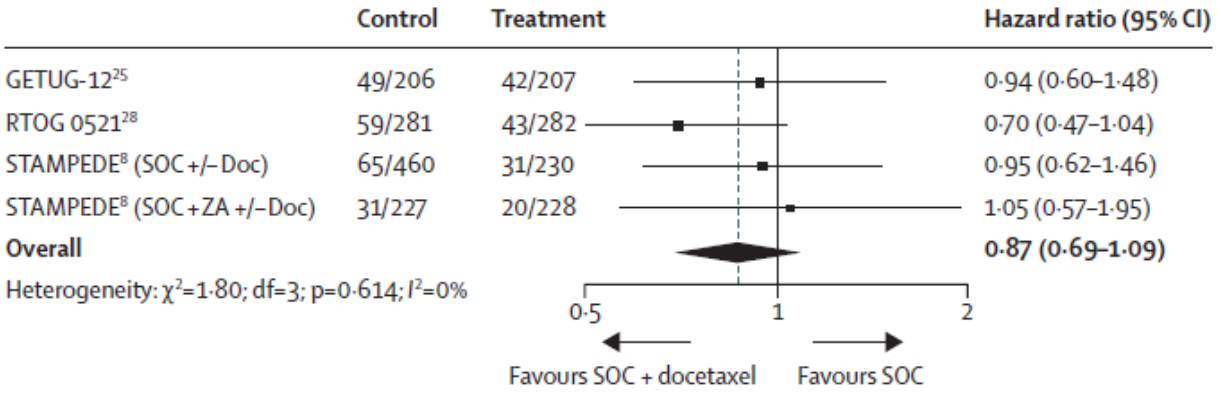
2992 hormona duyarlı metastatik prostat ca hastaya ADT +dositaksel eklenmesi ; 4-yıllık sağkalımı %9 artırıyor



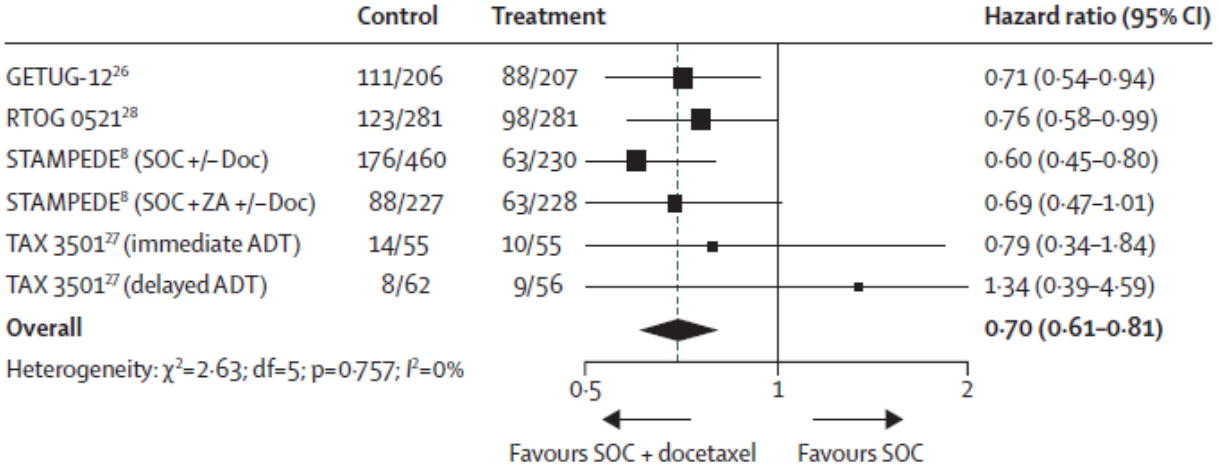
2992 hormona duyarlı metastatik prostat ca hastaya ADT +dositaksel eklenmesi ; 4 yılık %16 nüksüz süreyi uzatıyor

Hormon Duyarlı Metastatik Prostat Kanseri

Metaanaliz; ADT + Erken Dönem Kemoterapi

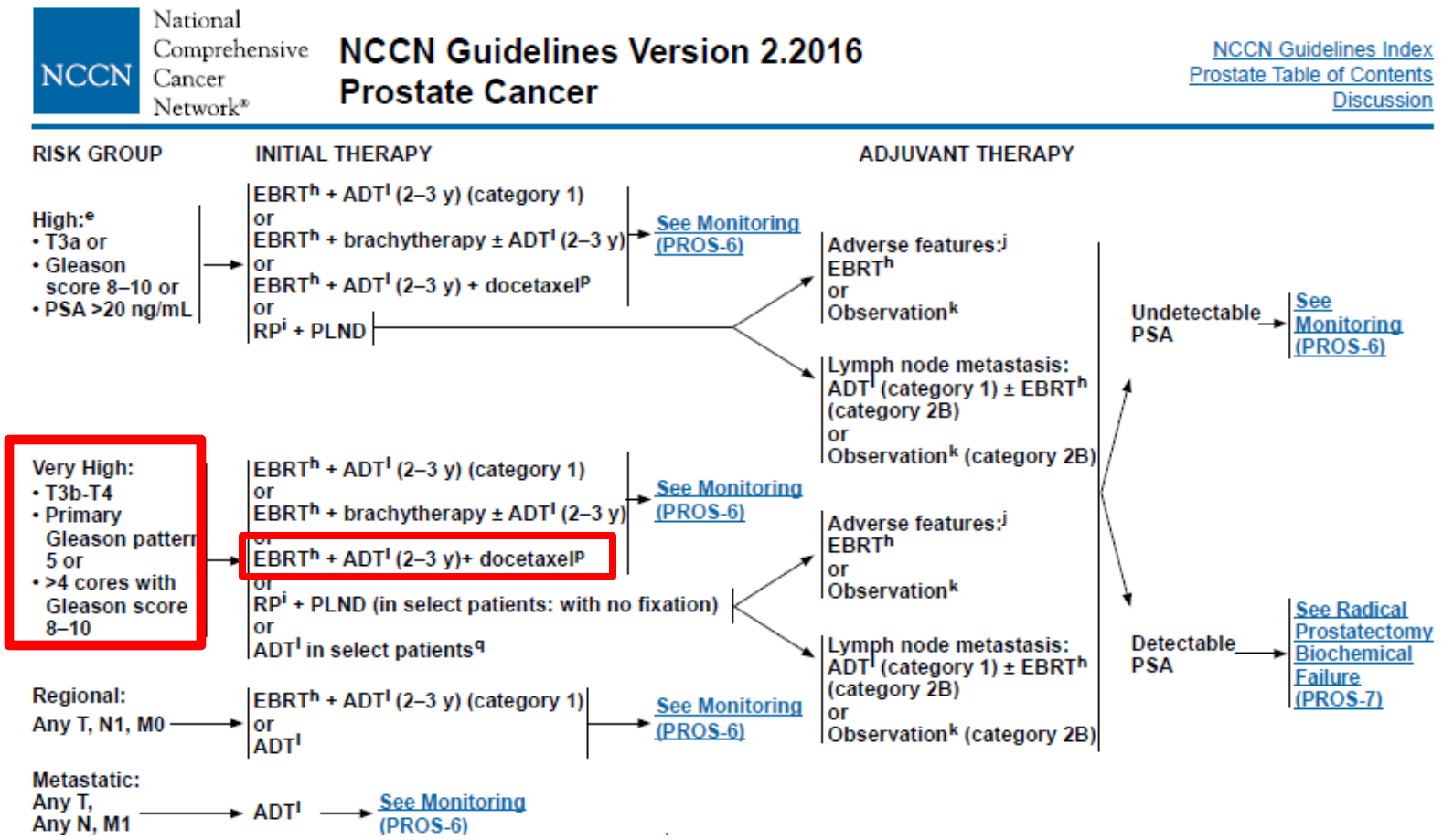


2992 hormona duyarlı lokal ileri prostat ca hastaya ADT +dositaksel eklenmesi ; sağkalım etkisi yok

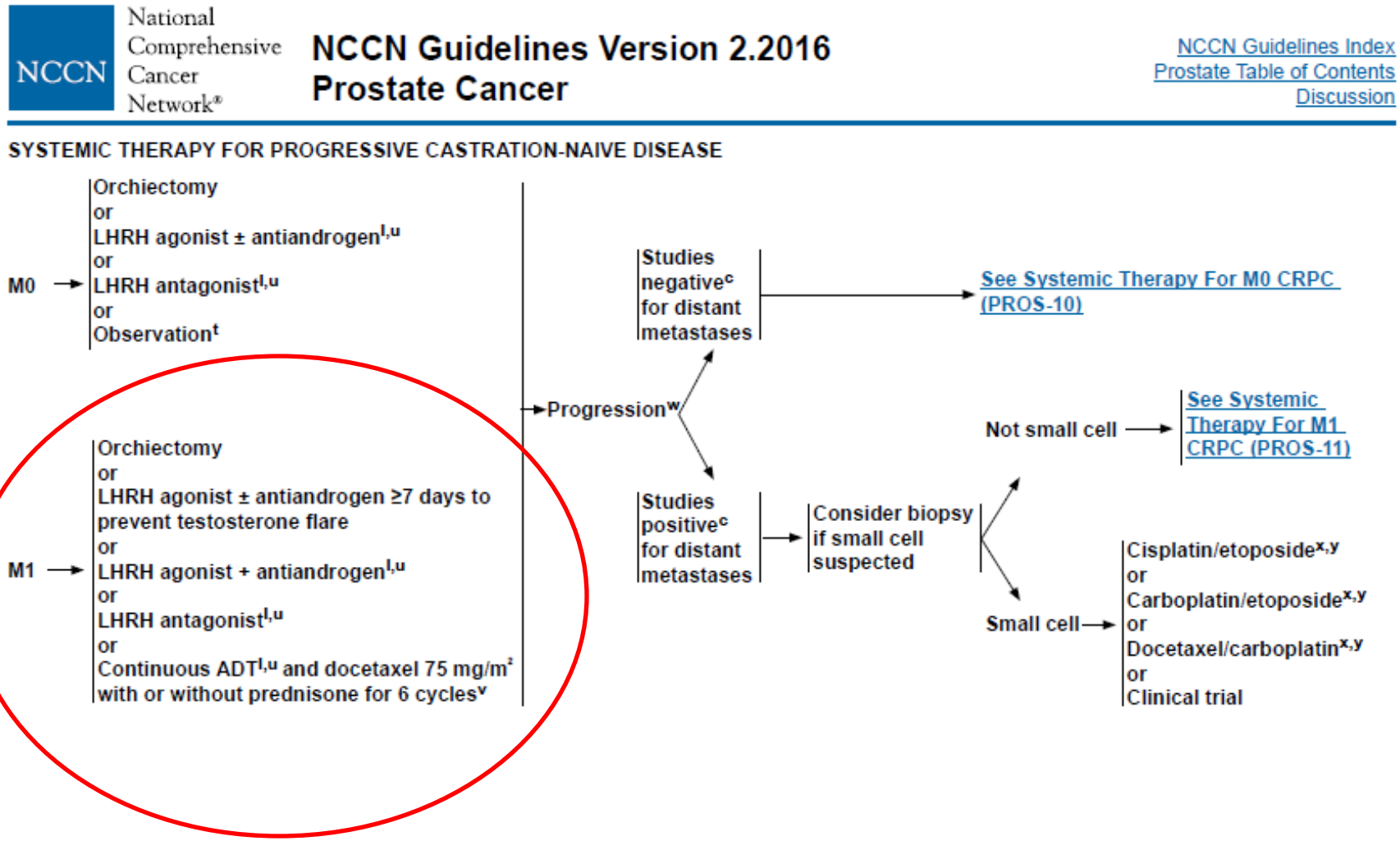


2992 hormona duyarlı lokal ileri prostat ca hastaya ADT +dositaksel eklenmesi ; 4-yıllık 8% nüksüz süreyi uzatıyor

Hormon Duyarlı Lokaliler Prostat Kanseri



Hormon Duyarlı Metastatik Prostat Kanseri



Hormon Duyarlı Metastatik Prostat Kanseri Sonuç

❑ Düşük volümlü hastalıkta

- ✓ Cerrahi Kastrasyon veya Medikal Kastrasyon
- ✓ CAB tedavi maliyetİ ve toksik yan etki yüksek, sağ kalım yararı minimal.
- ✓ Yan etki olarak intermittan kol, continue kola göre daha iyi sonuçlara sahip

  Genel sağkalım iki grupta eşit, prostat kanserine bağlı ölüm intermittan kolda, diğer nedenlere bağlı ölüm continue kolda daha fazla görülür.

❑ Yüksek volümlü hastalıkta

- ✓ Kemoterapi alabilecek performans durumundaki hastalarda ADT +KT
- ✓ Yaş, komorbidite gibi nedenlerle performans durumu kemoterapi almaya uygun olmayan hastalarda ADT