CONTROVERSIE NELL'ASSOCIAZIONE OT E CHIRURGIA

DOTT. SALVATORE VALERIO
OSPEDALE CONEGLIANO
ULSS7
REGIONE VENETO

CONTROVERSIE NELL'ASSOCIAZIONE OT E CHIRURGIA

- Terapia neoadiuvante
- Terapia adiuvante
- Recidiva biochimica

CHIRURGIA RADICALE ED ENDOCRINO TERAPIA

- **TERAPIA ORMONALE NEOADIUVANTE:**

  - ✓ **RIDUZIONE DELL'INCIDENZA DI MARGINI POSITIVI**
  - ✓ **NON VANTAGGI IN TERMINI DI SOPRAVVIVENZA LIBERA DA PROGRESSIONE O GLOBALE**
  - ✓ **ALLO STATO ATTUALE NON RACCOMANDAZIONE ALLA TERAPIA NEOADIUVANTE PRIMA DI TRATTAMENTO CHIRURGICO**

    (LIVELLO DI EVIDENZA 1)

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TUMOUR REVIEW

A systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy for localised and locally advanced prostate carcinoma

M.D. Shelley [a,*], S. Kumar [b,f], T. Wilt [c,g], J. Staffurth [d,h], B. Coles [e,j], M.D. Mason [d,i]

Summary

Background: We performed a systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy (NHT) in localised and locally advanced prostate cancer to assess the effectiveness of this therapy.

Methods: We searched MEDLINE, The Cochrane Library, Science Citation Index, LILACS and SIGLE for randomised trials comparing NHT plus primary therapy (radiotherapy or prostatectomy) with primary therapy alone. Data included information on study design, participants, interventions, and outcomes. Comparable data were extracted from eligible studies and pooled for meta-analysis with intention to treat principle.

Findings: NHT prior to prostatectomy did not improve overall or disease-free survival, significantly reduce positive margin rates (RR 0.49, 95% CI 0.42–0.56, $p < 0.00001$), confinement (RR 1.63, 95% CI 1.37–1.95, $p < 0.0001$) and lymph node invasion (RR 0.49, 95% CI 0.42–0.56, $p < 0.02$).

In one study NHT before radiotherapy significantly improved overall survival for men with Gleason 2–6 ($p = 0.015$). In addition, there was a significant improvement in both clinical disease free survival (RR 1.46, 95% CI 1.24–1.71, $p < 0.00001$) and biochemical disease-free survival (RR 1.59, 95% CI 1.00–2.55, $p = 0.05$). Toxicities included hot flushes, gastrointestinal, hepatic and miscellaneous adverse events.

Conclusions: NHT is associated with significant clinical benefit when given with radiotherapy and improves pathological outcome prior to prostatectomy but is of minimal value prior to radical prostatectomy. The decision to use hormone therapy should be discussed between the patient, the clinician and policy maker based on the benefits, toxicity and cost.

AZIENDA ULSS7 VENETO

CHIRURGIA RADICALE ED ENDOCRINO TERAPIA

- LA TERAPIA ORMONALE ADIUVANTE E RADIOTERAPIA DOPO CHIRURGIA + LINFADENECTOMIA, IN PAZIENTI N+.
  - ✓ VANTAGGIO SIGNIFICATIVO PER LA COMBINAZIONE NEI PAZIENTI CON METASTASI LINFONODALI, SIA IN TERMINI DI SOPRAVVIVENZA LIBERA DA MALATTIA CHE IN TERMINI DI SOPRAVVIVENZA GLOBALE (LIVELLO DI EVIDENZA 1)
  - ✓ È LEGITTIMO CONSIDERARE ILTRATTAMENTO ADIUVANTE CON CASTRAZIONE FARMACOLOGICA PER 18-36 MESI IN TUTTI I PAZIENTI CON LINFONODI POSITIVI DOPO PROSTATECTOMIA RADICALE.

Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

Edward M Messing, Judith Manola, Jorge Yao, Maureen Kiernan, David Crawford, George Wilding, P Anthony di'SantAgnese, Donald Trump, on behalf of the Eastern Cooperative Oncology Group study EST 3886

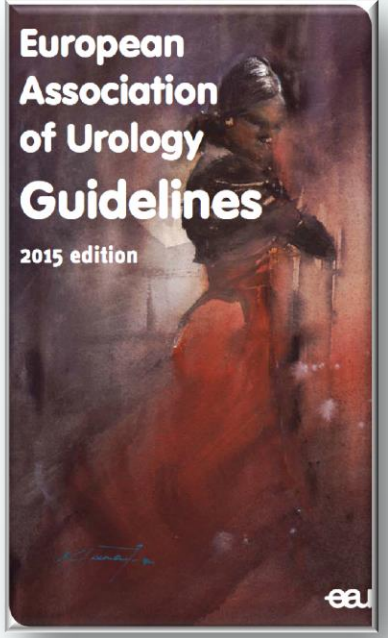
Summary

Background Appropriate timing of androgen deprivation treatment (ADT) for prostate cancer is controversial. Our aim was to determine whether immediate ADT extends survival in men with node-positive prostate cancer who have undergone radical prostatectomy and pelvic lymphadenectomy compared with those who received ADT only once disease progressed.

Methods Eligible patients from 36 institutes in the USA were randomly assigned in 1988–93 to receive immediate ADT (n=47) or to be observed (n=51), with ADT to be given on detection of distant metastases or symptomatic recurrences. Patients were followed up every 3 months for the first year and every 6 months thereafter. The primary endpoint was progression-free survival; secondary endpoints were overall and disease-specific survival. Analysis was by intention to treat. To ensure that the treatment groups were comparable, we did a retrospective central pathology review of slides and regraded the Gleason scores for available samples. This trial predates the requirement for clinical trial registration.

Findings At median follow-up of 11·9 years (range 9·7–14·5 for surviving patients), men assigned immediate ADT had a significant improvement in overall survival (hazard ratio 1·84 [95% CI 1·01–3·35], p=0·04), prostate-cancer-specific survival (4·09 [1·76–9·49], p=0·0004), and progression-free survival (3·42 [1·96–5·98], p<0·0001). Of 49 histopathology slides received (19 immediate ADT, 30 observation), 16 were downgraded from the original Gleason score (between groups ≤6, 7, and ≥8) and five were upgraded. We recorded similar proportions of score changes in each group (p=0·68), and no difference in score distribution by treatment (p=0·38). After adjustment for score, associations were still significant between treatment and survival (overall, p=0·02; disease-specific, p=0·002; progression-free survival, p<0·0001).

Interpretation Early ADT benefits patients with nodal metastases who have undergone prostatectomy and lymphadenectomy, compared with those who receive deferred treatment. The beneficial effects of early ADT, rather than an imbalance in risk factors, are likely to explain the differences in outcomes between treatments.



When nodal involvement is detected after RP:			
•	Adjuvant ADT is the standard of care for node-positive (pN+)	1b	A
	Adjuvant ADT with additional radiotherapy may have a role (see Section 6.3.3.3)	2b	B
•	Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	2b	B

RECIDIVA BIOCHIMICA

- Un problema sempre più frequente è rappresentato dai pazienti che, dopo terapia loco regionale, presentino esclusivamente una recidiva biochimica
- Definire I valori di PSA, indicativi di una ricaduta biochimica, sono aspetti importanti e molto controversi
- I pazienti sottoposti a prostatectomia radicale dovrebbero raggiungere un azzeramento del PSA dopo circa 6 settimane dall‘ intervento

RECIDIVA BIOCHIMICA

- **DEFINIZIONE:**

  "la definizione di recidiva biochimica più comunemente accettata prevede, come cut-off, il valoredi 0.2 ng/mL e almeno due determinazioni successive con valori in incremento"

PROSTATECTOMY BIOCHEMICAL RECURRENCE

- **"only 34% of those with BCF subsequently had a clinical recurrence"**

(Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999 May;281(17):1591-7.)

- **"and only a few died of PCa (5.8%)"**

Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol 2011 Jun;59(6):893-9.

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Management of Biochemically Recurrent Prostate Cancer After Local Therapy: Evolving Standards of Care and New Directions

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Abstract

Among men treated with prostatectomy or radiation therapy for localized prostate cancer, the state of an increasing prostate-specific antigen (PSA) level is known as biochemical recurrence (BCR). BCR can be predictive of the development of subsequent distant metastases and ultimately death, but BCR often predates other signs of clinical progression by several years. Although patients may be concerned about their rising PSA levels, physicians attempting to address patient anxiety must inform them that BCR is not typically associated with imminent death from disease, and that the natural history of biochemical progression may be prolonged. Misinterpretation of the significance of early changes in PSA may cause patients to receive androgen deprivation therapy (ADT) prematurely, especially in settings where the disease is unlikely to impact survival. In addition, knowledge of the morbidities associated with ADT (hot flashes, impotence, sarcopenia, metabolic syndrome, bone loss, and increased risk of vascular disease) has accelerated the search for alternative treatment options for these patients. Clinical trials investigating when and how to best use and supplement hormonal therapies in this patient population are under way, as are trials of novel nonhormonal targeted agents, immunotherapies, natural products, and other pharmaceuticals that have been approved by the US Food and Drug Administration (FDA) for other indications. This review will summarize the acceptable standards of care for the management of biochemically recurrent prostate cancer, and will also outline some novel experimental approaches for the treatment of this disease state.

RECIDIVA BIOCHIMICA

PROGNOSTIC FACTORS

T - STAGE

PSA BASELINE

PATHOLOGICAL FINDINGS

(GLEASON SCORE,SURGICAL MARGIN STATUS , LYMPH NODE STATUS)

RECIDIVA BIOCHIMICA
PSA DT

RISK GROUPS

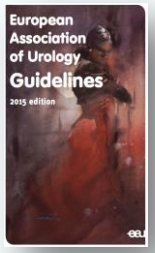
<3 M0NTHS

> 3-9 MONTHS

>9-15 MONTHS

> 15 MONTHS

- TIMING (3 MONTHS APART)



Recidiva biochimica

Local salvage treatment	LE	GR
Biochemical recurrence (BCR) after RP		
For patients with a PSA rise from the undetectable range and favourable prognostic factors (≤ pT3a, time to BCR > 3 yr, PSA-DT > 12 mo, Gleason score ≤ 7) surveillance and possibly delayed salvage RT (SRT) may be offered.	3	B
Patients with a PSA rise from the undetectable range should be treated with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Biochemical recurrence (BCR) after RT		
Selected patients with localised PCa at primary treatment and histologically proven local recurrence should be treated with salvage RP (SRP).	3	B
Due to the increased rate of side effects, SRP should be performed in experienced centres.	3	A
High intensity focused ultrasound (HIFU), cryosurgical ablation and salvage brachytherapy are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. Patients must be informed about the experimental nature of these approaches.	3	B
Systemic salvage treatment		
In asymptomatic men with BCR, ADT should not be given routinely.	3	A
Patients with a PSA-DT > 12 mo, should not receive ADT.	3	B
If salvage ADT (post-primary RT) is started, intermittent therapy should be considered in responding patients.	1b	A

TAKE HOME MESSAGE

- ***NO** alla OT neoadiuvante prima della prostatectomia radicale*
- ***SI** alla OT adiuvante nei pazienti pN+ (anche in combinazione alla RT)*
- ***NO** alla OT adiuvante in <u>tutte</u> le recidive biochimiche dopo prostatectomia radicale*
- ***SI** alla ricerca di nuove terapie non ormonali per la recidiva biochimica*

AZIENDA ULSS7 VENETO

grazie dell‘ attenzione!!!