Indikasjon og evidens for elektiv strålebehandling av bekkenfelt for cN0

Primær og postoperativ setting

Sigmund Brabrand

Bestråling av bekkenlymfeknuter – kliniske situasjoner

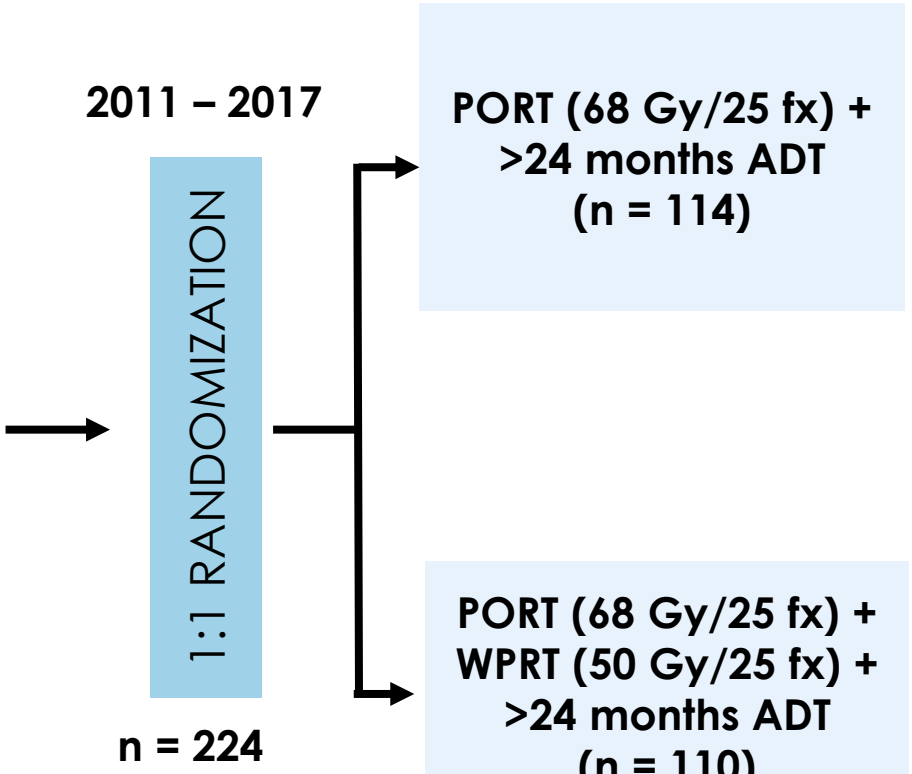
- Primærsituasjon
  - RadN1
  - RadN0, høy risiko for regionale mikrometastaser

- Postoperativ situasjon
  - Adjuvant (PSA <0,1)
    - pN1
    - pN0/pNx, høy risiko for regionale mikrometastaser
  - Salvage PSA ≥ 0,1 - < 0,2 uten PSMA PET/CT
    - pN1
    - pN0/pNx, høy risiko for regionale mikrometastaser
  - Salvage PSA ≥ 0,2 med PSMA PET/CT
    - pN1/radN0
    - pN1/radN1
    - pN0/pNx/radN0, høy risiko for regionale mikrometastaser
    - pN0/pNx/radN1

POP-RT trial

Eligibility criteria
- Rad N0M0 prostate cancer
- Estimated nodal risk ≥20% (Roach)
- cT1-T3a
  - + Gleason 8-10 + any PSA
  - + Gleason 7 + PSA >15 ng/mL
  - + Gleason 6 + PSA >30 ng/mL
- cT3b-T4a + any Gleason + any PSA
- Life expectancy of at least 5 years

Additional
- IMRT + IGRT in all patients
- No intraprostatic fiducials or MRI-based treatment planning
- WPRT CTV cranially to L4/L5
- Staging with MRI (pelvis), CT abdomen/pelvis (with contrast), technetium-99m bone scan or PSMA PET/CT (80% of patients)
- PORT 2,72 Gy/fx (78-81 Gy EQD2 a/b 3-1,5)



Primary end Point
- 5-year biochemical failure-free survival

Secondary end points
- Disease-free survival
- Overall survival
- Distant metastasis free survival
- Acute and late toxicities
- Patient-reported QOL

Roach formula: 2/3 x PSA + (Gleason score – 6) x 10

Murthy et al, JCO, 2021

POP-RT trial patient population

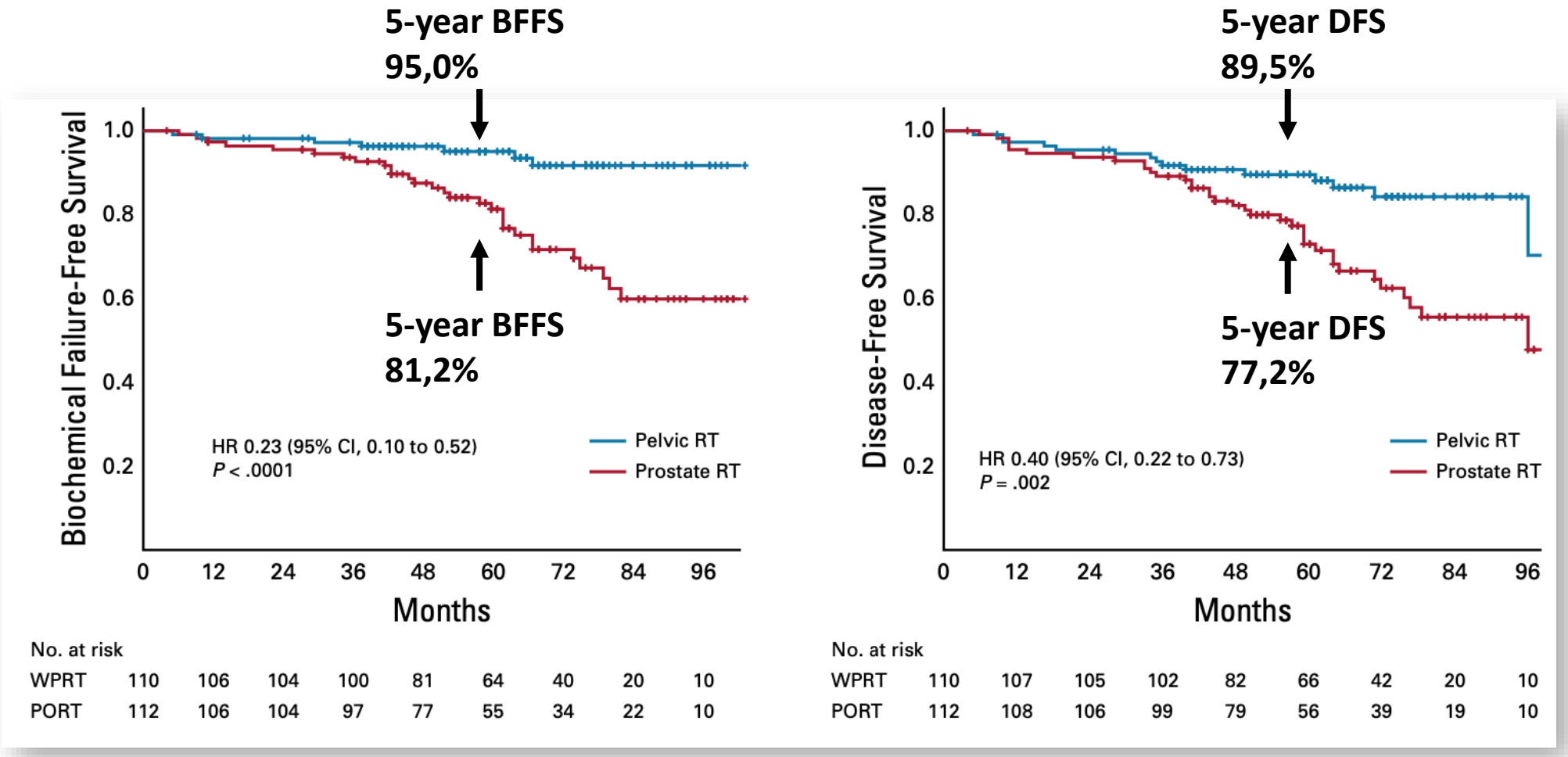
Characteristic	All Patients (N = 222), N (%)	PORT (n = 112), N (%)	WPRT (n = 110), N (%)
Median age, years	66	66	66
Median PSA, ng/mL	28.2	27.4	29.9
Nodal risk, %[a]			
≤ 40%	119 (53.6)	60 (53.6)	59 (53.6)
> 40%	103 (46.4)	52 (46.4)	51 (46.4)
Gleason grade group			
1	22 (9.9)	11 (9.8)	11 (10)
2	38 (17.1)	20 (17.9)	18 (16.4)
3	53 (23.9)	25 (22.3)	28 (25.5)
4	53 (23.9)	26 (23.2)	27 (24.5)
5	56 (25.3)	30 (26.8)	26 (23.6)
ADT			
Orchiectomy	42 (18.9)	26 (23.2)	16 (14.5)
Medical	180 (81.1)	86 (76.8)	94 (85.5)
History of TURP			
Yes	60 (27)	30 (26.8)	30 (27.3)
No	162 (73)	82 (73.2)	80 (72.7)
Tumor stage			
T1	2 (0.9)	1 (0.9)	1 (0.9)
T2	46 (20.7)	19 (17)	27 (24.5)
T3a	70 (31.5)	38 (33.9)	32 (29.1)
T3b	86 (38.7)	44 (39.3)	42 (38.2)
T4	18 (8.1)	10 (8.9)	8 (7.3)

Abbreviations: ADT, androgen deprivation therapy; PORT, prostate-only radiotherapy; PSA, prostate-specific antigen; TURP, transurethral resection of prostate; WPRT, whole-pelvic radiotherapy.

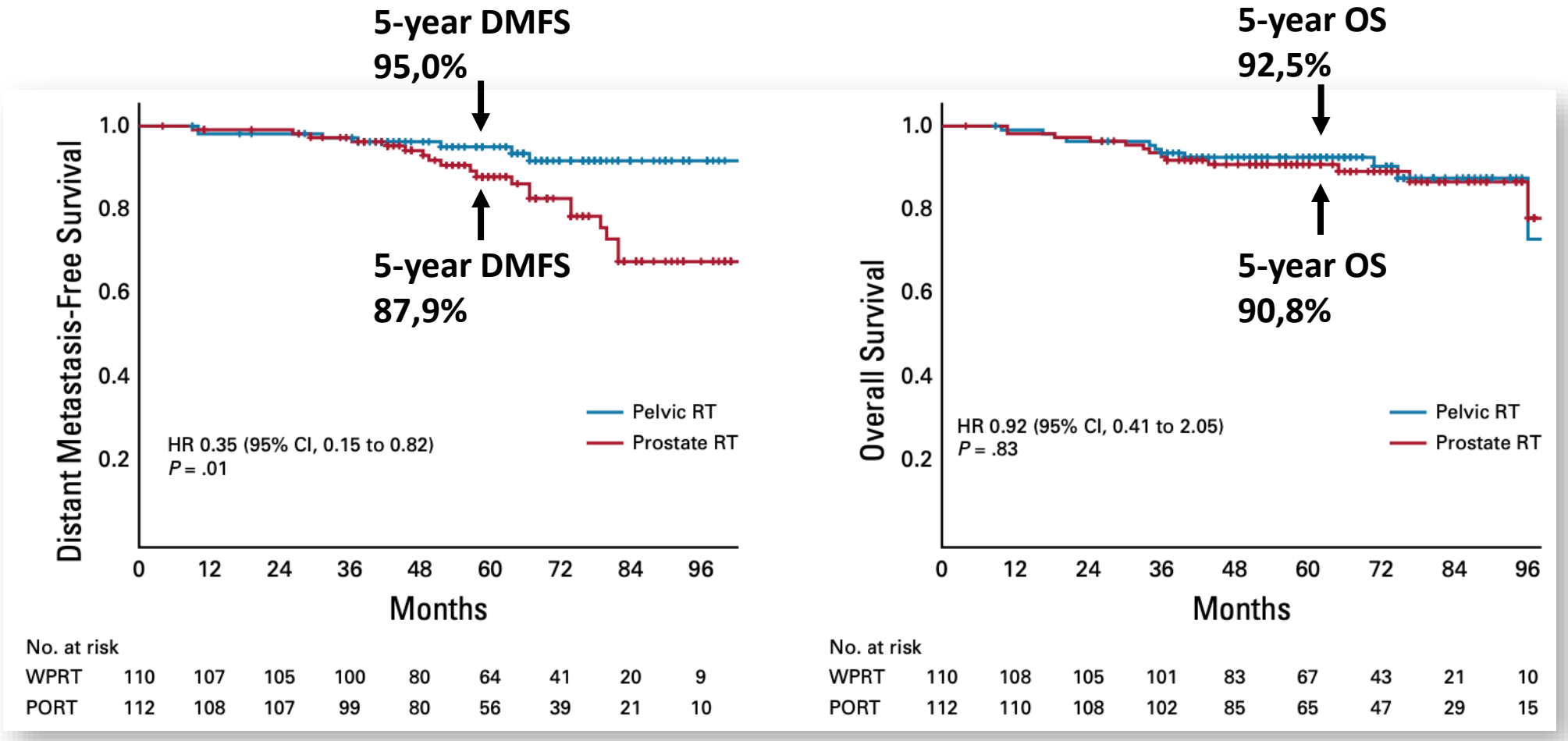
[a]By Roach formula, risk = 2/3 PSA + ([Gleason score − 6] × 10).

- Young study population, median 66 years
- Median baseline PSA 28,2 ng/mL
- Median Roach nodal risk 37,8% (IQR 25,1-53,4)
- About 50% of patients with Gleason grade group 4-5
- About 20% of patients performed orchiectomy. Risk of bias (but in favor of PORT)
- About 45% of patients with T3b-T4

POP-RT trial outcome I



POP-RT trial outcome II



POP-RT trial toxicity

RTOG Grade	All Patients (N = 222), N (%)	PORT (n = 112), N (%)	WPRT (n = 110), N (%)	*P* (grade 0-1 *v* grade ≥ II)
GU				
0	85 (38.3)	45 (40.2)	40 (36.4)	.02
I	105 (47.3)	57 (50.9)	48 (43.6)	
II	28 (12.6)	8 (7.1)	20 (18.2)	
III	4 (1.8)	2 (1.8)	2 (1.8)	
GI				
0	138 (62.2)	74 (66.1)	64 (58.2)	.28
I	70 (31.5)	33 (29.5)	37 (33.6)	
II	12 (5.4)	5 (4.5)	7 (6.4)	
III	2 (0.9)	0 (0)	2 (1.8)	

Abbreviations: GU, genitourinary; PORT, prostate-only radiotherapy; RTOG, Radiation Therapy Oncology Group; WPRT, whole-pelvic radiotherapy.

Increased toxicity of PLNRT

- Acute (≤3 months after RT):
  - No difference in GI and GI tox between groups
- Late (>3 months after RT):
  - Grade ≥ 2 GU tox

POP-RT trial conclusions

- The addition of pelvic lymph node radiotherapy increased 5-year biochemical failure free-, disease free- and distant metastasis free survival compared to prostate only radiotherapy
- However, no difference in overall survival was observed
- Pelvic lymph node radiotherapy did not increase acute GI or GU toxixity, although increased late GU toxicity was observed

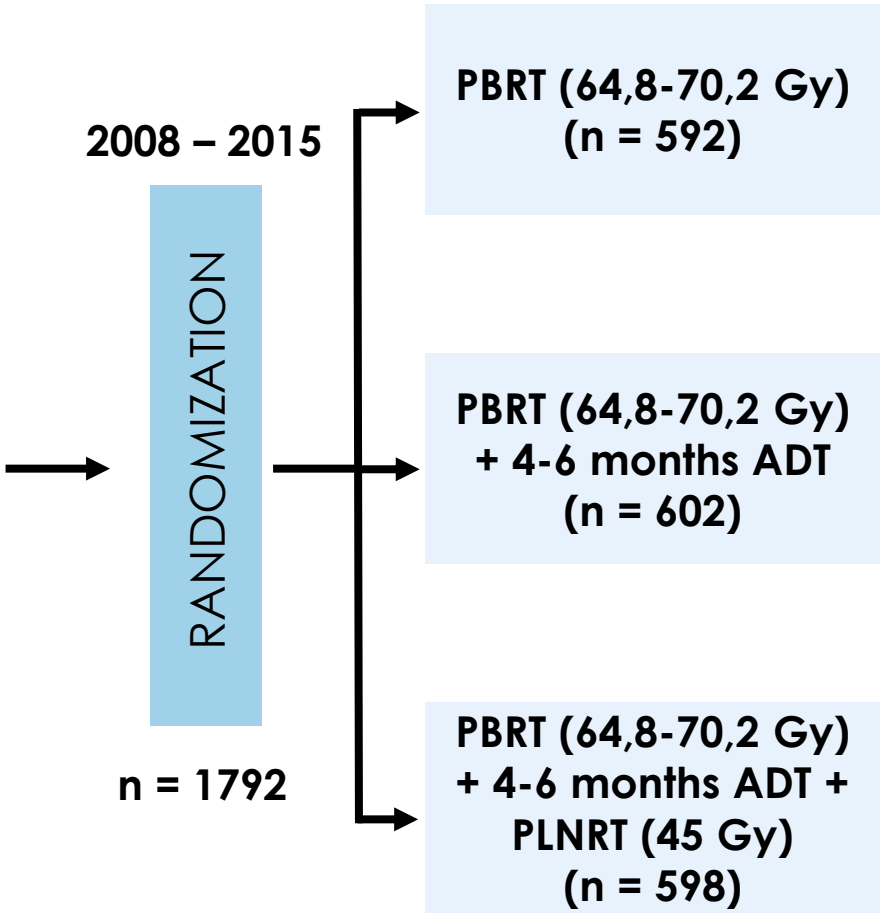
NRG Oncology/RTOG 0534 (SPPORT-trial)

Eligibility criteria

- Prostatectomy for prostate cancer
- PSA
  - Persistently detectable
  - Initially undetectable and rising to between 0,1-2,0 ng/ml
- pN0/pNx
- pT2/pT3
- Gleason score ≤9
- ECOG 0-1
- M0 on technetium-99m bone scan or CT abdomen/pelvis

Additional

- Radiotherapy given with 1,8 Gy pr fraction. IMRT used in 87% of patients.
- PLNRT CTV cranially to L5/S1
- No PSMA PET/CT or MRI before treatment
- CT or MRI scan of pelvis and technetium-99m bone scan during follow up on clinical indication



Primary end Point

- Freedom from progression (biochemical failure PSA ≥2,0 ng/ml over nadir PSA, clinical failure (local, regional or distant) or death)

Secondary end points

- Prostate cancer specific mortality
- Overall survival
- Adverse events rates
- Distant metastasis
- ++

Oslo universitetssykehus

Pollack et al, Lancet, 2022

SPPORT-trial patient population I

	PBRT alone (group 1; n=564)	PBRT plus short-term ADT (group 2; n=578)	PLNRT plus PBRT plus short-term ADT (group 3; n=574)
Age, years			
Mean	63·8 (6·9)	63·9 (6·9)	63·9 (6·5)
Median	64 (60–69)	64 (59–69)	64 (59–69)
Range	42–84	39–80	44–80
≤49	19 (3%)	15 (3%)	8 (1%)
50–59	118 (21%)	137 (24%)	138 (24%)
60–69	307 (54%)	299 (52%)	307 (54%)
≥70	120 (21%)	127 (22%)	121 (21%)
Race			
American Indian/Alaska Native	0	0	5 (1%)
Asian	3 (1%)	6 (1%)	8 (1%)
Black or African American	74 (13%)	69 (12%)	77 (13%)
Native Hawaiian or other Pacific Islander	1 (<1%)	4 (1%)	0
White	464 (82%)	482 (83%)	474 (83%)
Mixed race	3 (1%)	0	0
Unknown or not reported	19 (3%)	17 (3%)	10 (2%)
Ethnicity			
Hispanic or Latino	21 (4%)	23 (4%)	30 (5%)
Not Hispanic or Latino	511 (91%)	527 (91%)	517 (90%)
Unknown	32 (6%)	28 (5%)	27 (5%)
Zubrod performance status			
0	522 (93%)	539 (93%)	540 (94%)
1	42 (7%)	39 (7%)	34 (6%)

Young study population, about 20% of age ≥70 years

SPPORT-trial patient population II

Pathological seminal vesicle involvement			
No	482 (86%)	494 (86%)	488 (85%)
Yes	82 (15%)	84 (15%)	86 (15%)
Pathological tumour stage			
T2	292 (52%)	317 (55%)	304 (53%)
pT3 extraprostatic extension NOS	13 (2%)	15 (3%)	18 (3%)
pT3a extraprostatic extension	177 (31%)	162 (28%)	166 (29%)
pT3b seminal vesicle invasion	82 (15%)	84 (15%)	86 (15%)
Gleason score			
4	0	1 (<1%)	1 (<1%)
5	3 (1%)	1 (<1%)	5 (1%)
6	80 (14%)	85 (15%)	89 (16%)
7: 3+4	226 (40%)	240 (42%)	221 (39%)
7: 4+3	153 (27%)	148 (26%)	156 (27%)
7: primary or secondary not indicated	9 (2%)	5 (1%)	3 (1%)
8	57 (10%)	60 (10%)	57 (10%)
9	36 (6%)	38 (7%)	42 (7%)
Prostatectomy margins			
Positive	288 (51%)	289 (50%)	284 (50%)
Negative	267 (47%)	284 (49%)	287 (50%)
Unknown	9 (2%)	5 (1%)	3 (1%)

About 50% pT3a/pT3b

Less aggressive tumors? Less than 20% ISUP 4 and 5

SPPORT-trial patient population III

Pelvic lymphadenectomy			
No	189 (34%)	207 (36%)	209 (36%)
Yes	375 (67%)	371 (64%)	365 (64%)
Number of lymph nodes examined*			
Mean	7·2 (5·7)	7·8 (6·6)	7·2 (5·9)
Median	5 (3–10)	6 (3–11)	5 (3–10)
Range	0–34	1–54	1–32
Pre-radiotherapy baseline PSA (ng/mL)			
Mean	0·47 (0·38)	0·51 (0·39)	0·47 (0·37)
Median	0·32 (0·20–0·60)	0·40 (0·23–0·68)	0·32 (0·20–0·60)
Range	0·1–1·96	0·1–1·93	0·1–1·93
≥0·1 to ≤0·2 ng/mL	155 (28%)	126 (22%)	154 (27%)
>0·2 to ≤0·5 ng/mL	247 (44%)	256 (44%)	247 (43%)
>0·5 to ≤1·0 ng/mL	105 (19%)	130 (23%)	114 (20%)
>1·0 to <2·0 ng/mL	57 (10%)	66 (11%)	59 (10%)
Time from surgery to randomisation			
>0 to ≤6 months	64 (11%)	74 (13%)	69 (12%)
>6 to ≤12 months	89 (16%)	100 (17%)	81 (14%)
>12 to ≤18 months	60 (11%)	55 (10%)	71 (12%)
>18 months	351 (62%)	349 (60%)	353 (62%)
Median, years	2·3 (0·9–4·6)	2·1 (0·8–4·3)	2·1 (0·9–4·4)
Range	0·1–20·5	0·1–17·6	0·1–17·7
Postoperative PSA doubling time†			
>0 to ≤6 months	34 (22%)	32 (21%)	32 (20%)
>6 to ≤12 months	54 (35%)	55 (35%)	62 (39%)
>12 to ≤18 months	26 (17%)	33 (21%)	27 (17%)
>18 months	42 (27%)	36 (23%)	38 (24%)

Less extensive ePLND? Median 5-6 lymph nodes

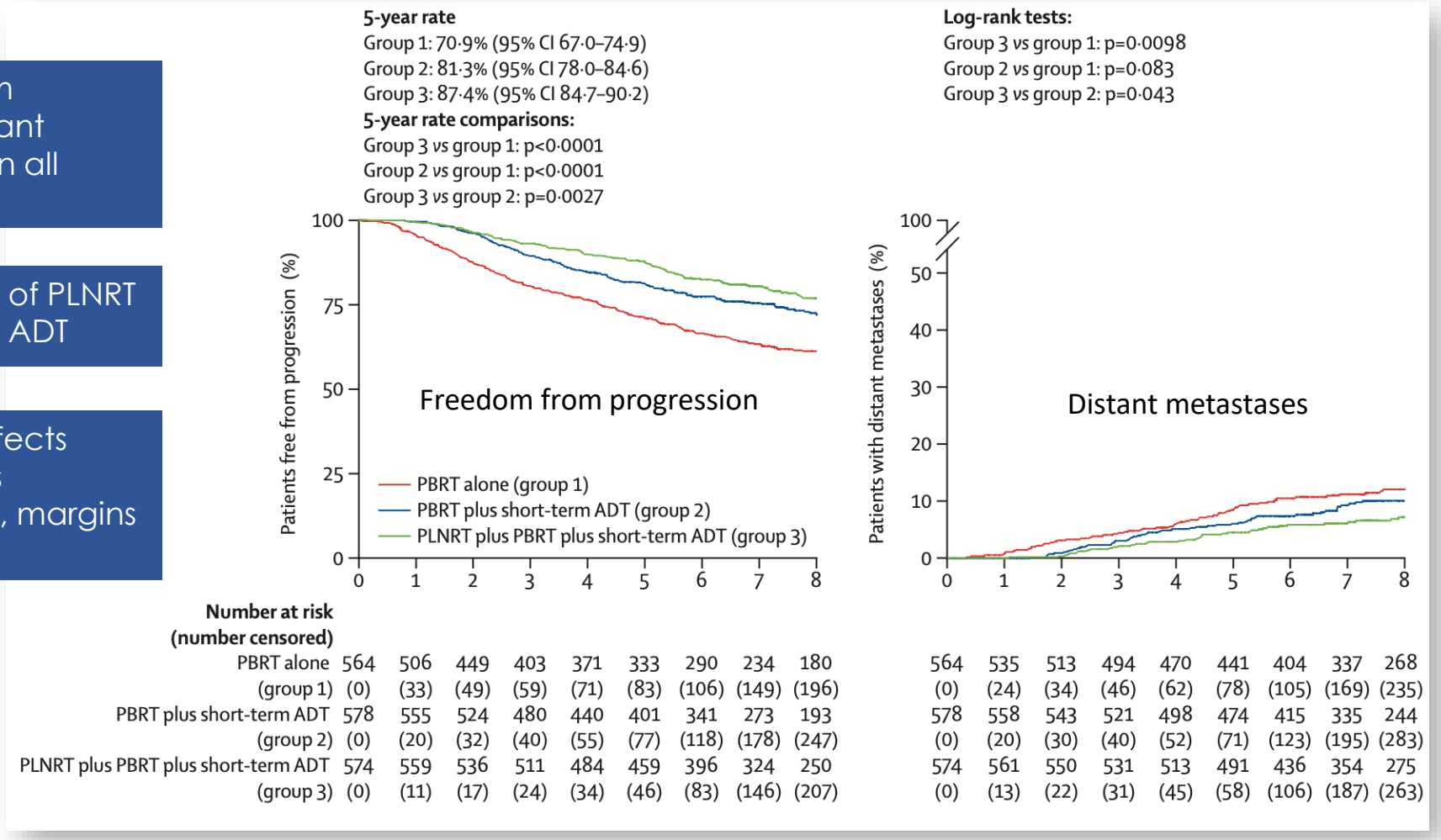
Median PSA 0,35 ng/ml (IQR 0,20-0,60)

SPPORT-trial outcome I

5-year freedom from progression: Significant differences between all treatment groups

Independent effect of PLNRT relative to PBRT and ADT

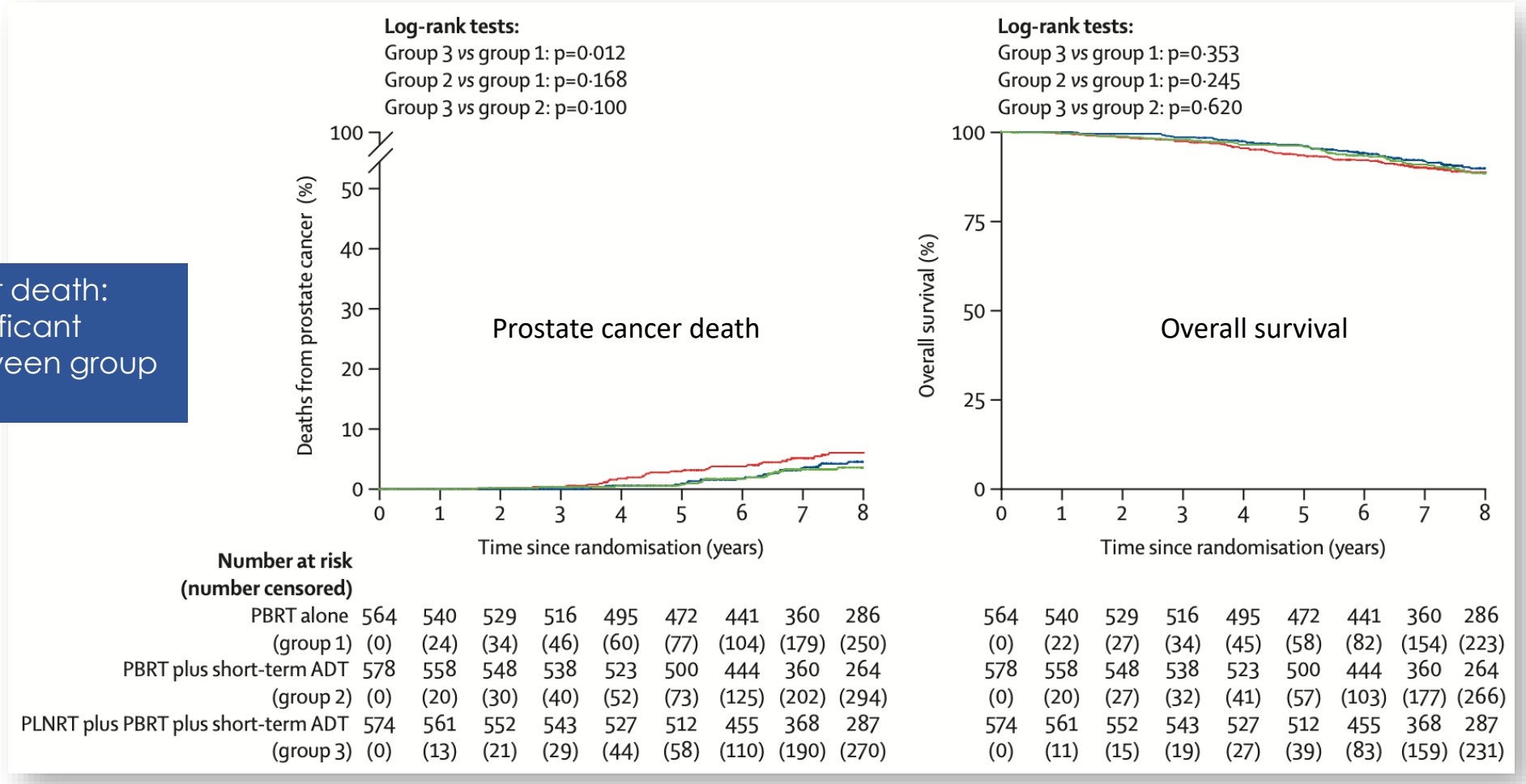
Similar treatment effects across all subgroups (pathological stage, margins and Gleason score)



Distant metastases: Statistically significant difference between group 1 and 3 only

SPPORT-trial outcome II

Prostate cancer death: Statistically significant difference between group 1 and 3 only



Number at risk (number censored)									
PBRT alone (group 1)	564 (0)	540 (24)	529 (34)	516 (46)	495 (60)	472 (77)	441 (104)	360 (179)	286 (250)
PBRT plus short-term ADT (group 2)	578 (0)	558 (20)	548 (30)	538 (40)	523 (52)	500 (73)	444 (125)	360 (202)	264 (294)
PLNRT plus PBRT plus short-term ADT (group 3)	574 (0)	561 (13)	552 (21)	543 (29)	527 (44)	512 (58)	455 (110)	368 (190)	287 (270)

	564 (0)	540 (22)	529 (27)	516 (34)	495 (45)	472 (58)	441 (82)	360 (154)	286 (223)
	578 (0)	558 (20)	548 (27)	538 (32)	523 (41)	500 (57)	444 (103)	360 (177)	264 (266)
	574 (0)	561 (11)	552 (15)	543 (19)	527 (27)	512 (39)	455 (83)	368 (159)	287 (231)

Overall survival: No differences

SPPORT-trial toxicity

	Group 1 (n=547, acute; n=545, late)	Group 2 (n=563, acute; n=559, late)	Group 3 (n=563, acute; n=562, late)	p value*	Group 2 vs group 1		Group 3 vs group 2	
					OR† (95% CI)	p value‡	OR† (95% CI)	p value‡
Acute adverse events§								
All								
Grade ≥2	98 (18%)	201 (36%)	246 (44%)	<0·0001	2·55 (1·93–3·37)	<0·0001	1·39 (1·10–1·77)	0·0034
Grade ≥3	18 (3%)	41 (7%)	63 (11%)	<0·0001	2·31 (1·31–4·07)	0·0019	1·60 (1·06–2·42)	0·012
Blood or bone marrow								
Grade ≥2	12 (2%)	10 (2%)	29 (5%)	0·0016	0·80 (0·34–1·88)	0·692	3·01 (1·45–6·26)	0·0016
Grade ≥3	3 (1%)	1 (<1%)	15 (3%)	0·0012	0·32 (0·03–3·11)	0·836	15·38 (2·03–116·85)	0·0041
Gastrointestinal								
Grade ≥2	11 (2%)	22 (4%)	38 (7%)	0·00041	2·01 (0·96–4·19)	0·032	1·76 (1·03–3·03)	0·020
Grade ≥3	1 (<1%)	5 (1%)	4 (1%)	0·286	4·89 (0·57–42·01)	0·074	0·80 (0·21–2·99)	0·631
Renal or genitourinary								
Grade ≥2	49 (9%)	68 (12%)	67 (12%)	0·177	1·40 (0·95–2·06)	0·046	0·98 (0·68–1·40)	0·544
Grade ≥3	5 (1%)	5 (1%)	8 (1%)	0·622	0·97 (0·28–3·37)	0·518	1·61 (0·52–4·95)	0·203
Late adverse events‖								
All								
Grade ≥2	308 (57%)	322 (58%)	350 (62%)	0·116	1·04 (0·82–1·32)	0·367	1·22 (0·96–1·55)	0·054
Grade ≥3	65 (12%)	87 (16%)	96 (17%)	0·047	1·36 (0·96–1·92)	0·040	1·12 (0·81–1·53)	0·246
Blood or bone marrow								
Grade ≥2	20 (4%)	10 (2%)	25 (4%)	0·038	0·47 (0·22–1·01)	0·973	2·60 (1·23–5·47)	0·0060
Grade ≥3	3 (1%)	2 (<1%)	7 (1%)	0·181	0·65 (0·11–3·90)	0·682	3·51 (0·73–17·0)	0·059
Gastrointestinal								
Grade ≥2	56 (10%)	57 (10%)	51 (9%)	0·753	0·99 (0·67–1·46)	0·518	0·88 (0·59–1·31)	0·738
Grade ≥3	4 (1%)	5 (1%)	8 (1%)	0·488	1·22 (0·33–4·57)	0·384	1·60 (0·52–4·92)	0·206
Renal or genitourinary								
Grade ≥2	202 (37%)	194 (35%)	223 (40%)	0·226	0·90 (0·71–1·16)	0·793	1·24 (0·97–1·58)	0·043
Grade ≥3	29 (5%)	37 (7%)	45 (8%)	0·201	1·26 (0·76–2·08)	0·182	1·23 (0·78–1·93)	0·186

Increased toxicity of PLNRT

- Acute (≤3 months after RT):
  - Grade ≥ 2 and ≥ 3 blood/bone marrow
  - Grade ≥ 2 GI
- Late (>3 months after RT):
  - Grade ≥ 2 blood/bone marrow
  - Grade ≥ 2 GU

SPPORT-trial conclusions

- The addition of pelvic lymph node radiotherapy increased 5-year progression free survival compared to combination of prostate bed radiotherapy and 4-6 months ADT
- However, no differences in cumulative incidence of distant metastases, prostate cancer deaths or overall survival were observed
- Pelvic lymph node radiotherapy increased both acute and late toxicity

Take-home messages fra POP-RT og SPPORT

- Selvstendig effekt av bekkenfelt utover lokal strålebehandling både i primær og adjuvant/salvage situasjon
  - POP-RT:
    - Biokjemisk residivfri overlevelse
    - Sykdomsfri overlevelse
    - Metastasefri overlevelse
    - *Ikke* totaloverlevelse
  - SPPORT
    - Biokjemisk residivfri overlevelse
    - *Ikke* risiko for fjernmetastaser, prostataspesifikk dødelighet eller totaloverlevelse

Take-home messages fra POP-RT og SPPORT

- POP-RT:
  - Absolutt bedring i 5-års metastasefri overlevelse på 7% (88-95%)
  - Ikke-planlagt effektmål
  - Risiko for bias: Ikke skissert bruk av radiologi i oppfølgingsfasen. Kan de med biokjemisk residiv være fulgt tettere med bilder?
- SPPORT:
  - Absolutt bedring i 5-års progresjonsfri overlevelse på 6% (81-87%)
- Ingen effekt på OS i noen av studiene
- Toksisitet
  - Absolutt økning i grad 2 GU langtidstoksisitet i POP-RT på 11% (7-18%)

Take-home messages fra POP-RT og SPPORT

- Hvilken effekt har utredning med PSMA PET/CT og ePLND?
  - Effekt av bekkenfelt i POP-RT på tross av radN0 ved PSMA PET/CT
  - Effekt av bekkenfelt i SPPORT på tross av pN0

Diskusjon

- Skal alle pasienter med risiko for lymfeknutemetastaser ≥20% ihht Roach ha elektivt bekkenfelt i primærsituasjon jmf POP-RT?
- Skal alle pasienter med pN0/pNx ha elektivt bekkenfelt i salvage situasjon jmf SPPORT?

Diskusjon – hvem skal ha elektivt bekkenfelt ved Radiumhospitalet?

- Jmf POP-RT og SPPORT er nytten (effektmål) av elektivt bekkenfelt relativt beskjeden i forhold til risiko (toksisitet)
- Relativ effekt øker mest sannsynlig med økende risiko for regionale mikrometastaser

- Indikasjon for elektivt bekkenfelt, med reservert for pasienter med størst relativ effekt

Indikasjon for bekkenfelt – Roach formel

Review

Elective nodal radiotherapy in prostate cancer

Gert De Meerleer, Charlien Berghen, Alberto Briganti, Christof Vulsteke, Julia Murray, Steven Joniau, Anne M Leliveld, Cesare Cozzarini, Karel Decaestecker, Kato Rans, Valerie Fonteyne, Olivier De Hertogh, Alberto Bossi

In patients with prostate cancer who have a high risk of pelvic nodal disease, the use of elective whole pelvis radiotherapy is still controversial. Two large, randomised, controlled trials (RTOG 9413 and GETUG-01) did not show a benefit of elective whole pelvis radiotherapy over prostate-only radiotherapy. In 2020, the POP-RT trial established the role of elective whole pelvis radiotherapy in patients who have more than a 35% risk of lymph node invasion (known as the Roach formula). POP-RT stressed the importance of patient selection. In patients with cN1 (clinically node positive) disease or pN1 (pathologically node positive) disease, the addition of whole pelvis radiotherapy to androgen deprivation therapy significantly improved survival compared with androgen deprivation therapy alone, as shown in large, retrospective studies. This patient population might increase in the future because use of the more sensitive prostate-specific membrane antigen PET–CT will become the standard staging procedure. Additionally, the SPORTT trial suggested a benefit of whole pelvis radiotherapy in biochemical recurrence-free survival in the salvage setting. A correct definition of the upper field border, which should include the bifurcation of the abdominal aorta, is key in the use of pelvic radiotherapy. As a result of using modern radiotherapy technology, severe late urinary and intestinal toxic effects are rare and do not seem to increase compared with prostate-only radiotherapy.

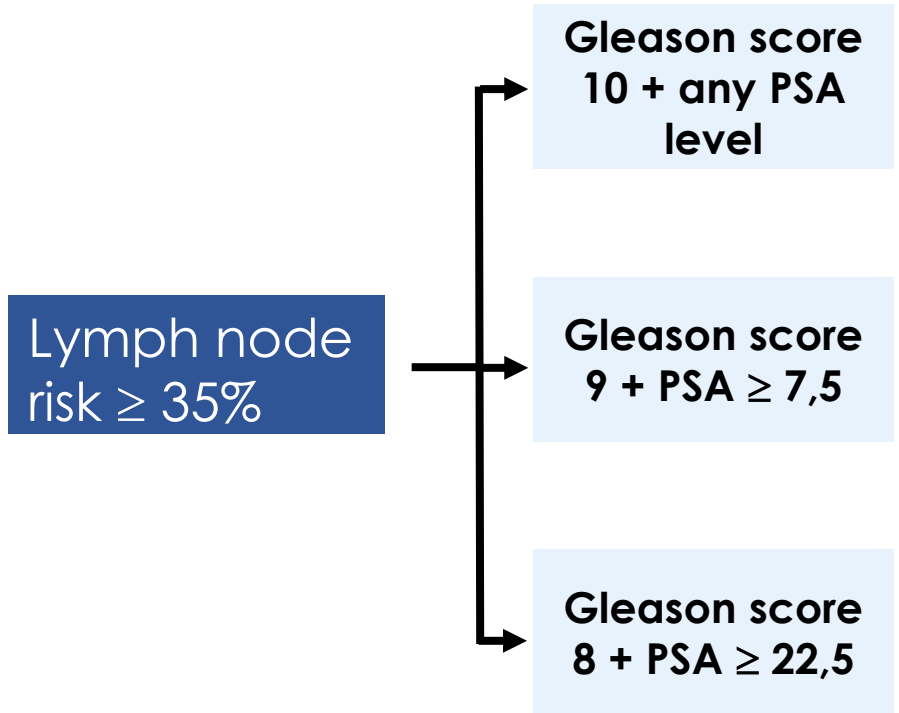
Lancet Oncol 2021; 22: e348–57

Department of Radiation Oncology (Prof G De Meerleer PhD, C Berghen MD, K Rans MD) **and Department of Urology** (S Joniau PhD), **University Hospitals Leuven, Leuven, Belgium; Department of Urology** (Prof A Briganti PhD) **and Department of Radiation Oncology** (C Cozzarini PhD), **IRCCS Ospedale San Raffaele, Milan, Italy; Department of Medical Oncology, Maria Middelares Hospital,**

node dissection (HR 0·48; p=0·024). This finding confirms the conclusions that only patients with a substantial risk of pathological pelvic nodes benefit from extended therapy (extended pelvic lymph node dissection or whole pelvis radiotherapy, or both). Although this cutoff is arbitrary, we want to suggest a cutoff value of 35% for lymph node invasion to enable whole pelvis radiotherapy to be done electively. This 35% cutoff is based on the median risk of lymph node invasion of 38% shown in the POP-RT trial. Additionally, in intermediate-risk patients, staging, treatment, or both, of the pelvic nodes can be omitted.[11,46]

Roach equation:

Lymph node risk (%) = (2/3 x PSA) + (Gleason score -6) x 10



Indikasjon for elektivt bekkenfelt – AKB-retningslinjer

- Ved primær strålebehandling av cancer prostata ved radN0 kan det vurderes tillegg av elektivt bekkenfelt ved risiko for lymfeknutemetastaser ≥35% etter Roach formel.
- Ved postoperativ strålebehandling av cancer prostata (adjuvant/salvage) kan det vurderes tillegg av elektivt bekkenfelt ved risiko for lymfeknutemetastaser ≥35% etter Roach formel basert på preoperativt PSA-nivå og Gleason score ved prostatektomi. Vurderingen gjelder uavhengig av pN0/pNx og/eller radN0 ved PSMA PET/CT.