

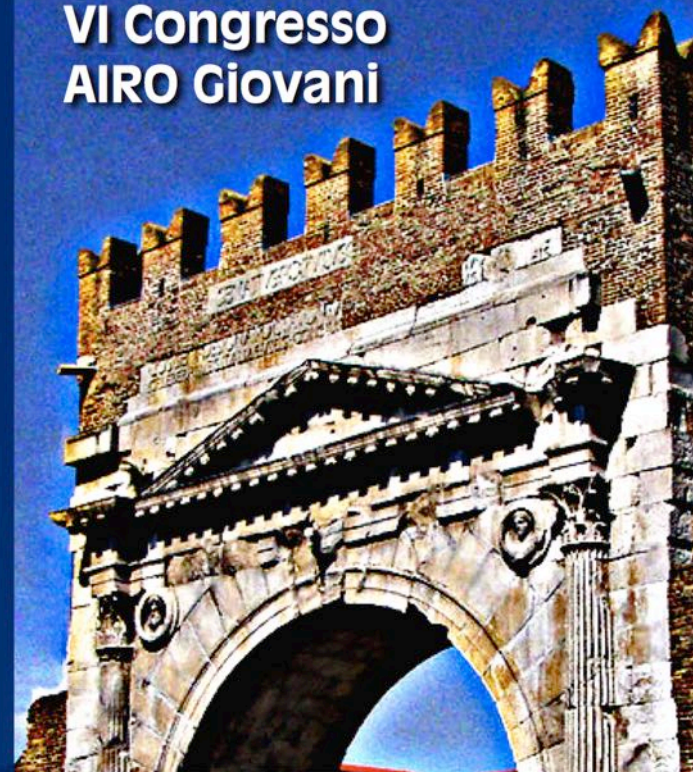
RT postoperatoria: adiuvante o di salvataggio?

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Associazione
Italiana
Radioterapia
Oncologica

**VI Congresso
AIRO Giovani**



**Adenocarcinoma della prostata:
il radio-oncologo e la gestione
terapeutica tra evidenze
e nuove prospettive**


Presidente del Congresso **FILIPPO ALONGI**

**Rimini
18 Maggio 2013
Hotel Sporting**



Background

- 1 in 3 men who undergo radical prostatectomy (RP) will develop biochemical recurrence
- 50-70% of patients with high risk pathologic features at RP will develop biochemical recurrence
- 50% of men with a rising PSA post-RP will develop clinical recurrence and die of prostate cancer



Local residual disease is present in majority of these men

Scenarios in high risk patients

Radiation therapy immediately after surgery with undetectable PSA

- =Adjuvant Radiotherapy

Radiation therapy at some point down the road from surgery due to a rising PSA

- =Salvage Radiation therapy

Radiation therapy immediately after surgery with a persistently detectable PSA

Adjuvant Radiotherapy

Given based on pathologic risk factors

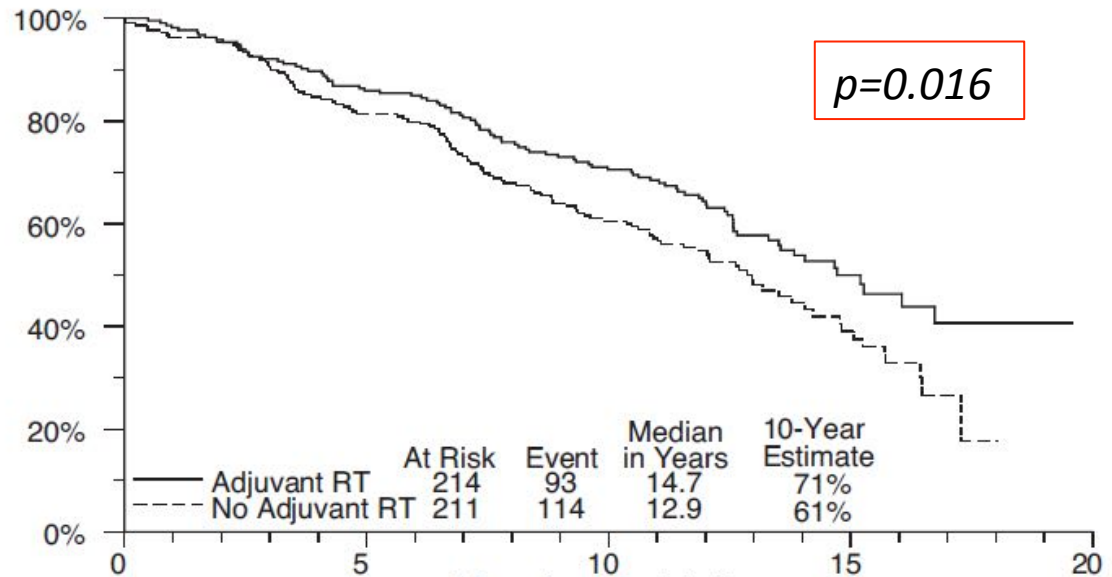
- Positive surgical margins (SM+)
- Extraprostatic extension (ECE)
- Seminal vesicle invasion (SVI)

How do we answer today to clinical question?

Level of evidence	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

SWOG 8794

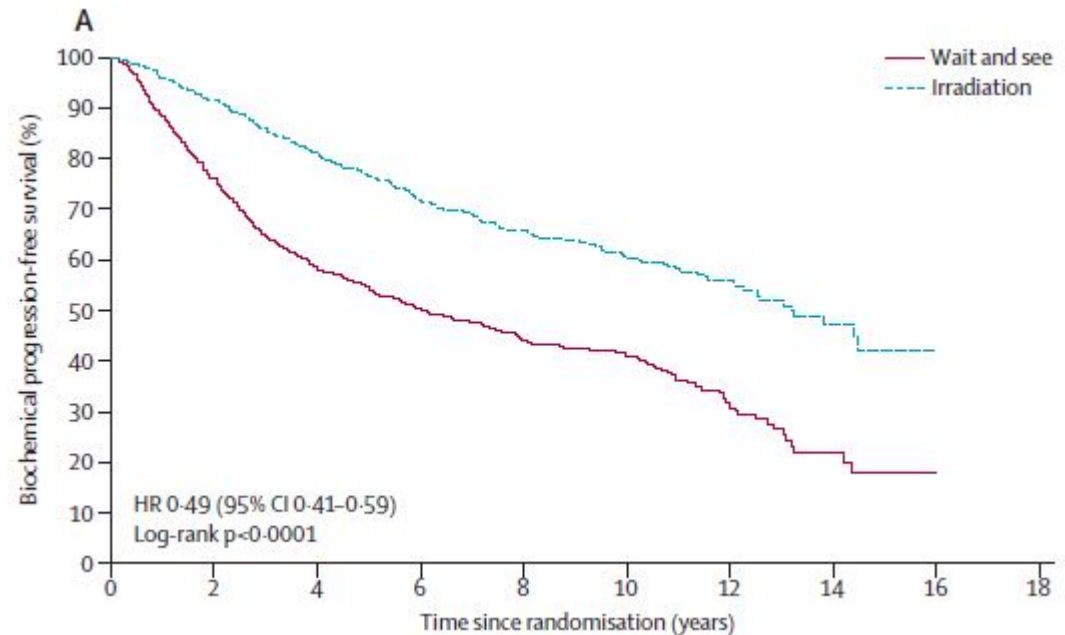
- 425 patients
- 1988-1997
- 1 or more: ECE, SVI, +SM
- pN0
- **60-64Gy vs observation**
- Median follow-up 12.7y



Conclusions: Adjuvant radiotherapy after radical prostatectomy for a man with pT3N0M0 prostate cancer significantly reduces the risk of metastasis and increases survival.

EORTC 22911

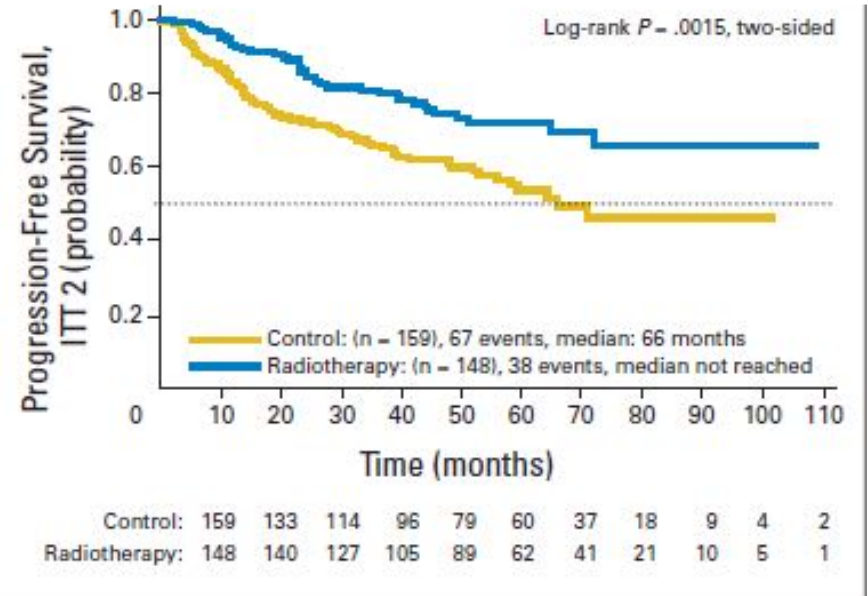
- 1005 patients
- 1992-2001
- 1 or more: ECE, SVI, +SM
- pN0
- **60Gy vs “wait & see”**
- Median follow-up 10.6y



Interpretation Results at median follow-up of 10.6 years show that conventional postoperative irradiation significantly improves biochemical progression-free survival and local control compared with a wait-and-see policy, supporting results at 5 year follow-up; however, improvements in clinical progression-free survival were not maintained. Exploratory analyses suggest that postoperative irradiation might improve clinical progression-free survival in patients younger than 70 years and in those with positive surgical margins, but could have a detrimental effect in patients aged 70 years or older.

ARO 96-02

- 385 patients
- 1997-2004
- pT3-4 +/- positive margin
- pN0
- **60Gy vs “wait & see”**
- Median follow-up 4.5y



Conclusion

Adjuvant RT for pT3 prostate cancer with postoperatively undetectable PSA significantly reduces the risk of biochemical progression. Further follow-up is needed to assess the effect on metastases-free and overall survival.

ARO 96-02 update (ASCO GU 2013)

After 10 years, biochemical progression-free survival was 61% for patients in the adjuvant radiation therapy group, compared with 40% for those in the wait-and-see group ($p = 0.000022$).

No differences between treatment arms in terms of metastasis-free survival ($P = 0.56$) or overall survival ($p = 0.59$), although the study was not powered to detect differences in these endpoints.

In the subgroup of patients with positive surgical margins after prostatectomy, however, adjuvant radiation therapy was associated with a significant improvement on metastasis-free survival compared with wait-and-see (55% vs 27%; HR, 0.49; $p < 0.0001$).

Summary of RCTs over adjuvant RT

- Adjuvant RT vs observation improves OS and reduces the rate of distant metastases, but these effects are only evident with longer follow up.
- At 5 and 10 years it improves local control and reduces the risk of biochemical failure.
- Moderate or severe acute and late toxicity is minimal.

Caveats of RCTs

- Routine use of sensitive PSA assays were not available when the study were designed.
- Not all patients had an undetectable PSA at time of randomization
- Central pathology review was performed in all patients in ARO and 73% of men in SWOG and was not performed in EORTC.
- Studies not designed to assess superiority of adjuvant treatment over salvage treatment

PSA evaluation: possible bias?

Study	Definition of nadir
ARO	postoperative PSA < 0.1ng/dL
EORTC	PSA < 0.2 ng/dL
SWOG	PSA ≤ 0.4 ng/dL

Study	Number of men who did not nadir
ARO	78/388 (20%)
EORTC	108/1005 (10%)
SWOG	127/376 (33%) did not achieve PSA ≤ 0.2 ng/dL NB: only had PSA information for 376/425 men postoperatively

Salvage radiotherapy

Delivered at the time of PSA recurrence or for a persistently detectable PSA following surgery

Presumes local residual or recurrent disease

Provides the only potentially curative secondary therapy

Salvage radiotherapy evidences

Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling

Nitin Ohri ^{a,*}, Adam P. Dicker ^a, Edouard J. Trabulsi ^b, Timothy N. Showalter ^a



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Clinical Investigation: Genitourinary Cancer

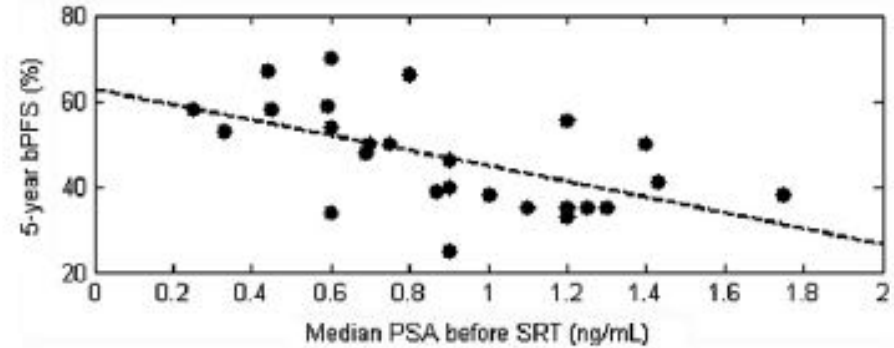
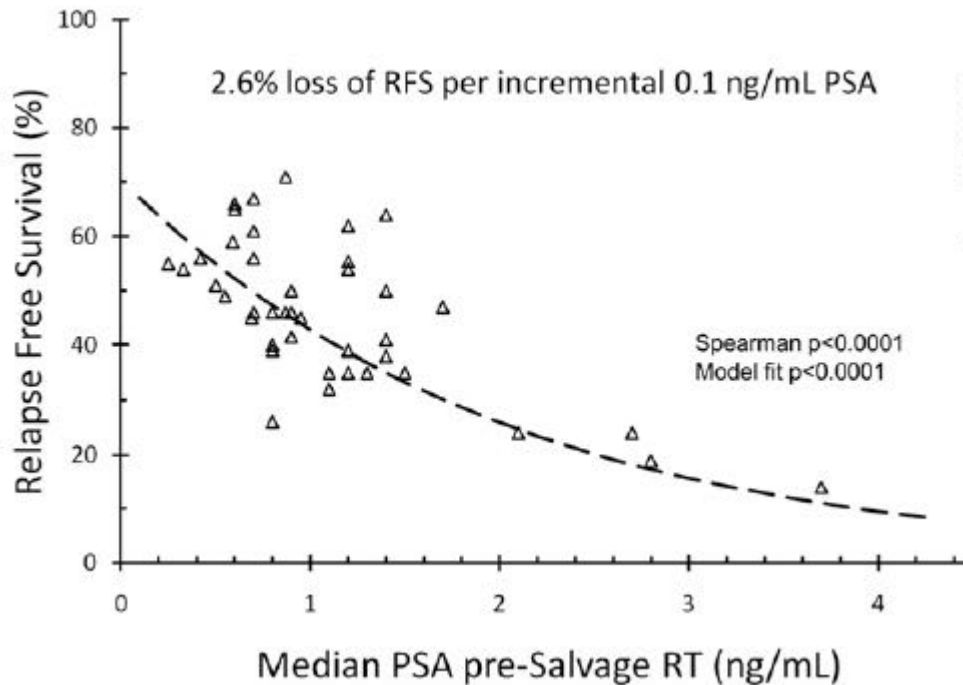
The Timing of Salvage Radiotherapy After Radical Prostatectomy: A Systematic Review

Christopher R. King, PhD, MD

Systematic reviews features

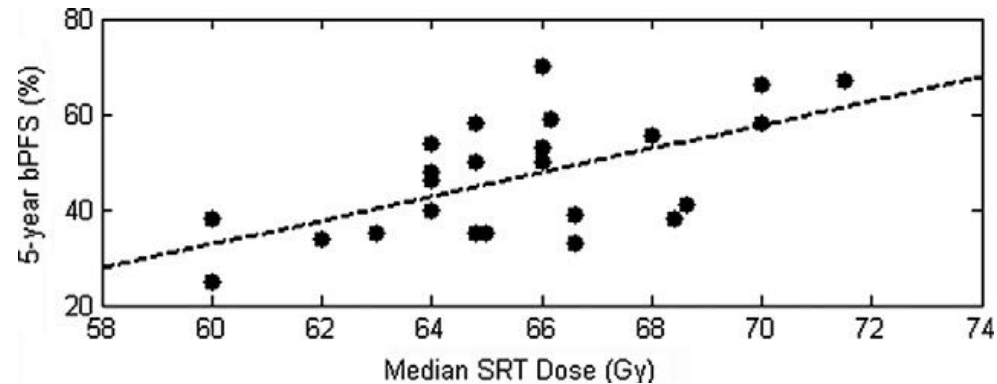
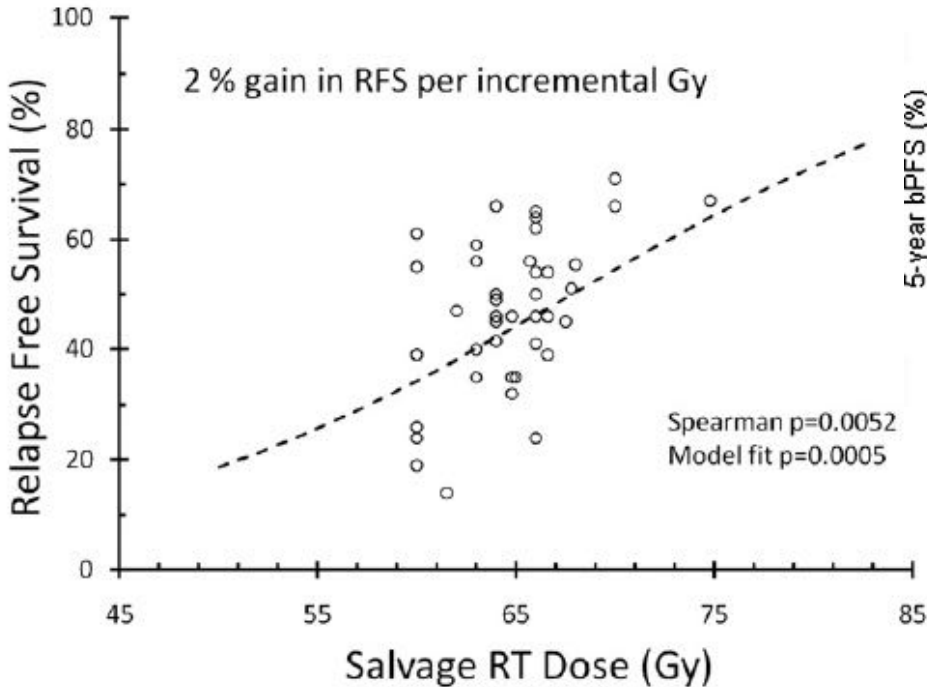
- 25 and 41 articles analyzed respectively
- More than 5000 patients evaluated
- Miscellaneous inclusion criteria
- Aim to define optimal patient and treatment characteristics for salvage radiotherapy

Results: the importance of timing



- pre-SRT PSA affects RFS outcome of treated patients
- King's work demonstrated an average loss of 2.6% in RFS for each incremental 0.1 ng/mL rise in PSA before SRT.

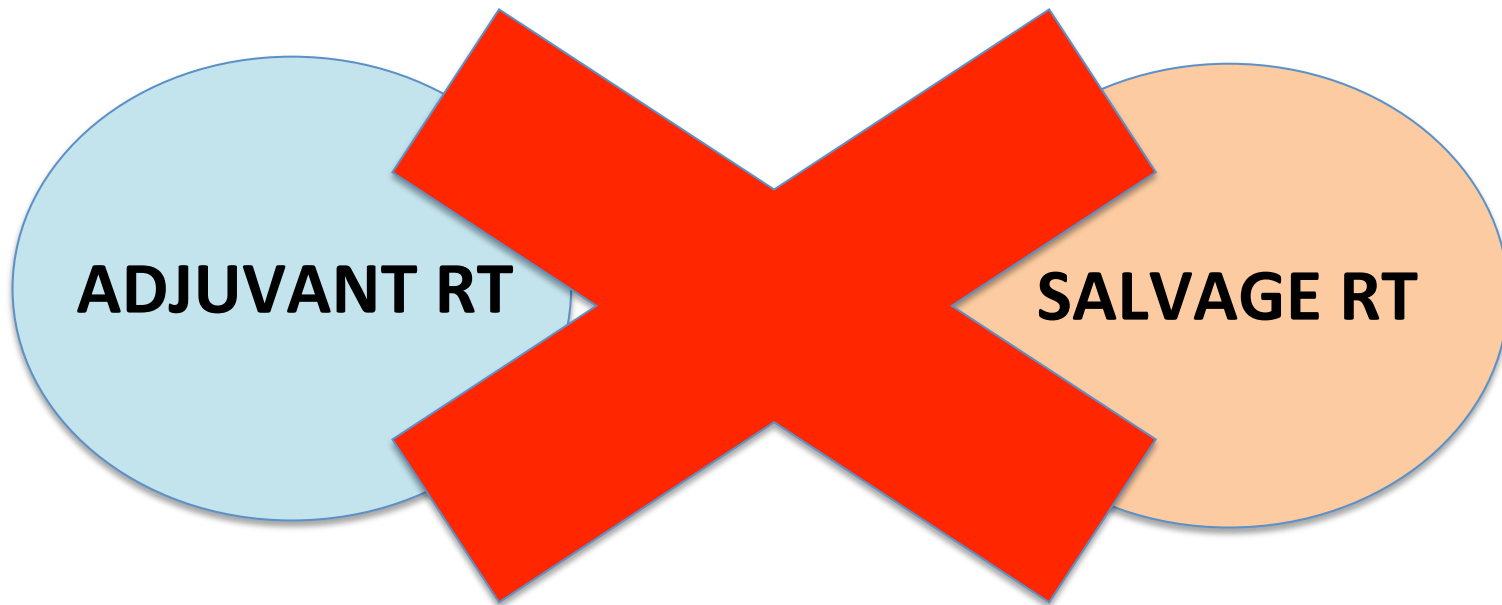
Results: the importance of dose



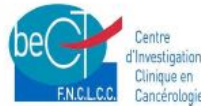
- SRT dose is an independent prognostic factor for relapse free survival (RFS) in both reviews.
- King's work demonstrated a 2% increase in RFS for each additional Gray.

Adjuvant or Salvage Radiotherapy ?

- Studies not designed to assess superiority of adjuvant treatment over salvage treatment



Ongoing phase III trials ART vs SRT



GETUG

French Study Group for Genito-Urinary Tract Tumours
Protocol AFU-GETUG 20/0310
EudraCT n°:2010-022037-29

**PHASE III RANDOMISED STUDY TO EVALUATE THE BENEFIT OF
ADJUVANT HORMONAL TREATMENT WITH LEUPRORELIN
ACETATE (ELIGARD® 45MG) FOR 24 MONTHS AFTER RADICAL
PROSTATECTOMY IN PATIENTS WITH HIGH RISK OF
RECURRENCE.**



NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

RADICALS

Radiotherapy and Androgen Deprivation
In Combination After Local Surgery
A randomised controlled trial in prostate cancer

TROG 08.03 RAVES Trial

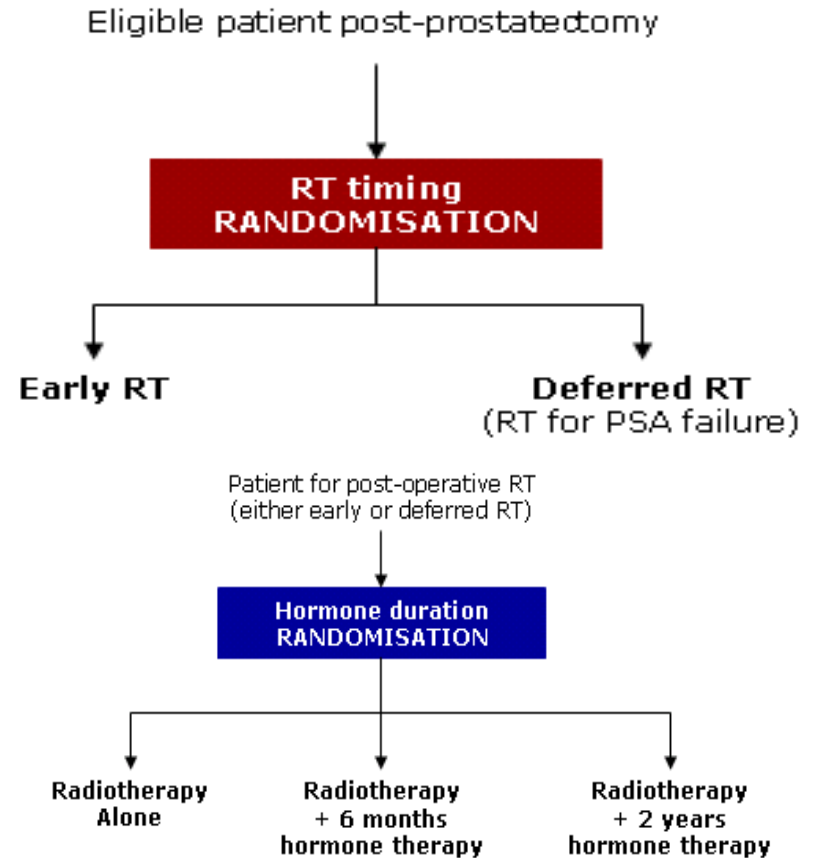
A phase III multi-centre randomised trial comparing adjuvant radiotherapy (RT) with early salvage RT at biochemical recurrence in patients with positive margin and/or stage pT3 disease following radical prostatectomy

Radiation therapy and Androgen Deprivation In Combination after Local Surgery (RADICALS)

● Eligibility:

- Post-op PSA ≤ 0.2 ng/ml
- >4 but <22 wks after RP
- One or more of:
 - pT3/4
 - Gleason 7-10 (biopsy /RP)
 - Pre-op PSA ≥ 10 ng/ml
 - Positive margins

- RT dose(both arms):
66Gy or 52.5Gy (2.6Gy/fx)
- 3DCRT/IMRT



Accrual: $\approx 2000/4000$

Conclusions

- Given that the majority of men who have undergone a RP have a longer life expectancy, radiotherapy should be considered for those with high-risk features following radical prostatectomy.
- The optimal timing is unclear with nowadays evidence.
- Results from ongoing phase III trials will probably define the best approach for high risk patients, with an high level of evidence.
- Role of hormonal therapy in this setting will also probably be more defined.