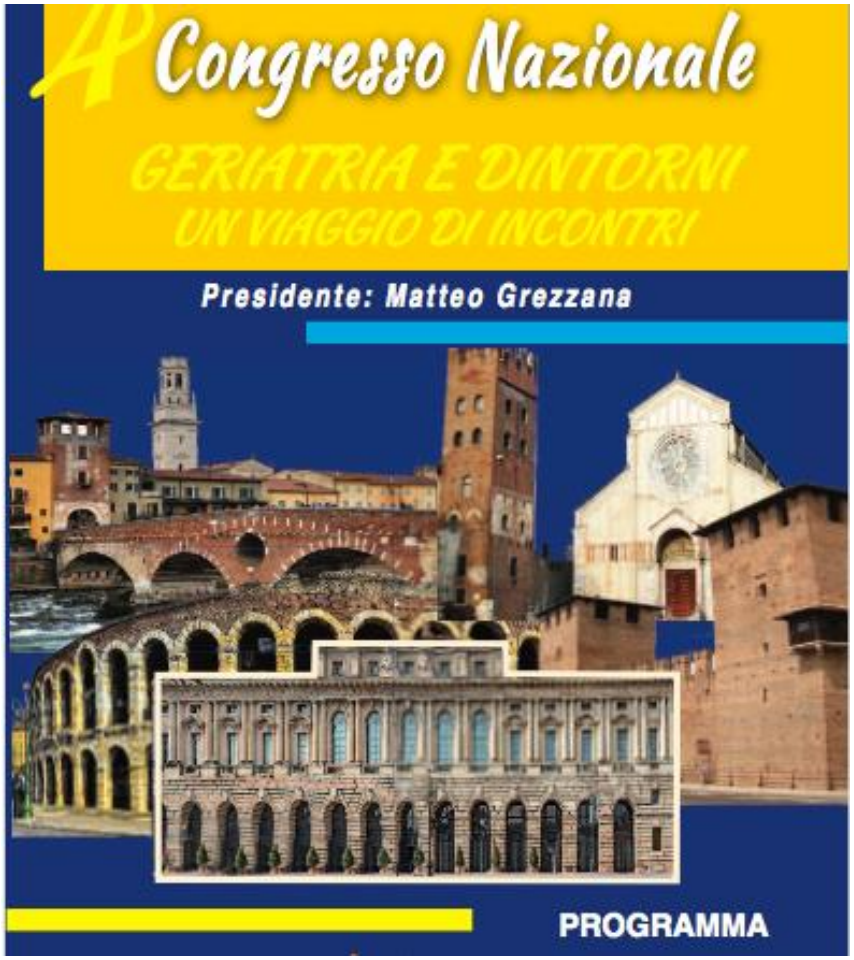
6 Dicembre 2019

Simposio

Le complicanze internistiche legate alla terapia oncologica

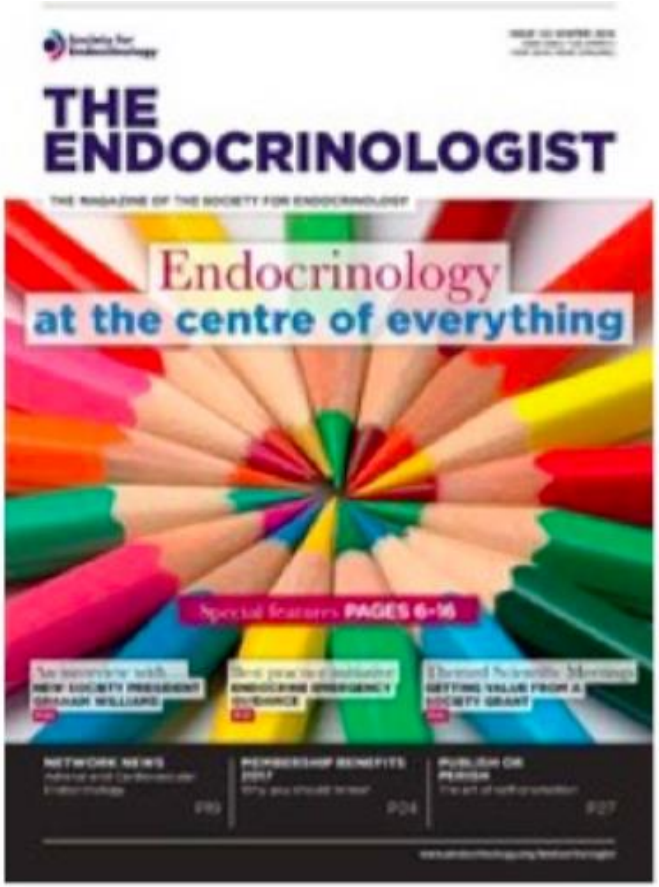


Dr ssa Michela Armigliato

UOC Medicina Interna

Legnago

Internista??Endocrinologo ???



Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata (19%)	Mammella (30%)	Mammella (14%)
2°	Polmone (15%)	Colon-retto (12%)	Colon-retto (13%)
3°	Colon-retto (14%)	Polmone (12%)	Polmone (11%)
4°	Vescica* (12%)	Tiroide (5%)	Prostata (10%)
5°	Stomaco (4%)	Utero corpo (5%)	Vescica* (8%)

TABELLA 6. Primi cinque tumori più frequentemente diagnosticati e proporzione sul totale dei tumori (esclusi i carcinomi della cute) per sesso. Stime per l'Italia 2019

* Comprende sia tumori infiltranti sia non infiltranti.

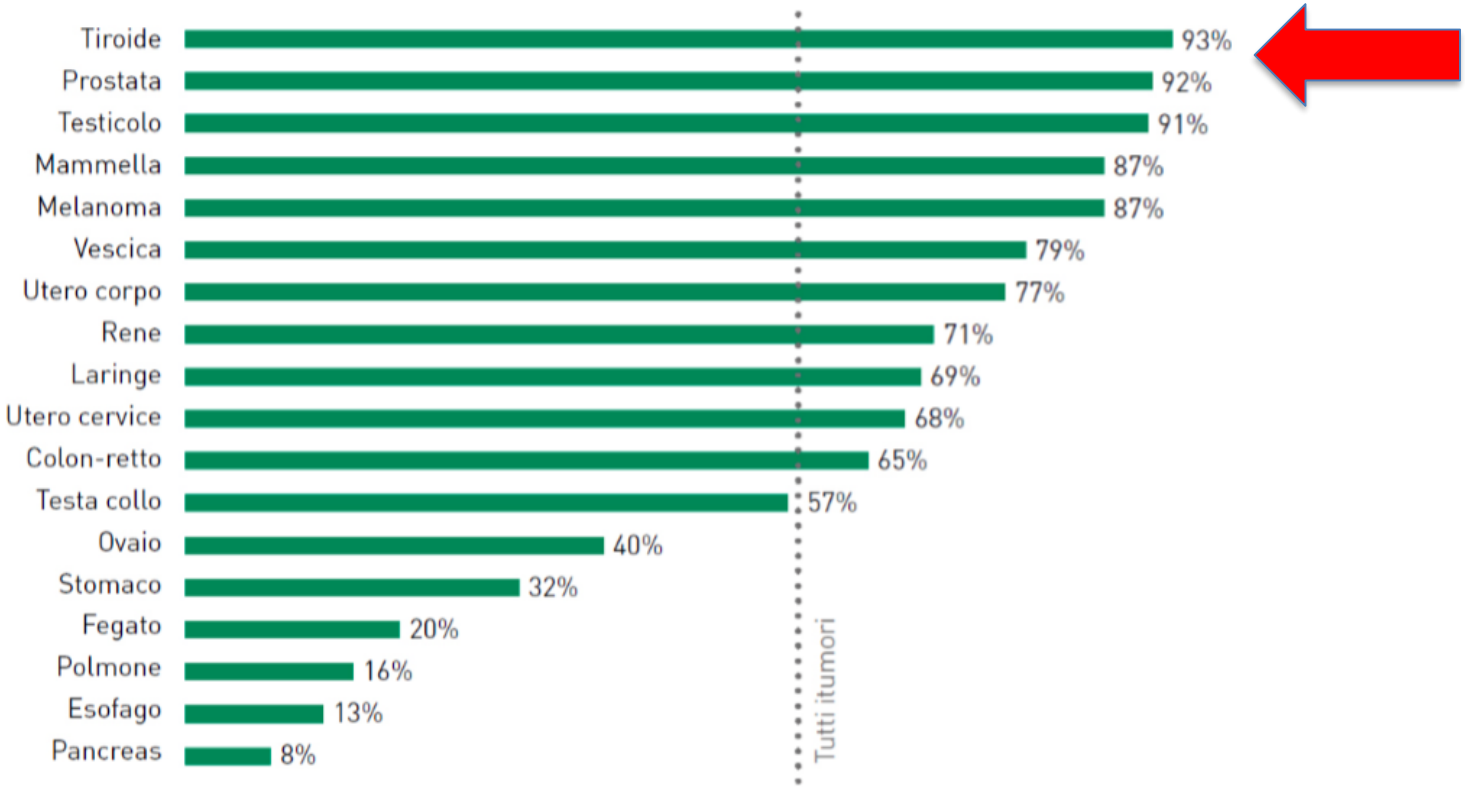


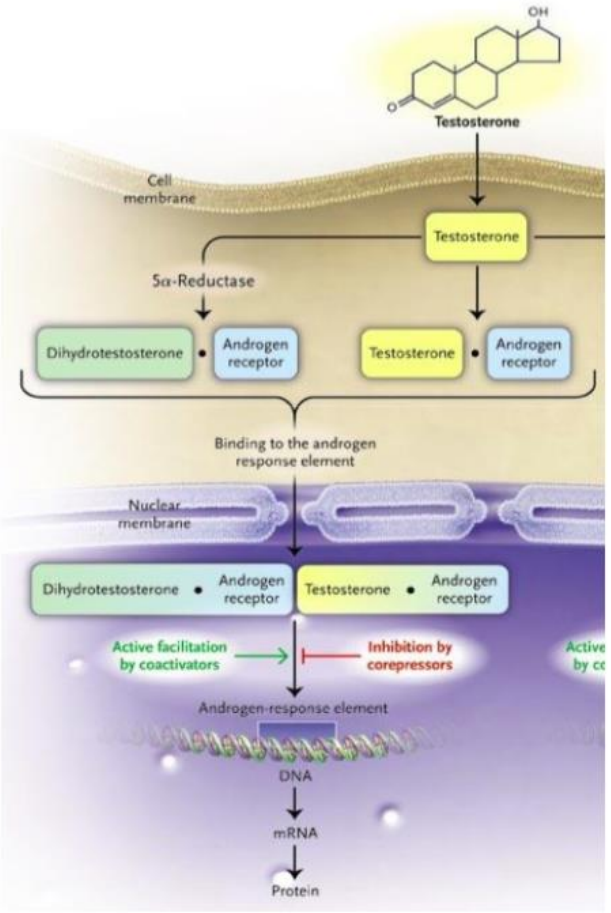
FIGURA 4. Sopravvivenza netta a 5 anni dalla diagnosi (standardizzata per età) per il periodo di incidenza 2005-2009 (pool AIRTUM), uomini e donne

Carcinoma prostata (CaP)

Il carcinoma della prostata è un classico esempio di tumore endocrino-correlato

La crescita e la progressione tumorale sono alimentate dal testosterone e dipendono dai livelli di testosteronemia

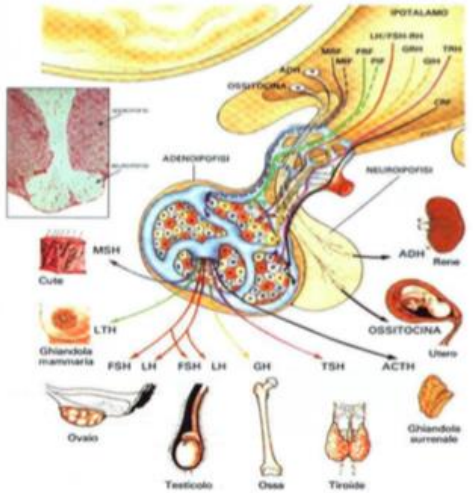
Obiettivo terapia medica:
mantenere i livelli di testosteronemia
sotto la soglia di castrazione
(≤20-50 ng/dl)



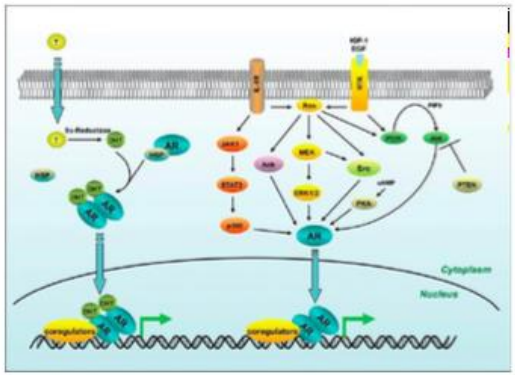
Blocco androgenico (ADT):
castrazione farmacologica

Androgen deprivation therapy (ADT)

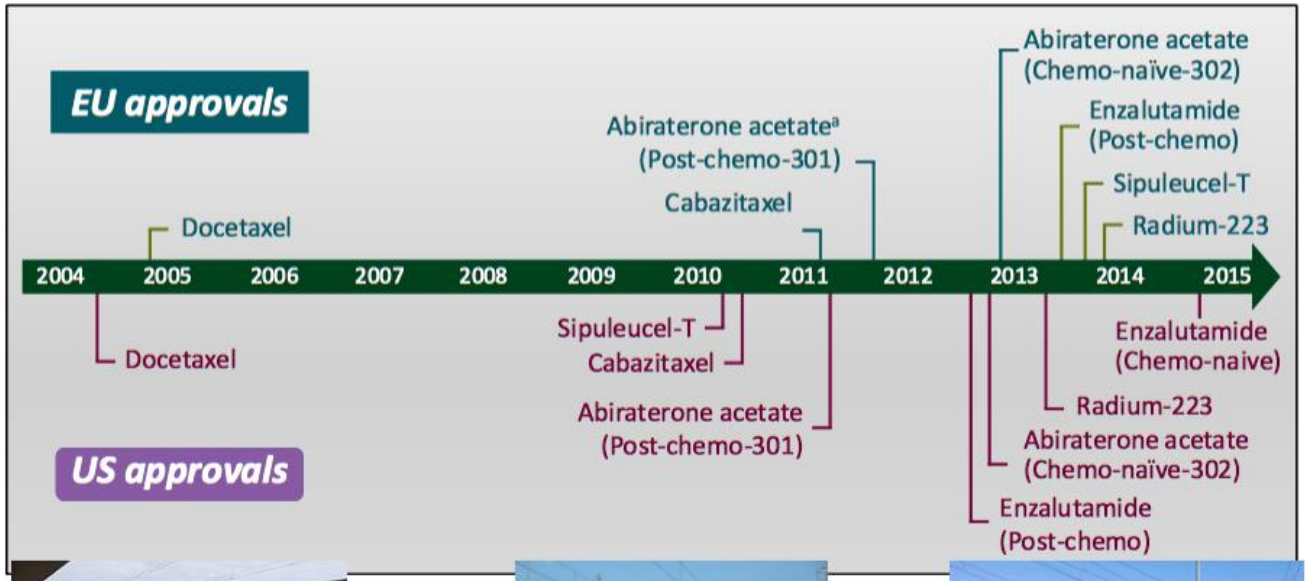
PCa è un tumore androgeno dipendente



- **Bilateral orchiectomy**
- **Estrogens (dietilstilbestrolo, DES)**
- **LHRH agonist (leuprorelina, buserelin, goserelin)**
- **LHRH antagonist (degarelix)**
- **Non steroidal anti-androgens (flutamide, bicalutamide, nilutamide)**
- **Steroidal anti-androgens (ciproterone acetato, megestrone acetato..)**



Deprivazione ormonale nel Ca prostata: evoluzione dal **treno a vapore** al **freccia rossa**



L’urologo chiede all’endocrinologo

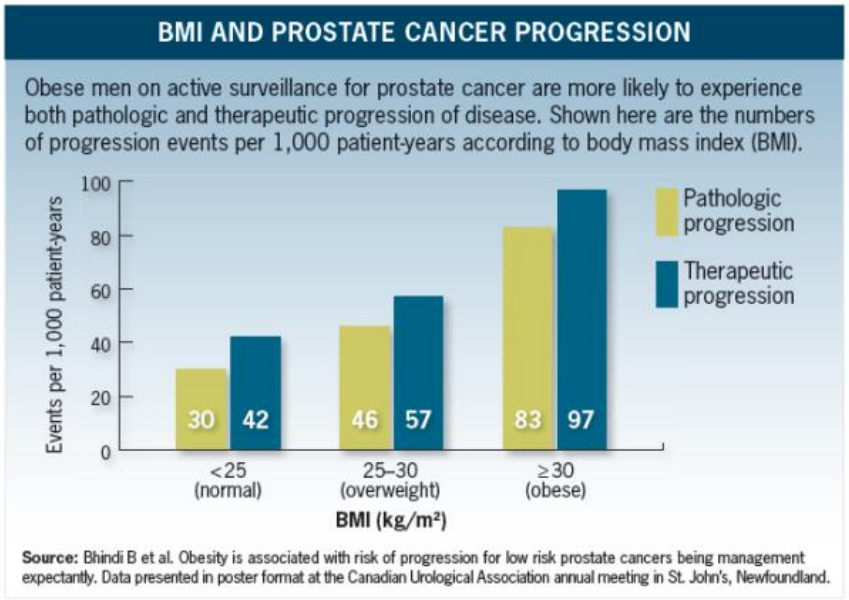
1) **Obesità:relazione con CaP?**

2) **Effetti collaterali della deprivazione ormonale:**
   sindrome metabolica ed eventi cardiovascolari ?

3) **Salute dell’osso e Ca prostatico?**

Domanda 1

relazione tra BMI e CaP?



IARC 2002: 30-60 min attività fisica al giorno
Ca colon, mammella, corpo utero e Ca prostata

Domanda 2

Blocco androgenico (ADT) nel CaP:effetti collaterali

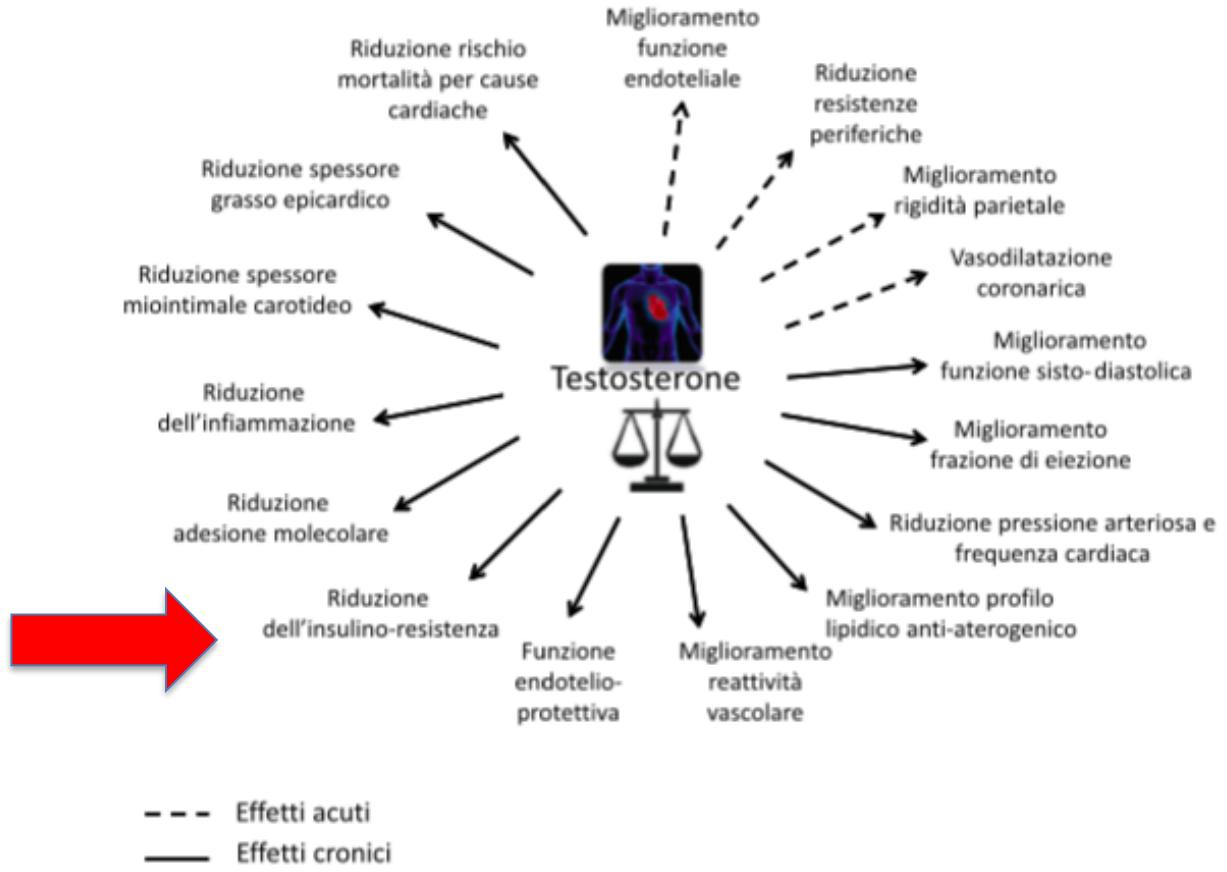
The Castration Syndrome

- Loss of libido and sexual interest, erectile dysfunction, impotence
- Fatigue
- Hot flushes
- Decline in intellectual capacity, emotional liability, depression
- Decrease in muscular strength
- Increase in (abdominal) fat apposition
- Osteoporosis
- Cardiovascular

Anemia

Effetti del testosterone sull'apparato cardiovascolare

Fig. 2 Effetti della terapia sostitutiva con testosterone sul sistema cardiovascolare



GnRh agonisti e effetti avversi cardiovascolari

Table 2

Pathophysiology of Adverse Cardiovascular Effects of Gonadotropic Releasing Hormone Agonists. LDL: Low density lipoprotein, HDL: High density lipoprotein.

Indirect Effects	Direct Effects	Low Testosterone
↑ Fat mass	? ↓ Cardiac contractility	↓ Vasodilation
↓ Lean body mass	↑ T-Cell activation and destabilization of fibrous cap/plaque rupture	↓ HDL
↑ Insulin resistance / Hyperinsulinemia		↑ Visceral Obesity
↑ LDL, ↑ HDL and ↑ Triglycerides		↑ Prothrombotic state
↑ Diabetes mellitus		
↑ Metabolic syndrome		
↑ Endothelial dysfunction		
↑ Arterial wall thickness		

Circulation. 2010 February 16; 121(6): 833–840. doi:10.1161/CIRCULATIONAHA.109.192695.

Androgen-Deprivation Therapy in Prostate Cancer and Cardiovascular Risk:

A Science Advisory From the American Heart Association, American Cancer Society, and American Urological Association *Endorsed by the American Society for Radiation Oncology*

Glenn N. Levine, MD, FAHA[1][Chair], Anthony V. D'Amico, MD, PhD[2], Peter Berger, MD, FAHA[3], Peter E. Clark, MD[4], Robert H. Eckel, MD, FAHA[5], Nancy L. Keating, MD, MPH[6], Richard V. Milani, MD, FAHA[7], Arthur I. Sagalowsky, MD[8], Matthew R. Smith, MD, PhD[9], and Neil Zakai, MD[10] American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association

50 % entro 12 mesi

La sindrome metabolica

criteri diagnostici NCEP (adulti)

Almeno 3 dei seguenti criteri:

1. Obesità addominale:
   circonferenza vita >88 cm nelle ♀ e >102 cm nei ♂
1. Trigliceridi ≥ 150 mg/dl
2. Colesterolo HDL <40 mg/dl nei ♂ e <50 mg/dl nelle ♀
3. Pressione arteriosa ≥ 130/85 mmHg
4. Glicemia a digiuno ≥ 110 mg/dl

National Cholesterol Education Program NCEP, III Report, JAMA 16: 285 (5) 2001

Metabolic syndrome in patients with prostate cancer undergoing intermittent androgen-deprivation therapy

Mohammadali Mohammadzadeh Rezaei, MD; Mohammadhadi Mohammadzadeh Rezaei, MD; Alireza Ghoreifi, MD; Behzad Feyzzadeh Kerigh, MD

Department of Urology, Mashad University of Medical Sciences, Iran

Cite as: *Can Urol Assoc J* 2016;10(9-10):E300-5. http://dx.doi.org/10.5489/cuaj.3655
Published online September 13, 2016

Abstract

Introduction: The presence of metabolic syndrome in men with prostate cancer (PCa) undergoing androgen-deprivation therapy (ADT), especially intermittent type, has not been completely evaluated. The aim of this study is to evaluate metabolic syndrome in men with PCa undergoing intermittent ADT.
Methods: In this longitudinal study, we studied the prevalence of metabolic syndrome and its components in 190 patients who were undergoing intermittent ADT. The metabolic syndrome was defined according to the Adult Treatment Panel III criteria. All metabolic parameters, including lipid profile, blood glucose, blood pressures, and waist circumferences of the patients were measured six and 12 months after treatment.
Results: Mean age of the patients was 67.5 ± 6.74 years. The incidence of metabolic syndrome after six and 12 months was 6.8% and 14.7%, respectively. Analysis of various components of the metabolic syndrome revealed that patients had significantly higher overall prevalence of hyperglycemia, abdominal obesity, and hypertriglyceridemia in their six- and 12-month followups, but blood pressure has not been changed in the same period except for diastolic blood pressure after six months.
Conclusions: Although there was an increased risk of metabolic syndrome in patients receiving intermittent ADT, it was lower than other studies that treated the same patients with continuous ADT. Also it seems that intermittent ADT has less metabolic complications than continuous ADT and could be used as a safe alternative in patients with advanced and metastatic PCa.

Introduction

Prostate cancer (PCa) is the most common non-cutaneous cancer diagnosed in men and the second most common cause of cancer related death, with a lifetime risk of death at 2.57%.[1,2] Statistics suggest that its incidence and the death rate are rapidly increasing, despite improved detection rates. This may be due to rapid increases in the population age and changes in dietary habits.[3]

Radical prostatectomy and radiotherapy are the preferred treatments in men with confined PCa. However, androgen-deprivation therapy (ADT) is the main treatment of advanced and metastatic PCa. The modalities of ADT include surgery (orchiectomy) or medical therapy.[4] Today, with progression in new medical drugs (gonadotropin-releasing hormone [GnRH] agonists and antagonists), most patients choose medical therapy, so the overall use of ADT has increased in the past two decades. Also because of the increasing rate of PCa diagnosis in younger men, hormonal therapy is being used for extended periods of time.[5] Different studies showed that most men with PCa die of conditions other than their primary malignancy, so changes in treatment modalities and diagnosis and management of adverse effects have become more important. Therefore, different strategies for ADT, such as intermittent treatment have been described. Intermittent androgen suppression may reduce the side effects of therapy during off-treatment periods.[6]

The resulting hypogonadism due to ADT may leads to adverse results, such as osteoporosis, unfavourable body composition (increase in body mass index, increased fat mass, reduced lean body mass and muscle strength), sexual dysfunction, and reduced quality of life. Recent studies suggest male hypogonadism is an independent risk factor for the development of metabolic syndrome and diabetes.[7] However, the presence of metabolic syndrome in men with PCa undergoing ADT, especially intermittent type, has not been completely evaluated. In this study, we evaluated metabolic syndrome in men with PCa undergoing intermittent ADT.

Methods

In this longitudinal study, we studied the patients who were undergoing intermittent ADT. All patients did not have metabolic syndrome at the start of study. Exclusion criteria were abnormal liver function tests or serum creatinine, history of any medical diseases (such as thyroid disease, hypogonadism, or glucocorticoid use), and any history of chemotherapy. Also, if prostate-specific antigen (PSA) and symptoms

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Circulation. 2016 February 2; 133(5): 537–541. doi:10.1161/CIRCULATIONAHA.115.012519.

Cardiovascular Effects of Androgen Deprivation Therapy for the Treatment of Prostate Cancer: ABCDE Steps to reduce Cardiovascular Disease in Patients with Prostate Cancer

Nirmanmoh Bhatia, MD[1,2], **Marilia Santos, MD**[5,6], **Lee W. Jones, PhD**[7], **Joshua A. Beckman**[1], **David F. Penson, MD**[3,4], **Alicia Morgans, MD**[3,4], and **Javid Moslehi, MD**[1,2,3]

ADT
Tossicità cardiovascolare
Entro i primi 6 mesi

Figure 2.
"ABCDE" algorithm for prostate cancer survivors.

Decisioni difficili

CP localizzato	CP avanzato
Sorveglianza attiva	Radioterapia
Chirurgia	Terapia focale
Radioterapia	Deprivazione androgenica
Terapia focale	Chemioterapia
	Altro

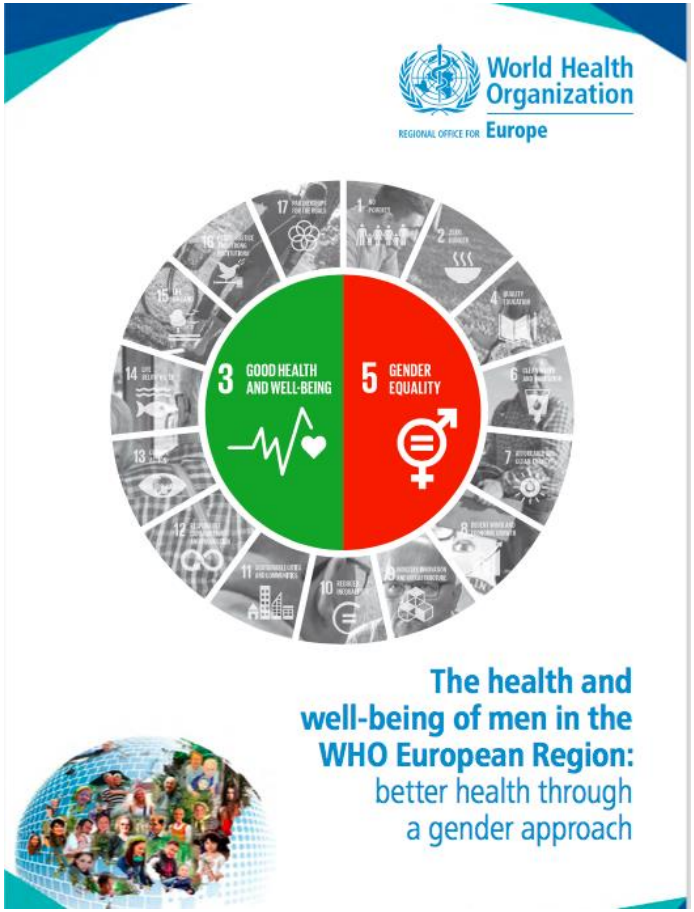
Deprivazione ormonale androgenica **non indicata nelle forme a basso rischio e localizzate** e nella **terapia adiuvante(sempre nel Ca P a basso rischio) in particolare** in pazienti ad **alto rischio cardiovascolare (ex IMA o scompenso cardiaco, comorbidità) per aumento eventi cardiovascolari fatali e non fatali PRECOCI**

Domanda 3

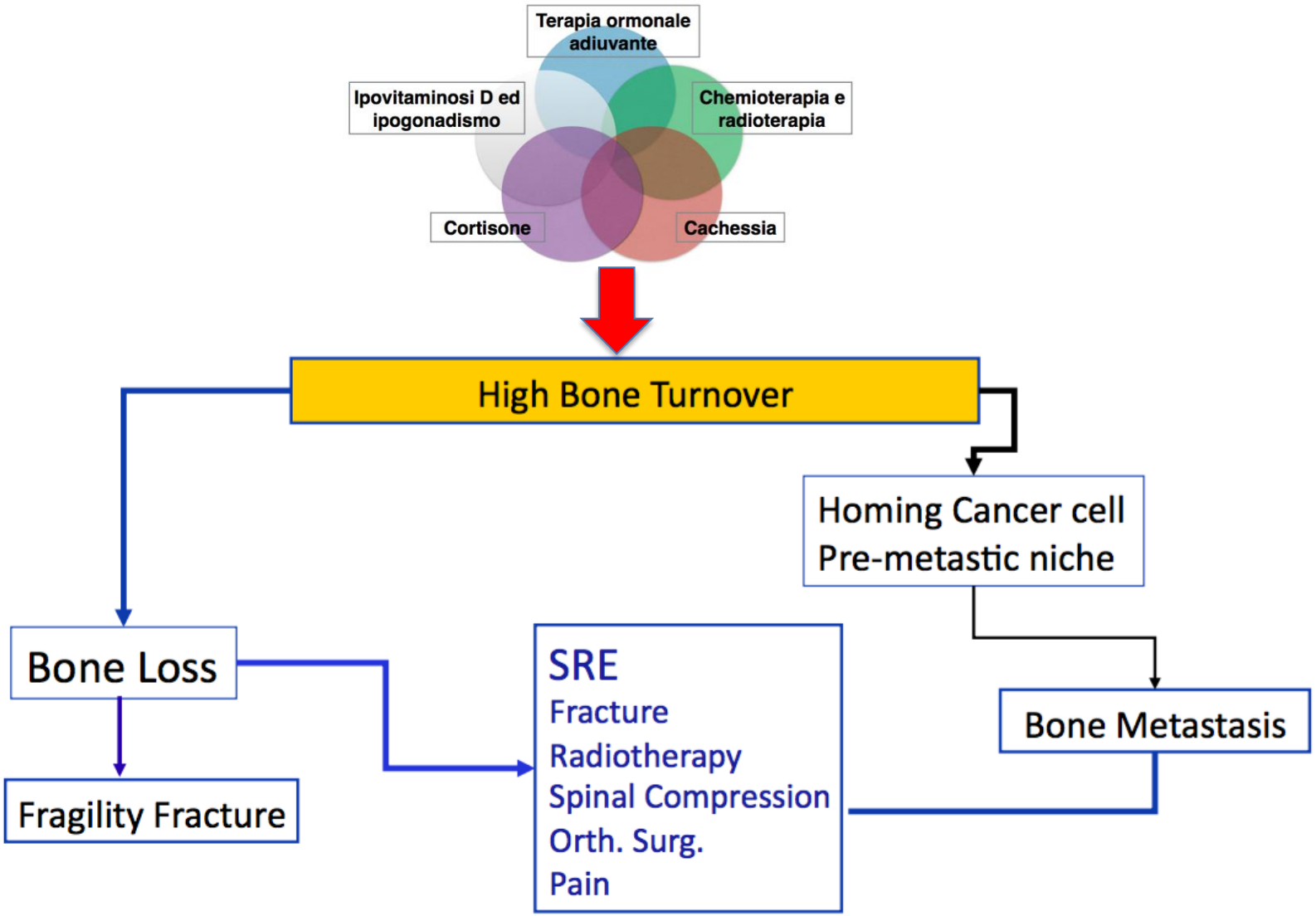
Ca prostata e salute dell'osso

Medicina orientata al genere

1. Differenze strutturali ossee(bone high turnover)
2. Fattori di rischio(ipogonadismo , fumo, alcool, steroidi)
3. Prevenzione primaria
4. Prevenzione secondaria
5. Aderenza terapeutica
6. Ritardo diagnostico
7. "Bridging trial"



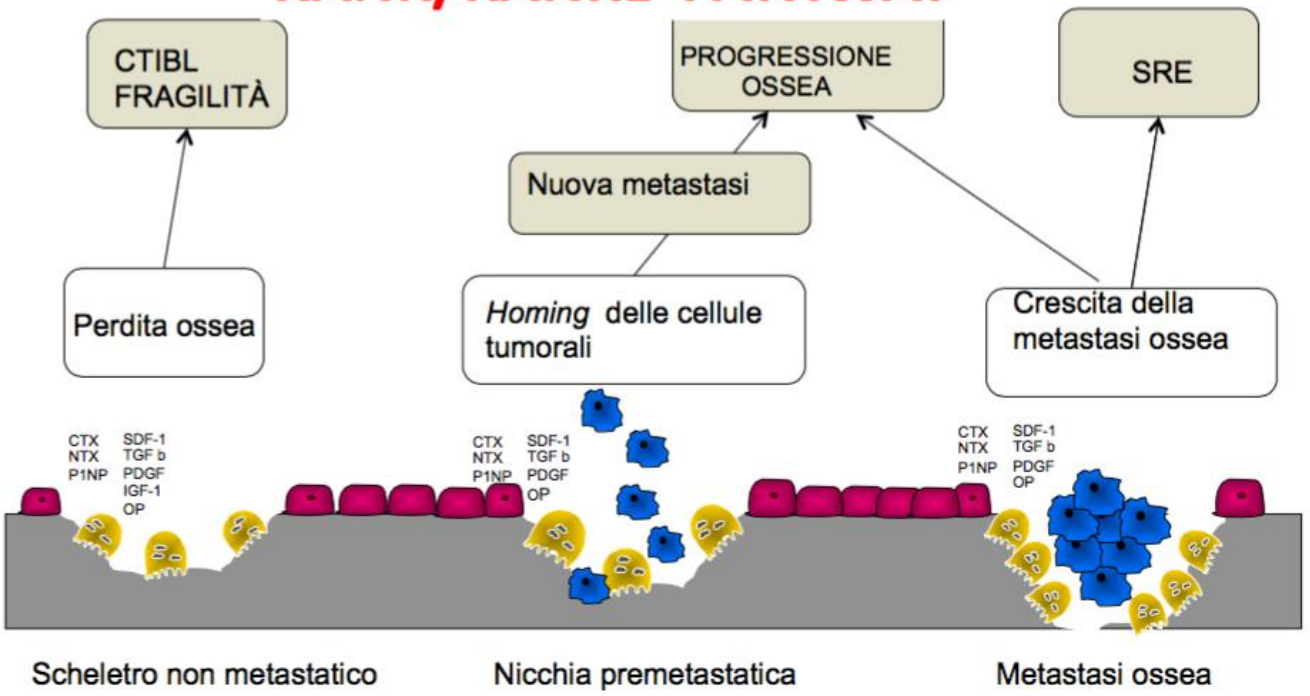
Cancer Treatment Bone Loss (CTIBL)



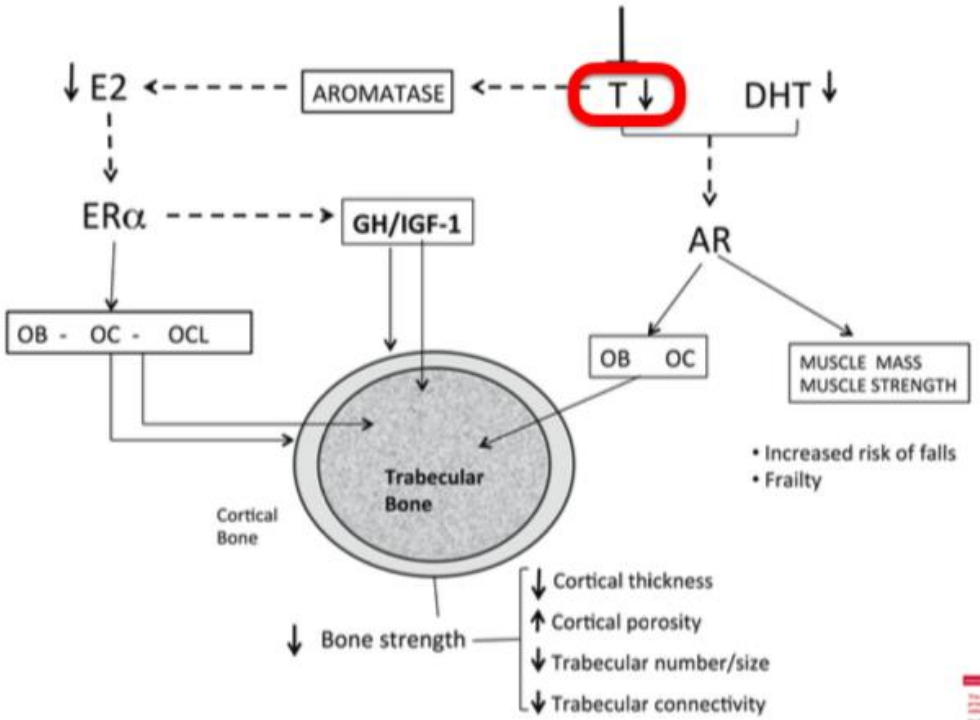
BONE HEALTH CONCEPT IN CANCER PATIENTS

(eta' –livelli vit D – Terapia ormonale adiuvante- metastasi)

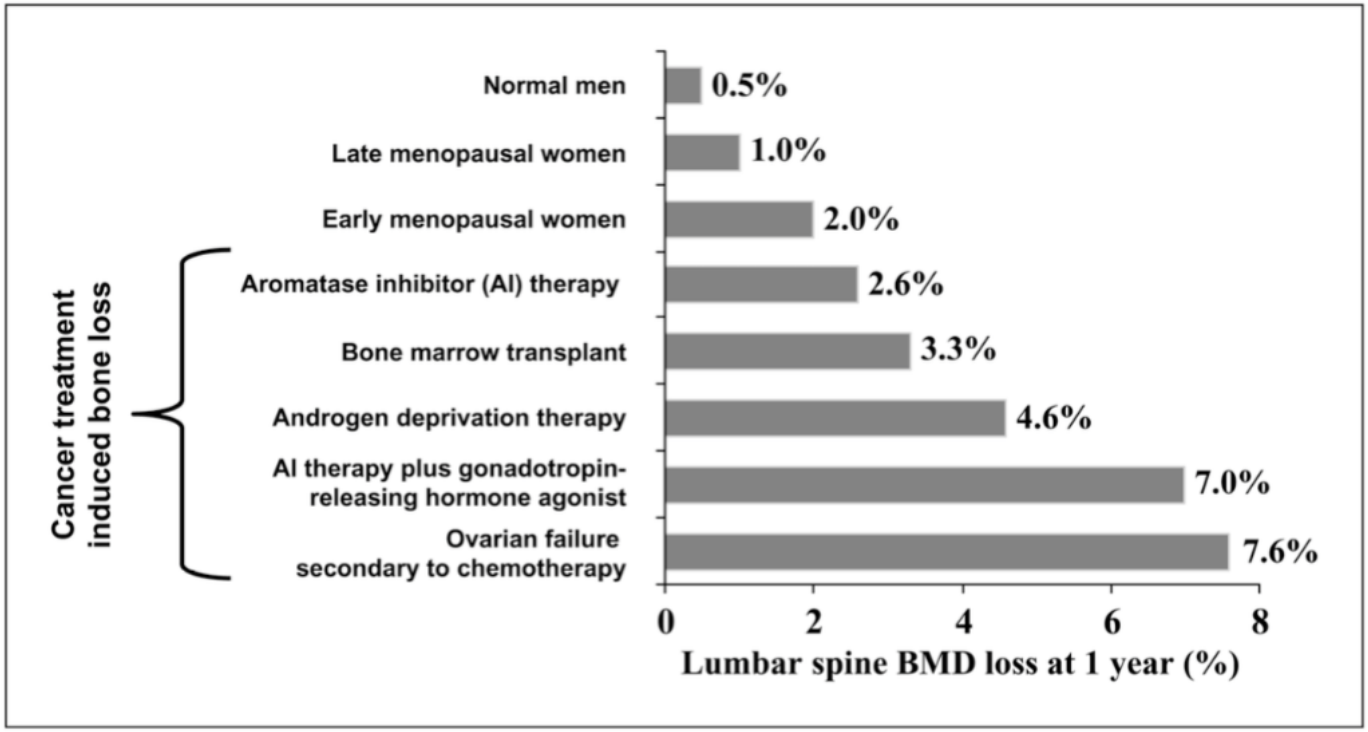
RANK/RANKL PATHWAY



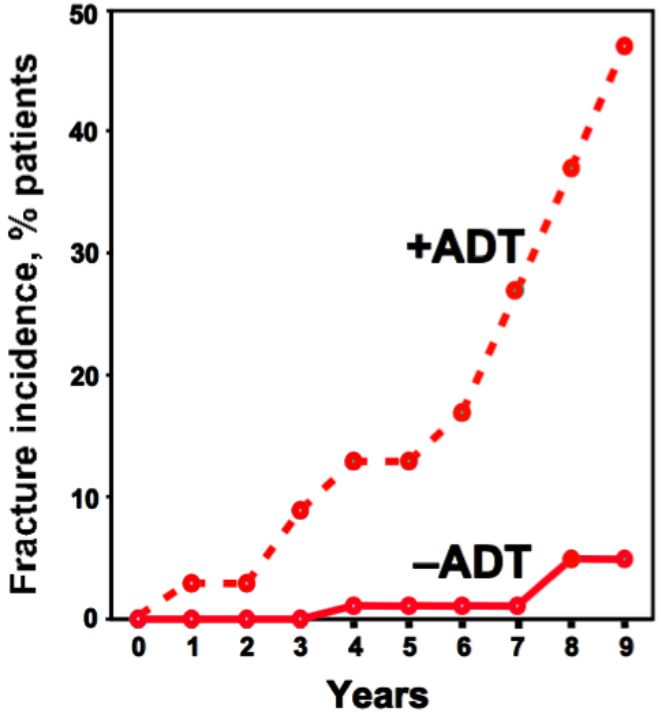
Terapia ormonale adiuvante: Analoghi del GnRH



Terapia ormonale adiuvante



Androgen Deprivation Therapy Increases Fracture Risk



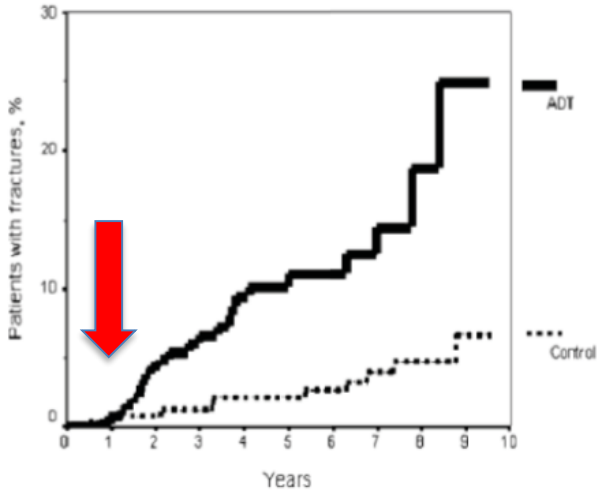


Fig. 1 Kaplan–Meier plots of patients with fractures after ADT (patient group) or diagnosis (control group)

Fracture risk in patients with prostate cancer on androgen deprivation therapy

Ana M. López · María A. Pena · Rafael Hernández

Fratture ossee da deprivazione ormonale e sopravvivenza

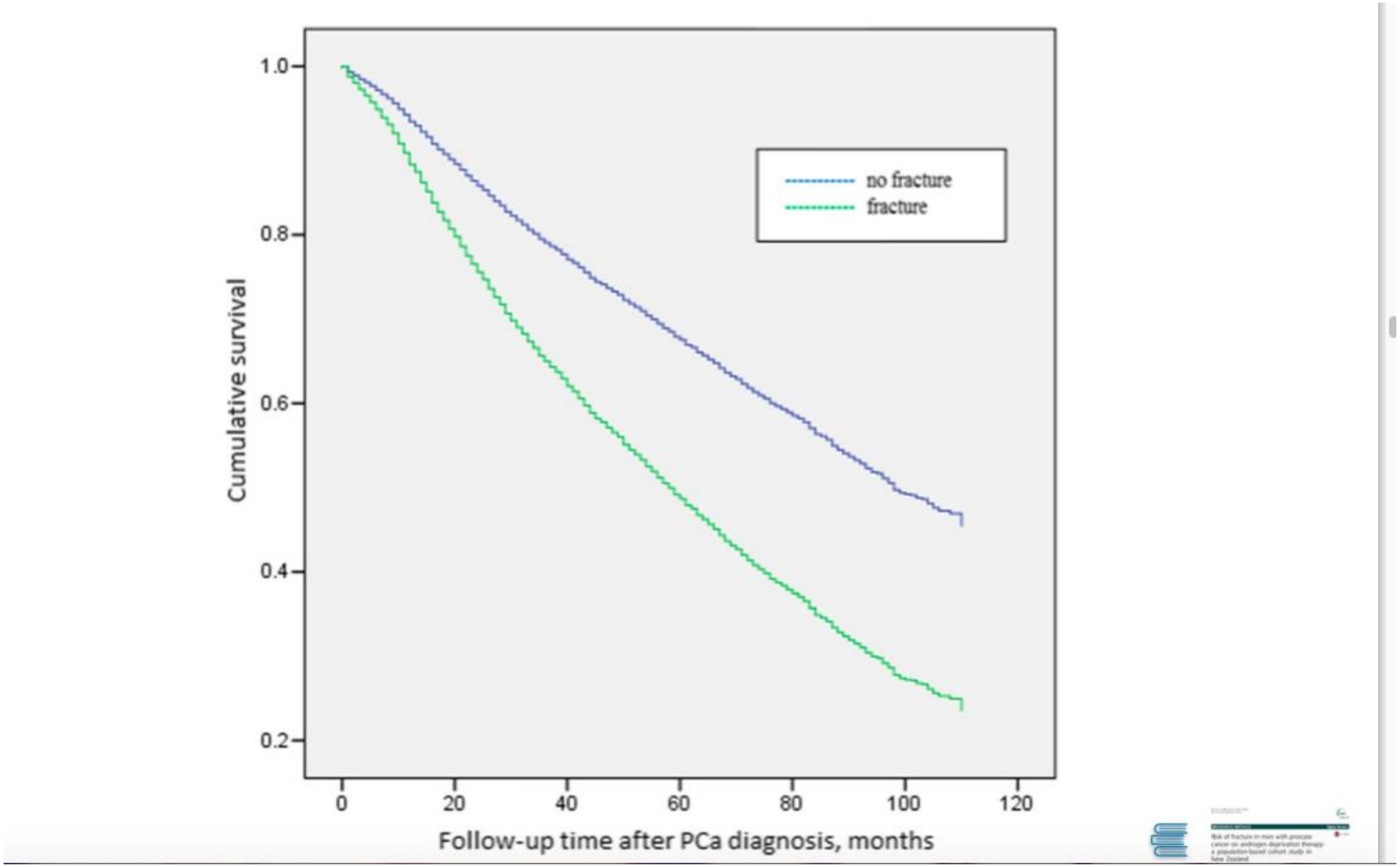


TABELLA 1 Sintesi dei benefici della terapia dell'osteoporosi negli uomini [111]

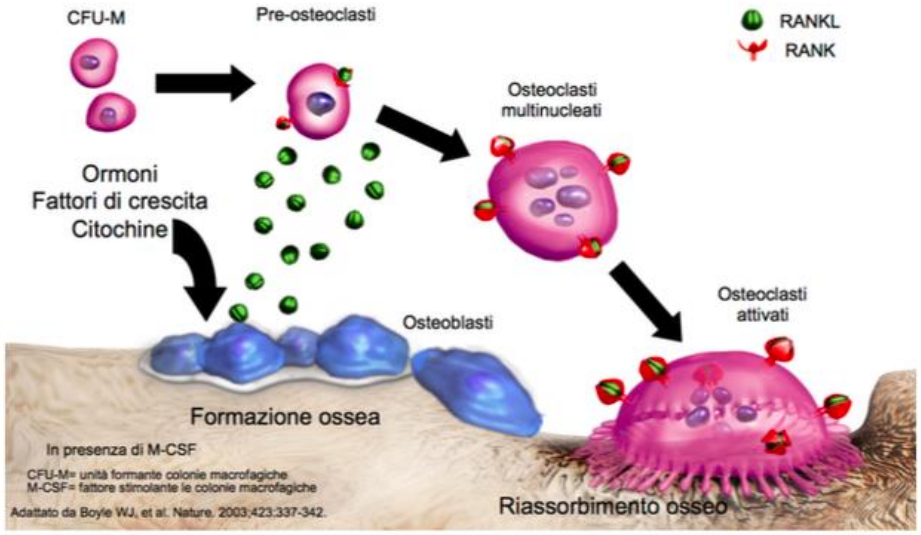
	Trattamento	Osteoporosi primaria			Terapia di deprivazione androgenica			Osteoporosi secondaria all'uso di glucocorticoidi		
		BMD	Frattura vertebrale	Frattura non vertebrale	BMD	Frattura vertebrale	Frattura non vertebrale	BMD	Frattura vertebrale	Frattura non vertebrale
Bisfosfonati	Alendronato	x	x		x			x		
	Risedronato	x	x							
	Ibandronato	x								
	Pamidronato				x					
	Acido zoledronico	x	x	x	x			x		
Terapie alternative	Denosumab	x			x	x				
	Ranelato di Stronzio	x								
	Teriparatide	x	x					x	x	

Modificato da Sim I-W, Ebeling PR. Treatment of osteoporosis in men with bisphosphonates: rationale and the latest evidence. Ther Adv Musculoskel Dis 2013;5(5):259-267. Riprodotto per gentile concessione.

DENOSUMAB 60 mg 1 fl sc ogni 6 mesi (piattaforma AIFA)

Anticorpo monoclonale umano, inibitore reversibile del RANK ligando (Denosumab)

Il RANK Ligando è un mediatore essenziale della formazione, funzione e sopravvivenza degli osteoclasti

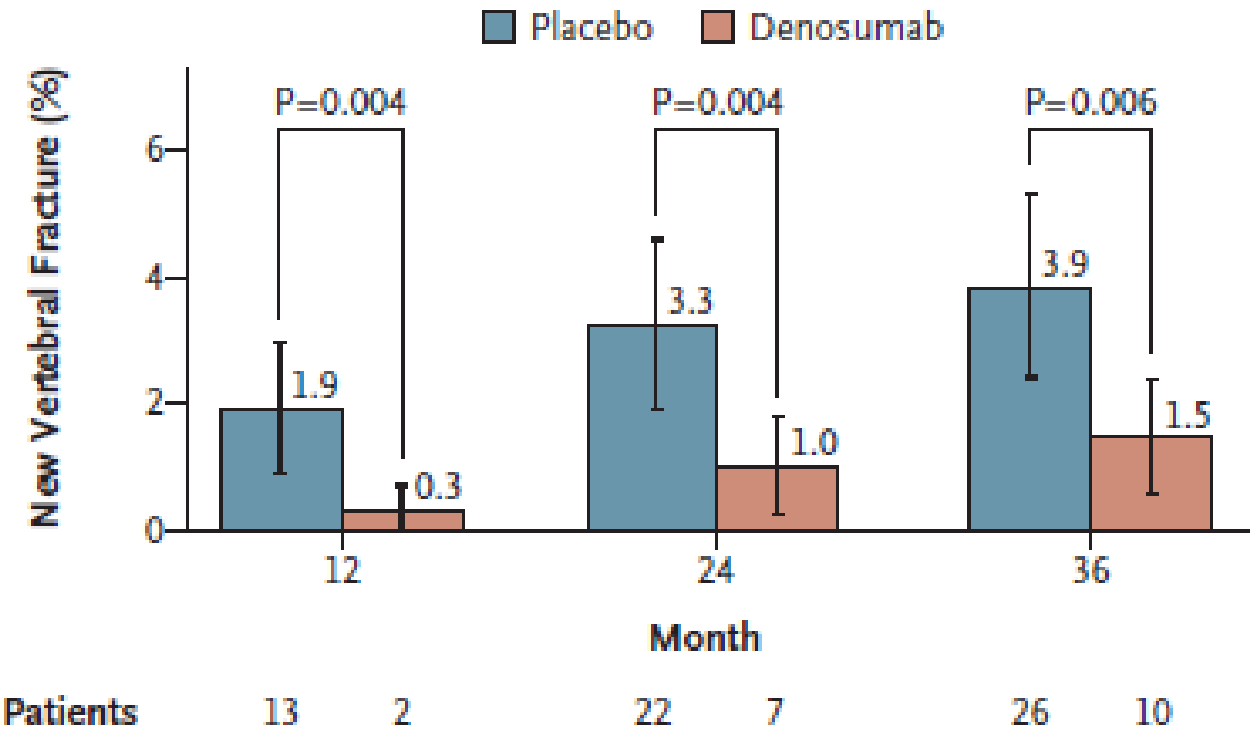


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2009 VOL. 361 NO. 8

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Blair Egerdie, M.D., Narciso Hernández Toriz, M.D., Robert Feldman, M.D., Teuvo L.J. Tammela, M.D., Fred Saad, M.D., Jiri Heracek, M.D., Ph.D., Maciej Szwedowski, M.D., Chunlei Ke, Ph.D., Amy Kupic, M.A., Benjamin Z. Leder, M.D., and Carsten Goessl, M.D., for the Denosumab HALT Prostate Cancer Study Group*

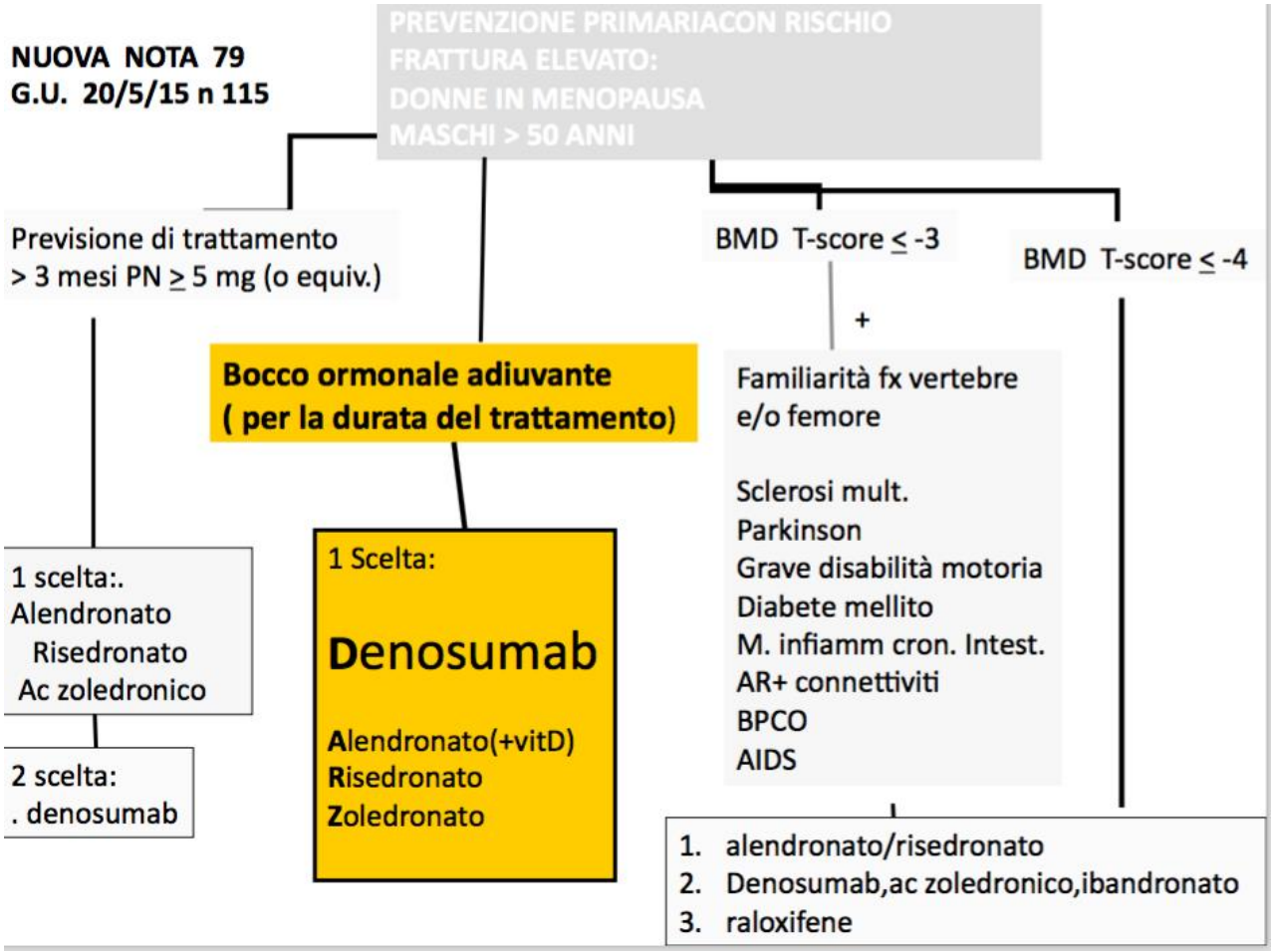


Terapia ormonale adiuvante nel carcinoma prostatico: GnRH - linee guida

Nuove linee guida AIOM sul tumore della prostata 2017

NOTA 79

Rimborsabilità in prevenzione primaria nota AIFA 79

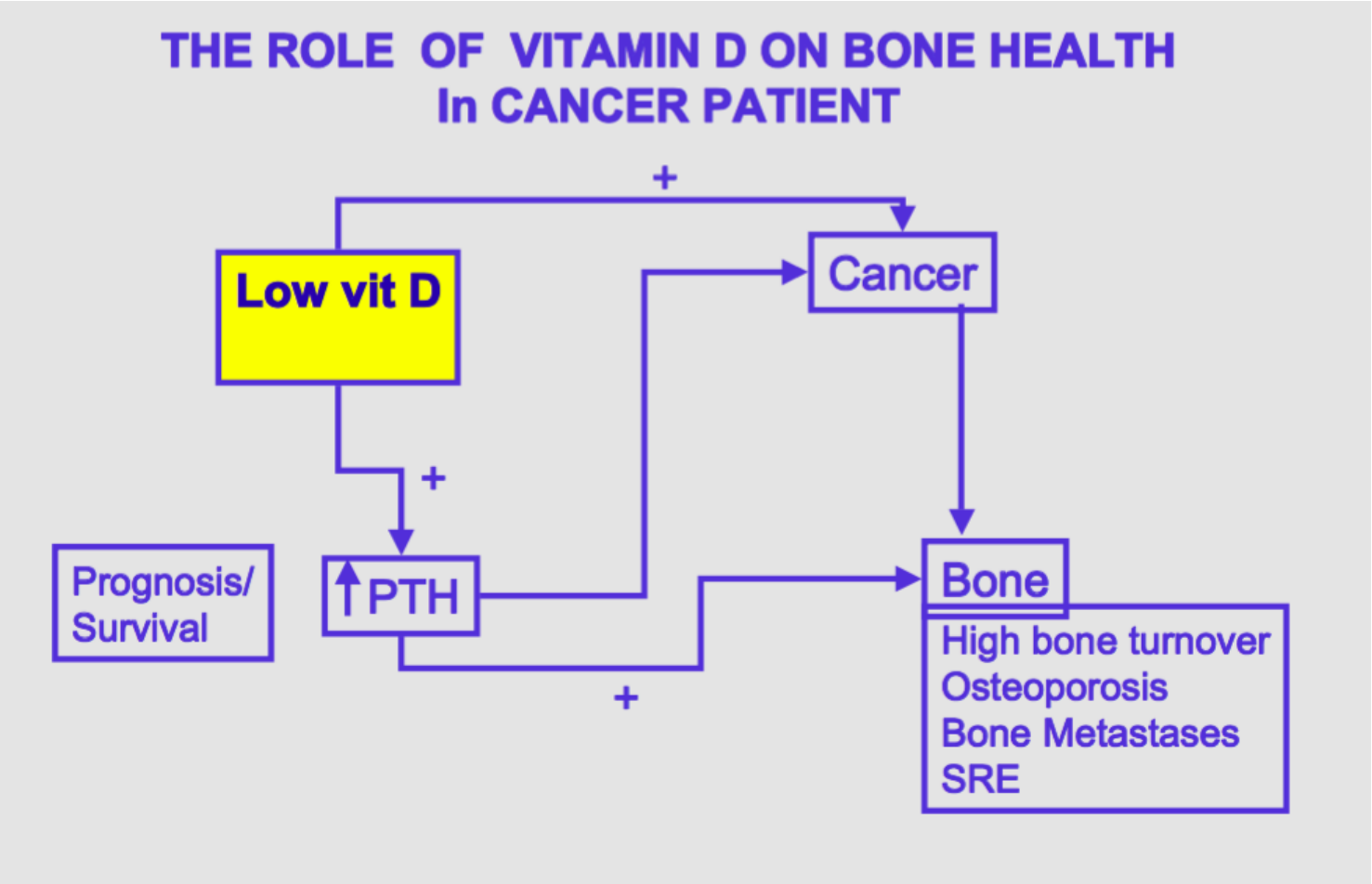


Maschi età >50 aa

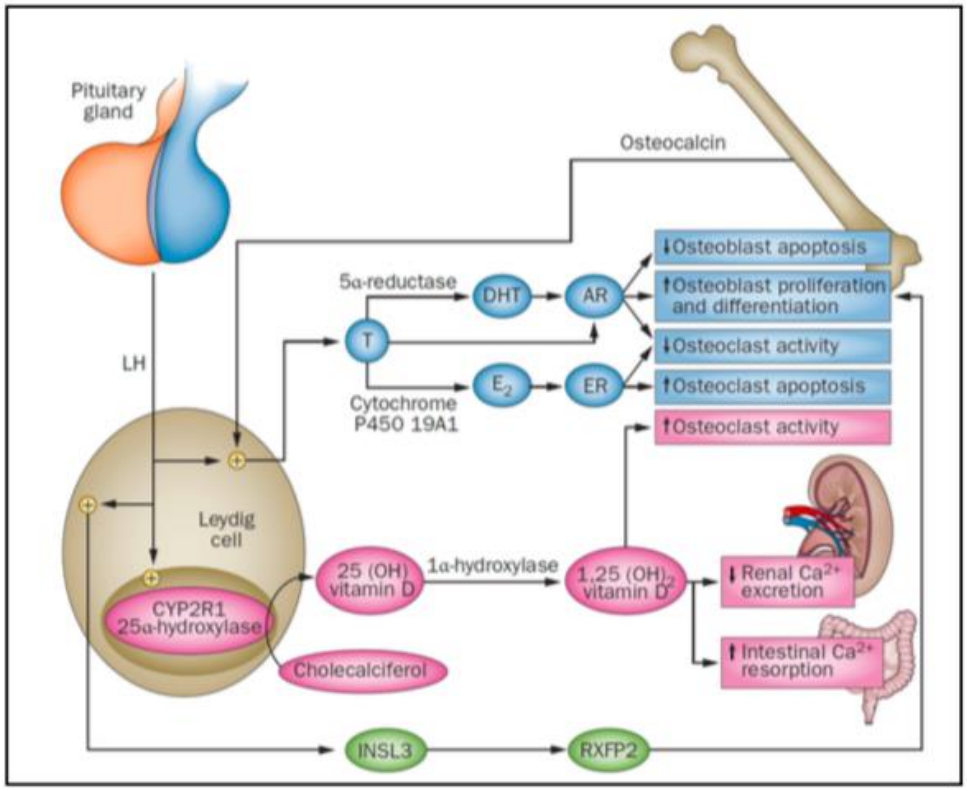
Denosumab 60 mg sc 2 x anno; Ac zoledronico 5 mg ev anno

Risendronato os 35 mg /sett;alendonato os 70 mg sett

Ruolo della vitamina D

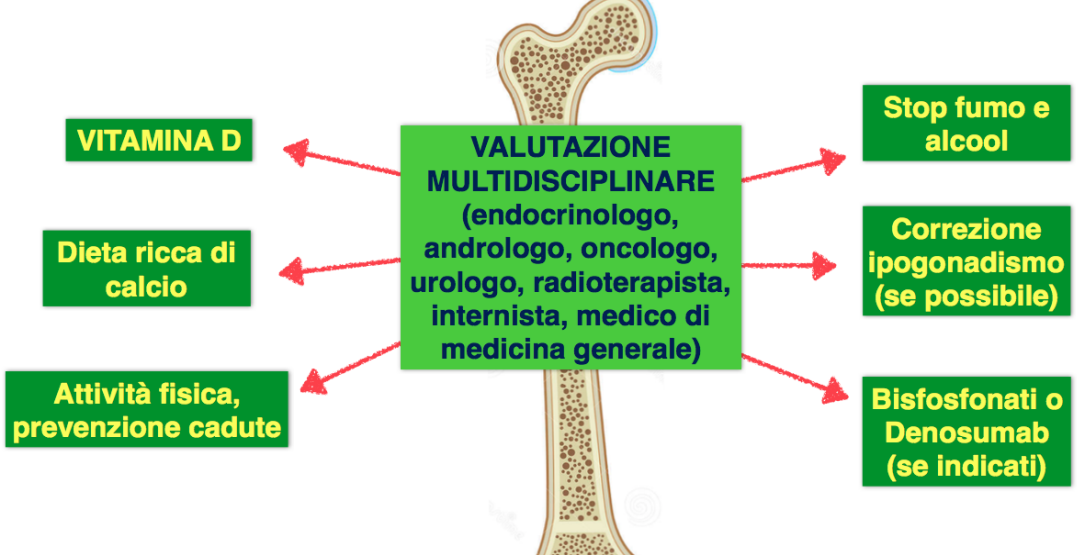


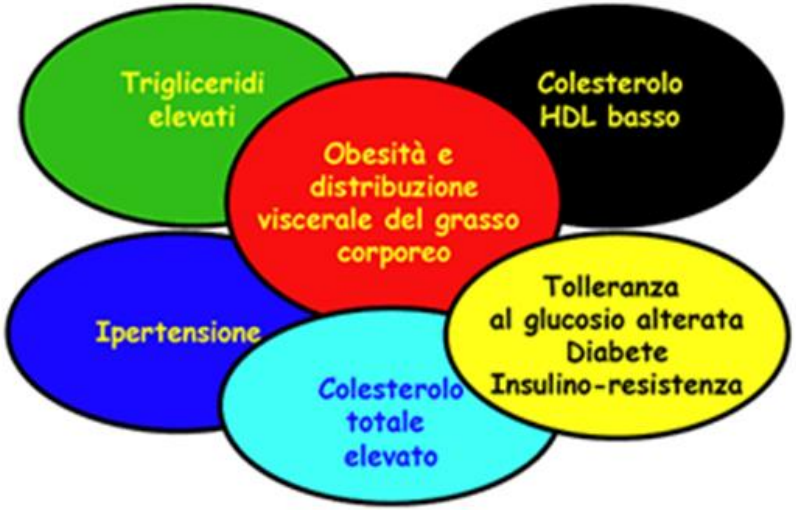
Ipovitaminosi D



Ferlin A 2013 Nat Rev Endocrinol 9, 548-554

Quale vitamina D?





Endocrinologo?

Corretta selezione, intervento PRECOCE sulle complicanze

E monitoraggio del paziente candidato ad ADT